EXPLORATION OF PAIN IN ADOLESCENTS AND ADULTS WITH CYSTIC FIBROSIS

by
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ABSTRACT

Pain is reported to be highly prevalent in the CF population but why certain individuals with CF experience pain, its role in clinical outcomes, and how it should be addressed is poorly understood. The purpose of this dissertation was to explore and describe pain in individuals with moderate to severe cystic fibrosis lung disease. This dissertation is a multi-method study comprising of a quantitative secondary analysis and a qualitative study. The three study aims were to: identify the physiologic, psychological, and social factors that are associated with pain; determine the characteristics of individuals with CF that are associated with worse clinical outcomes; explore and describe ways adolescents and adults with CF experience pain. Results from the secondary analysis showed that pain is associated with worse physical quality of life (QOL), worse mental well-being, and worse depressive symptoms and that those receiving a lung transplant or who died were almost six times more likely to report pain (HR: 5.83; 95% CI: 1.82-18.67; p-value: 0.003) controlling for sex, physical QOL and mental well-being. The qualitative study revealed the similarities and differences between adolescent and adult experiences with pain with the emergence of five themes: CF is a Pain, Pain Restricts Life, Sharing the Pain, Supported and Treated, and Disbelieved and Stigmatized. In conclusion, pain in adolescents and adults with cystic fibrosis is associated with debilitating symptoms and worse clinical outcomes. Further research is needed to identify the underlying mechanisms of pain in those with CF and to explore attitudes regarding pain assessment and treatment in both providers and patients with the overarching goal of developing CF-specific, patient-centered interventions to alleviate this symptom and improve outcomes for this population.

Committee: Noah Lechtzin, MD, MHS (chair); Gayle Page, PhD, RN, FAAN; Christopher Goss, MD, MSc; Kamila Alexander, PhD, RN, MPH, Janiece Walker, PhD, RN, MSN
This manuscript is dedicated to my son, Daniel Allgood, without whom I would be lost.

I would like to acknowledge the following people and organizations for their role in the completion of this dissertation:

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Those who suffer from cystic fibrosis; your enduring spirits will always live on, and I hope that this dissertation contributes in some small way to improving your health and the lives of you and your families.
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CHAPTER I: INTRODUCTION AND BACKGROUND

Introduction

Cystic Fibrosis (CF) is a life-limiting autosomal disease affecting approximately 40,000 people in the United States and 70,000 people worldwide.¹ The disease is characterized by recurrent respiratory infections, pancreatic insufficiency, diabetes mellitus, sinus disease, and other complications such as male infertility.² Twenty years ago the average life expectancy for a person with CF was 18 years old. Advancements in disease management have increased the predicted life expectancy to 41 years old¹ and, for the first time in history, the CF population has more adults than pediatric patients. Despite these advances, patients suffer from a heavy symptom burden including cough, dyspnea, fatigue, pain, anxiety, and depression, as well as functional limitations due to decreased lung capacity and frequent hospitalizations to treat acute pulmonary exacerbations. The most common cause of death in CF is respiratory failure.

Background and Rationale

Pain. Pain is a complex, multi-dimensional process that negatively affects physical and mental functioning, quality of life, and productivity.³ The prevalence of pain in the general population is widespread and can be accounted for up to 80% of all general practitioner visits.⁴ Just as the impact and prevalence of pain is widespread, so is its interpretation. The pain experience is subjective and can differ in terms of frequency, duration, and severity, even in those with identical sources of pain. Evidence of Pain in Cystic Fibrosis. Prevalence numbers are difficult to report due to the inconsistent measures used across a limited number of studies, but, research indicates that up to 89% of CF patients experience pain within a two month period, with up to one third of those reporting pain as strong to severe, and approximately 30% of patients experiencing pain lasting for greater than 6 months in a 12-month period.⁵,⁶ Longitudinal data observing the effects of pain on health outcomes has been reported in two studies and both found that pain is associated with an
increased risk for poor quality of life and mortality.\textsuperscript{7,8} Despite these findings, the literature suggests that pain is underreported in the CF population and not fully assessed and treated by healthcare providers.\textsuperscript{9-11}

**Purpose of Dissertation Research**

The purpose of this dissertation was to explore and describe pain in individuals with moderate to severe cystic fibrosis lung disease.

**Specific Aims/Hypotheses**

The specific aims and hypotheses of this dissertation were:

**AIM 1: Identify the physiologic, psychological, and social factors that are associated with pain**

H\textsubscript{1.1}: Lung function is not associated with pain.

*Lower Forced expiratory volume in 1-second percent predicted (FEV1\%) will not be associated with higher reports of pain*

H\textsubscript{1.2}: Respiratory symptoms are associated with pain.

*Higher scores on the St. Georges Respiratory Questionnaire (SGRQ)\textsuperscript{12} and the Cystic Fibrosis Questionnaire-Revised (CFQ-R) Respiratory Symptom domain\textsuperscript{13} indicating a high respiratory symptom severity will be associated with higher reports of pain*

H\textsubscript{1.3}: Physical quality of life (QOL) is related to pain

*Lower scores on the Physical QOL Domain of the CFQ-R indicating lower quality of life related to physical functioning will be associated with higher reports of pain*

H\textsubscript{1.4}: Mental well-being is associated with pain

*Higher scores on the Mental Component Scale of the Medical Outcomes Study Short Form 36 (SF-36)\textsuperscript{14} indicating lower quality of life related to mental well-being will be associated with higher reports of pain*

*Higher total scores on the Center for Epidemiological Studies Depression Scale (CESD) indicating more depression will be associated with higher reports of pain*
H1.5: Socio-economic status (SES) is associated with pain

Lower socio-economic status as determined by the demographic information provided on the CFQ-R will be associated with higher reports of pain.

AIM 2: To determine how pain and respiratory symptoms contribute to predictions for survival

H2.1: Pain is associated with worse clinical outcomes

The presence of pain as indicated on the Pain Domain of the SF-36 will be associated with higher risk for mortality

H2.2: Lung function is associated with worse clinical outcomes

Lower FEV1% will be associated with a higher risk for mortality

H2.3: Respiratory symptoms are associated with worse clinical outcomes

Higher scores on the SGRQ and the Respiratory Symptoms Domain of the CFQ-R, indicating a high respiratory symptom severity, will be associated with higher risk for mortality

H2.4: Worse mental well-being is associated with worse clinical outcomes

Higher scores on the Mental Component Scale of the SF-36 indicating lower quality of life related to mental well-being will be associated with higher risk for mortality

AIM 3: To explore and describe ways adolescents and adults with CF experience pain.

Goal: The goal of this study is to explore how adolescents and adults with self-reported moderate to severe pain perceive their pain, its effects on their social, physical, emotional, and work lives, and how their healthcare team addresses pain.

Significance of Research

Pain is reported to be highly prevalent in the CF population but why certain individuals with CF experience pain, its role in clinical outcomes, and how it should be addressed is poorly understood. The quantitative analysis presents data on the associations with pain and how it contributes to risk for mortality in a cohort of individuals with moderate to severe lung disease.
The qualitative results from this dissertation provide rich insight into the stark differences between how adolescents and adults perceive and live with their pain. This dissertation lays the foundation for the author’s long-term research goals to develop symptom management interventions for individuals with CF. There are considerable gaps in the literature, specifically in those individuals with moderate to severe CF. This is the first time in history that the CF population has had more adults than children, and as our ability to extend survival increases, so will the burden of symptoms in those with more severe disease increase. If the presence of pain is truly a predictor of survival in these patients, it is imperative we develop timely pain assessment and interventions to improve health outcomes and QOL.
CHAPTER II: SYSTEMATIC REVIEW OF THE LITERATURE

This review of literature is the first of three papers that comprises this dissertation. It is the author’s intent to submit this paper to the Journal for Nursing Research. The required format for submission is APA 6.0. The word count for review articles are limited to 4500 words, with 300 for the abstract and a limit of 50 references.

Title:  
PAIN IN CHILDREN AND ADULTS WITH CYSTIC FIBROSIS: A SYSTEMATIC REVIEW

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Abstract

**Background:** Individuals with cystic fibrosis (CF) suffer from a wide range of symptoms including pain. The impact of pain across the lifespan, how pain changes over time, and the difference between acute pains attributable to a specific underlying CF co-morbidities compared to chronic pain development in individuals with CF is still poorly understood.

**Purpose:** The purpose of this systematic review is to present a comprehensive summary of the available literature on pain in individuals with CF and inform CF specific pain research development.

**Methods:** Our search strategy followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (Moher D, et al., 2009). A search was conducted of articles published in the English language with no date limitations using PubMed, CINAHL, and EMBASE. Boolean search phrases including words such as “cystic fibrosis”, “pain”, “children”, “adolescents”, and “adults” were used in multiple combinations to search the literature.

**Results:** A total of 22 articles were included in the review. 5 articles were rated high evidence and no studies were large randomized control trials. Pain prevalence is difficult to assess due to heterogeneity in studies, but exists in those with CF at rates far higher than in the general population, is not limited to one location, and affects various aspects of quality of life (QOL).

**Conclusions:** Current pain in CF literature is limited by the scope and size of the studies. There is a need for larger studies of quality exploring pain development, for the establishment of clinical guidelines to assess and treat pain in those with CF, for the development of pain intervention studies.
**Introduction**

Cystic fibrosis (CF) is a complex multi-system life-limiting disease caused by mutations in the cystic fibrosis transmembrane conductance regulator gene (CFTR) (Mall MA, 2014). This autosomal recessive mutation creates unusually thick secretions in the lungs, contributes to the development of severe lung disease, recurrent infections, pancreatic insufficiency, malnutrition, diabetes, liver disease and infertility in males. Recent advances in how the disease is treated has increased the median survival age to approximately 41 years old from 18 years old twenty-five years ago (Cystic Fibrosis Foundation Patient Registry, 2015). Despite these improvements, patients still experience a heavy symptom burden from coughing, dyspnea (Boland J, 2013), fatigue (Perin, et al., 2012), depression, anxiety, and pain that negatively affects quality of life and clinical outcomes (Hayes, et al., 2011) (Quittner, et al., 2014) (Sawicki, Sellers, & Robinson, 2008).

It is estimated that pain in the general population accounts for up to 80% of all primary care visits in the United States (Schiller, Lucas, Ward, & Peregoy, 2010). Pain is a highly subjective experience that is notoriously difficult to treat due to the multi-faceted convergence of physical, emotional, and psychosocial factors (Carlino, Frisaldo, & Bendetti, 2014). Furthermore, pain experiences can shift in individuals from acute and episodic to chronic and pervasive in response to highly individual characteristics and underlying disease processes including sex, age, mental health status, and psychosocial aspects (Ossipov, Morimura, & Porreca, 2014) (Tsang, et al., 2008).

Despite reports of pain as a symptom of CF requiring specific assessments and treatments to help improve clinical outcomes as far back as 1969 (Gracey M, 1969), pain research in those with CF has been largely limited to epidemiological surveys and small-scale complementary and alternative medicine interventions. The impact of pain across the lifespan, how pain changes over time, and the difference between acute pains attributable to a specific underlying CF co-morbidity
such as distal intestinal obstructive syndrome – compared to chronic pain development in individuals with CF is still poorly understood.

The purpose of this systematic review is to present a comprehensive summary of the available literature on pain in individuals with CF and inform CF specific pain research development.

**Methods**

**Study Population**

The patient population of interest was defined as individuals of any age with a diagnosis of cystic fibrosis based on positive sweat chloride test and/or positive CF genotyping. Randomized clinical trials, quasi experimental trials, and observational studies investigating any aspect of pain, including the treatment of pain, clinical outcomes of pain, and/or socio-demographic factors associated with pain and that included at least one measure of pain were included in this study. Study exclusion criteria included studies assessing procedural pain or pain associated with a specific known acute condition – such as studies describing distal obstruction intestinal syndrome (DIOS) with pain listed as a symptom.

**Search Strategy**

Our search strategy followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (Moher D, et al., 2009). A search was conducted of articles published in the English language with no date limitations using PubMed, CINAHL, and EMBASE. Boolean search phrases including words such as “cystic fibrosis”, “pain”, “children”, “adolescents”, and “adults” were used in multiple combinations to search the literature.

**Data Collection Process**

A standardized data collection form was established according to PRISMA and the Cochrane Database guidelines (Higgins & Green, 2011). This included a description of the study sample, socio-demographic factors, clinical characteristics, description of the statistical methods, study results, and an assessment of risk of bias. Studies were graded according to the Johns
Hopkins Nursing Evidence Based Practice (JHNEBP) Evidence Rating Scales (Newhouse, Dearhold, Poes, Pugh, & White, 2005). Studies were rated as low quality if the study provided little evidence with inconsistent results, if there were an insufficient sample size, and/or conclusions cannot be drawn from the presented data. Studies were rated as good quality if the study presented reasonably consistent results, there was a sufficient sample size for the type of study/statistics used, some control group was used where appropriate, and fairly definitive conclusions were able to be drawn. Studies were rated high quality if the results were consistent with a sufficient sample size, there was an adequate control where applicable, and definitive conclusions could be drawn.

Results

Study Selection

The study selection was a total of 3,405 potentially relevant abstracts and articles. A total of 2,666 abstracts were reviewed for eligibility after removing duplicates (n=739). A total of 76 articles were eligible for full-text review. Twenty-two articles met inclusion/exclusion criteria after full-text review. No additional articles were found from screening the reference list of these 22 articles. Both authors independently conducted all steps of the article review process. There were no discrepancies between the authors on which articles were to be included.

Summary of Risk of Bias, Study Design, and Age Inclusion

According to the JHNEBP Evidence Rating Scales, 22.7% (n=5) of studies were high quality (Abbott, et al., 2009) (Hayes, et al., 2011) (Koch, Bromme, Wollslager, Horneff, & Keyszer, 2008) (Lechtzin, et al., 2016) (Ravilly, Robinson, Suresh, Wohl, & Berde, 1996), 40.9% (n=9) were moderate quality (Abbott, et al., 2001) (Blackwell & Quittner, 2014) (Festini, Ballarin, Codamo, Doro, & Loganes, 2004) (Flume, Ciolino, Gray, & Lester, 2009) (Keleman, et al., 2012) (Koh, Harrison, Palermo, Turner, & McGraw, 2005) (Palermo, Harrison, & Koh, 2006) (Sermet-Gaudelus, et al., 2009) (Stenekes, et al., 2009), and 36.3% (n=8) were low quality (Hubbard, Broome, & Antia, 2005) (Hubert, et al., 2014) (Lee, Holdsworth, Holland, & Button, 2009) (Lin &
Ly, 2005) (McNamara, 2016) (Munck, et al., 2012) (Swender, Thompson, Schneider, McCoy, & Patel, 2014) (Uchmanowitz, Janjowska-Polanska, Wlekilk, Rosinczuk-Tonderus, & Debska, 2014). The characteristics of the included studies, including study aim, sample description, summarized results, major limitations and article ratings are presented in Table 1. There were no large randomized controlled trials studies available to include in the review, however, 9.1% (n=2) studies were small-scale randomized control pilot studies (Hubert, et al., 2014) (Swender, Thompson, Schneider, McCoy, & Patel, 2014), 18.2% (n=4) were quasi-experimental (Lee, Holdsworth, Holland, & Button, 2009) (Lin & Ly, 2005) (McNamara, 2016), (Munck, et al., 2012) and 72.7% (n=16) were observational studies. Of the observational studies, the majority, 45.5% (n=10) were cross-sectional patient-reported outcome surveys (Festini, Ballarin, Codamo, Doro, & Loganès, 2004) (Flume, Ciolino, Gray, & Lester, 2009) (Hubbard, Broome, & Antia, 2005) (Keleman, et al., 2012) (Koch, Bromme, Wollschlager, Horneff, & Keyszer, 2008) (Koh, Harrison, Palermo, Turner, & McGraw, 2005) (Palermo, Harrison, & Koh, 2006) (Sermet-Gaudelus, et al., 2009) (Stenekes, et al., 2009) (Uchmanowitz, Janjowska-Polanska, Wlekilk, Rosinczuk-Tonderus, & Debska, 2014), 22.7% (n=5) (Abbott, et al., 2009) (Abbott, et al., 2001) (Blackwell & Quittner, 2014) (Hayes, et al., 2011) (Lechtzin, et al., 2016) were prospective cohort patient-reported outcome surveys, and 4.5% (n=1) was a retrospective chart review (Ravilly, Robinson, Suresh, Wohl, & Berde, 1996).

36.4% (n=8) of studies explored pain in samples of adults with CF – defined as over the age of 18 years old and attending an adult CF clinic (Abbott, et al., 2009) (Festini, Ballarin, Codamo, Doro, & Loganès, 2004) (Flume, Ciolino, Gray, & Lester, 2009) (Hayes, et al., 2011) (Hubert, et al., 2014) (Keleman, et al., 2012) (Lee, Holdsworth, Holland, & Button, 2009) (Lin & Ly, 2005) (Swender, Thompson, Schneider, McCoy, & Patel, 2014). One additional study (4.5%) defined their adult sample as 16 years old and older attending an adult CF clinic (Uchmanowitz, Janjowska-Polanska, Wlekilk, Rosinczuk-Tonderus, & Debska, 2014), and three (13.6%) specifically recruited adolescents, defined as individuals attending a pediatric CF clinic and
between the ages of 13-18 years old (Abbott, et al., 2001) (Blackwell & Quittner, 2014) (Lechtzin, et al., 2016). Three studies (13.6%) stated that the sample was of children but inclusion criterion varied from as young as age 7 to as old as age 21 (Koh, Harrison, Palermo, Turner, & McGraw, 2005) (Munck, et al., 2012) (Palermo, Harrison, & Koh, 2006), not surprisingly as most pediatric CF care centers will see patients up to age 21. Another six studies (27.3%) included both children and adults, with varying age ranges from as young as five years old to as old as 61 years old (Abbott, et al., 2009) (Koch, Bromme, Wollschlager, Horneff, & Keyszer, 2008) (McNamara, 2016) (Ravilly, Robinson, Suresh, Wohl, & Berde, 1996) (Sermet-Gaudelus, et al., 2009) (Stenekes, et al., 2009). One study did state their sample was of adolescents and adults but failed to report the age range (Hubbard, Broome, & Antia, 2005). It was unclear in all studies other than those specific to adolescents and the Sermet-Gaudelus comparison study, if the sample’s age range was chosen a priori or was a result of sample recruitment.

Pain Instruments

The type of pain instruments used varied greatly from study to study with 27.2% (n=6) either developing their own (Festini, Ballarin, Codamo, Doro, & Loganes, 2004) (Koh, Harrison, Palermo, Turner, & McGraw, 2005) (Palermo, Harrison, & Koh, 2006) (Sermet-Gaudelus, et al., 2009) (Stenekes, et al., 2009), or using a variety of smaller valid measures to make up a bigger survey (Hubbard, Broome, & Antia, 2005) (Munck, et al., 2012). There was no direct mention within the articles as to why a survey was developed specifically vs. using an established instrument. The Brief Pain Inventory (BPI) was used in 18.2% (n=4) of the studies: three adult studies (Flume, Ciolino, Gray, & Lester, 2009) (Hayes, et al., 2011) (Keleman, et al., 2012) and one adolescent study (Lechtzin, et al., 2016). The BPI is a comprehensive pain assessment tool that assesses pain and its impact on function. The short form is the most widely used version of the instrument and takes about 5 minutes to complete (MD Anderson Center, 2017). The SF-36 pain domain was also used by 18.2% of the studies. Two enrolled only adults (Abbott, et al., 2009) (Uchmanowitz, Janjowska-Polanska, Wlekilk, Rosinczuk-Tonderus, & Debska, 2014) and two
studies enrolled only children (Abbott, et al., 2001) (Blackwell & Quittner, 2014). The SF-36 is a measure used to assess health-related quality of life and includes multiple domains including one specifically for pain. It contains 36 items and allows for individual scoring of domains or for composite scoring (RAND Health, 2016). The visual analog scale is a continuous single item scale usually 10 centimeters long anchored by two verbal descriptors – typically no pain and worst pain (Hawker, Mian, Kendzerska, & French, 2011). Patients are asked to draw a vertical line where they are currently feeling pain. The VAS was used by three experimental studies (13.6%) (Hubert, et al., 2014) (Lee, Holdsworth, Holland, & Button, 2009) (Lin & Ly, 2005) and one observational study (4.5%) (Koch, Bromme, Wollschlager, Horneff, & Keyszer, 2008). The numeric rating scale (NRS) and the FACES scale, two single-item measures similar to the VAS were each used once (Munck, et al., 2012) (Swender, Thompson, Schneider, McCoy, & Patel, 2014).

Prevalence

There is considerable difficulty in summarizing the prevalence of pain in these studies given the varied assessment tools used. Some measures asked about pain recall over a month or two period, and others simply assessed for the presence of pain at the time of the survey. Additionally, some studies only enrolled participants that were known to have pain in order to test an intervention, therefore, did not discuss pain characteristics of the sample. Regardless, in those studies that did assess prevalence, pain prevalence in adults ranged from 64% to 94.1% (Festini, Ballarin, Codamo, Doro, & Loganes, 2004) (Flume, Ciolino, Gray, & Lester, 2009) (Hayes, et al., 2011) (Keleman, et al., 2012) (Sermet-Gaudelus, et al., 2009) and from 46% to 89% in children (Blackwell & Quittner, 2014) (Lechtzin, et al., 2016) (Koh, Harrison, Palermo, Turner, & McGraw, 2005) (Palermo, Harrison, & Koh, 2006) (Sermet-Gaudelus, et al., 2009). Chronic pain – defined as pain occurring every day for at least a period of three months (American Association of Pain Medicine, 2017) was only specified as such by two studies, Hayes et al. and Ravilly et al. Hayes et al. reported 27% of their adult sample met the criterion for chronic pain (Hayes, et al.,
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2011) and Ravilly et al. reported that 84% of the charts they reviewed indicated the patients had chronic pain prior to death and that there was a marked increase in head and chest pain in the last months of life (Ravilly, Robinson, Suresh, Wohl, & Berde, 1996).

Location of Pain

Among the various instruments used to capture pain location, four locations: the abdomen, chest, head, and back, were consistently given as an option (Blackwell & Quittner, 2014) (Festini, Ballarin, Codamo, Doro, & Loganes, 2004) (Flume, Ciolino, Gray, & Lester, 2009) (Hayes, et al., 2011) (Hubbard, Broome, & Antia, 2005) (Koh, Harrison, Palermo, Turner, & McGraw, 2005), (Lechtzin, et al., 2016) (Lin & Ly, 2005) (Ravilly, Robinson, Suresh, Wohl, & Berde, 1996) (Stenekes, et al., 2009). Pain location frequencies in all studies, regardless of the age of the sample were as follows: 11-60% reported pain in the abdomen, 6-64% reported pain in the chest, 21-63% reported pain in the head, and 6-70% reported back pain. When specifically comparing children vs. adult pain locations, the range for abdominal pain in children was 42-60%, compared to 12-36% in adults, chest pain in children was 10-37%, compared to 6-50% in adults, head pain in children was 28-35% in children, compared to 22-63.5% in adults, and back pain in children was 6-16% compared to 16-70% in adults. One study actively compared children to adults in terms of pain location and found a statistically significant difference in abdominal pain in children compared to adults (p=0.05) and in back pain in adults compared to children (p=0.03) (Sermet-Gaudelus, et al., 2009).

Pain frequency, duration, and intensity

Three studies, one specific to a pediatric sample, one specific to adolescents, and one specific to adults reported that 46% (Koh, Harrison, Palermo, Turner, & McGraw, 2005) (Palermo, Harrison, & Koh, 2006), 35% (Lechtzin, et al., 2016), and 89% (Keleman, et al., 2012) of their respective samples experienced pain at least once a week over a one month recall period, and Festini et al. reported that 29.7% of their sample of adults experienced pain more than 10 times within a 2-month period (Festini, Ballarin, Codamo, Doro, & Loganes, 2004). Another study with
an adolescent-only sample did not report specific frequency data, but did note that when compared to normative data, adolescents with CF experienced pain more frequently (Abbott, et al., 2001). Chronic pain, defined by two studies as pain occurring most days for greater than six months, was reported as occurring in 27% of an adult-only sample (Hayes, et al., 2011). A retrospective chart review of individuals 5 years and up with CF reported that 84% of individuals met the criteria for having chronic pain prior to their deaths (Ravilly, Robinson, Suresh, Wohl, & Berde, 1996). Mean pain intensity scores on a scale of one to ten was reported to be 4.17 and 5.95 in two studies that did not separate the sample by age. Sermet-Gaudelus et al, reported a mean pain intensity score for adults to be 6.0 compared to 2.12 for adolescents. This difference was found to be statistically significant (p=0.004) (Sermet-Gaudelus, et al., 2009). Lechtzin et al, reported that 43% of the adolescent sample experienced their worst pain intensity to be between 0-3 out of 10, and 50% 4-6 (Lechtzin, et al., 2016). In adults, Festini et al reported that 41.4% of their sample experienced their worst pain to have a range of 4-7 and 10.8% reported their worst pain to be at a 10 (Festini, Ballarin, Codamo, Doro, & Loganes, 2004).

Descriptions of Pain

Only one study, a 6-day pain assessment study by Blackwell et al., assessed how adolescents with pain describe their pain (Blackwell & Quittner, 2014). The study assessment tool provided the participants with a list of pain qualifiers and they were asked to choose which words most represented their pain. The study sample chose the words sore, aching, pounding, cramping, and stiff to characterize their pain.

Impact of Pain on Quality of Life

40.9% (n=9) of the studies specifically examined the relationships between pain and quality of life. Of these studies, the Cystic Fibrosis Questionnaire – Revised (CFQ-R) (American Thoracic Society, 2007) (n=4), the Cystic Fibrosis Quality of Life (CF-QOL) (n=2) (Gee L, 2000), and the Medical Outcomes Study Short Form 36 (SF-36) (n=3) (RAND Health, 2016) were used to assess this relationship. Sermet-Gaudelus et al. developed their own assessment of QOL and did
not report validity nor reliability data for their measure (Sermet-Gaudelus, et al., 2009). Among those studies with a pediatric sample, domain-specific correlations were found between pain and physical function (Lechtzin, et al., 2016) (Palermo, Harrison, & Koh, 2006), emotional function (Palermo, Harrison, & Koh, 2006), body image (Lechtzin, et al., 2016), digestion (Lechtzin, et al., 2016), respiratory symptoms (Blackwell & Quittner, 2014) (Palermo, Harrison, & Koh, 2006), and role function (Palermo, Harrison, & Koh, 2006). In studies with an adult sample, domain-specific correlations were found between pain and physical function (Abbott, et al., 2009) (Keleman, et al., 2012) respiratory symptoms (Hayes, et al., 2011), role function (Hayes, et al., 2011), digestion (Hayes, et al., 2011), CF treatments (Keleman, et al., 2012), work activity (Keleman, et al., 2012), and social activity (Keleman, et al., 2012). Sermet-Gaudelus et al found that overall, pain significantly affects QOL and that there was a significant difference between QOL in children compared to adults (Sermet-Gaudelus, et al., 2009). Lechtzin et al. found that pain at baseline was associated with worse QOL at six-months in an adolescent sample (Lechtzin, et al., 2016), and Abbot et al. found pain and physical function to be predictors for survival in an adult sample (Abbott, et al., 2009).

Pain Intervention Studies

There are no studies exploring pharmacological interventions to treat pain in individuals with CF. Interventions under investigation included osteo-manipulative treatment (OMT) (n=2) (Hubert, et al., 2014) (Swender, Thompson, Schneider, McCoy, & Patel, 2014), yoga (n=1) (McNamara, 2016), acupuncture (n=1) (Lin & Ly, 2005), massage therapy (n=1) (Lee, Holdsworth, Holland, & Button, 2009), and behavioral interventions (n=1) (Munck, et al., 2012). Both randomized control trials used OMT vs. sham treatments for controls in adults, with one also including a usual care arm in addition to the control arm for comparison. Hubert et al reported no difference between sham/usual care and intervention groups in terms of absolute pain levels, but did report a non-statistically significant difference between the amounts of pain medications taken between the groups after treatment (Hubert, et al., 2014). Swender et al. reported positive results in
OMT on pain compared to the sham group, but results were only reported in terms percentage of improved pain levels – 43.8% in the intervention compared to 23.5% in the sham (Swender, Thompson, Schneider, McCoy, & Patel, 2014). These results are difficult to interpret given the lack of mean pain scores pre and post treatment and the lack of description regarding the study’s statistical analysis. Two of the quasi-experimental studies focused on children (50.0%) (McNamara, 2016) (Munck, et al., 2012). McNamara et al. explored the use of yoga to help children manage symptoms associated with CF and found a non-significant decrease in pain from baseline after a 6-week yoga intervention and Munck et al. used behavioral interventions to help manage abdominal pain and reported a positive effect on pain, quality of life, and anxiety. Lin et al explored the use of acupuncture on pain in adults with CF. They reported a statistically significant reduction in mean pain scores on a VAS (3.2 +/- 1.1, p<0.05) with an average length of effect at 3.0 days +/- 1.1 (Lin & Ly, 2005). Lee et al. explored the use of massage therapy on pain in adults with CF and found that individuals both clinically stable with pain and those acutely ill with pain had a statistically significant reduction in mean pain scores post-treatment (1.8, 95% CI: 1.5-2.1, p<0.001) (Lee, Holdsworth, Holland, & Button, 2009). Duration of effect was not reported.

Discussion

This paper summarizes the available literature describing pain in individuals with cystic fibrosis. Though variable in quality and limited by the large percentage of cross-sectional study designs, these studies report pain as a prevalent symptom in individuals with CF and its negative impact on health-related quality of life throughout the lifespan.

There is considerable difficulty when trying to extract pain prevalence data due to the varied methodological approaches used, inconsistent use of valid and reliable pain measures, large variation in age ranges – and lack thereof of age-specific analyses – and inconsistencies in study quality. Similar limitations have been encountered in other systematic reviews attempting to summarize the prevalence of pain in general populations (King, et al., 2011) (Mansfield, Sin, Jordan, & Jordan, 2016). Regardless, the reported pain prevalence rates in these studies far exceeds
the general U.S. adult population prevalence of 26% (American Association of Pain Medicine, 2017) and suggests that pain is a significant contributor to the symptom burden experienced by those with CF. Whether or not there is a true difference in the prevalence of pain between the pediatric and adult population remains to be seen. The heterogeneity of studies makes a direct comparison impossible. Sermet-Gaudelus et al. was the only study that actively compared children to adults and, although they reported a non-statistically significant difference in pain prevalence between children and adults, 59% compared to 89%, they did find that pain in adults is more intense, has greater duration, and is characterized as continuous vs. episodic compared to their pediatric sample (Sermet-Gaudelus, et al., 2009). Lechtzin et al. found similarly that adolescents self-report their pain as being more episodic compared to their previous study of adults that report their pain as having greater duration (Hayes et al.) (Lechtzin, et al., 2016).

With the exception the studies by Hayes et al (Hayes, et al., 2011) and Ravilly et al. (Ravilly, Robinson, Suresh, Wohl, & Berde, 1996) there is no distinction in these reviewed studies between the prevalence of acute and episodic pain vs. persistent and chronic pain. Chronic pain, generally defined as pain that occurs every day for a duration of greater than three months, is of most interest in current pain research trends due to the public health concerns regarding opioid use and abuse. It is estimated that chronic pain is responsible for an estimated $100 billion (American Association of Pain Medicine, 2017) in annual costs to the healthcare system. Chronic pain is associated with depression, loss of physical functioning, loss of productivity, and decreased sleep quality (American Association of Pain Medicine, 2017), is notoriously difficult to treat, and typically requires a multi-modal approach using pharmacological, behavioral, and complementary therapies to achieve relief. The development of chronic pain conditions either from an acute pain event that persists, or a pervasive chronic condition that has established itself over time, is still poorly understood, but thought to be due to nociceptive plasticity in the endogenous pain pathways (Ossipov, Morimura, & Porreca, 2014), inflammatory processes (Voscopoulos & Lema, 2010), and changes to the hypothalamus-pituitary-adrenal (HPA)-axis in response to chronic stressors.
(Kuehl, Michaux, Richter, Schachinter, & Anton, 2010). Although the source of pain in those with CF is not consistent, the deleterious effects of pain, from the cellular level up to health-related quality of life, remains the same. There is a need for CF clinicians to increase their awareness of pain in this population, to increase their competencies in pain assessment and treatment, and to understand the various treatment options available that exist to timely intervene on pain before chronicity develops.

This review illustrates the difficulty in not having a standardized reliable and valid tool in use for pain assessment in individuals with CF. Generalizability of the pain condition is next to impossible given the current available literature and lack of consistent pain measures. There are currently several well-used valid and reliable measure for health-related quality of life and symptoms that are used extensively for data collection in CF research. The CFQ-R is, perhaps arguably, the most prevalent instrument used, and was derived from the SF-36. The pain domain of the SF-36 was incorporated into the CFQ-R, but the questions were developed to be specific only to abdominal pain. As this review shows, abdominal pain is the most prevalent location of pain within the pediatric population, but not so for adults. Given that this is the first time in history the CF adult population has exceeded that of the pediatric population, it may be time to re-assess these QOL indicators for use in an aging population.

Despite the reviewed studies reporting pain prevalence and its effects on QOL, there is still a lack of awareness within the CF community as to the role of pain on clinical outcomes, on how pain should be assessed and addressed, and of available treatment options. The Cystic Fibrosis Foundation maintains a Patient Registry that collects annually all clinic visit data, such as BMI, lung function values, prescribed medications, and infection status, from all patients with CF who attend a CF Care Center in the United States. However, pain is not currently a parameter of interest in this registry. There is a need to develop a CF-specific pain assessment tool that can be clinically used to identify potential sources of pain symptomology, both acute and chronic. This assessment could then become a parameter of the CFF patient registry and used to track pain over
time, to identify those who may need interventions, and to raise awareness within the clinical setting that pain is a symptom of CF that negatively impacts health status. This registry data could then be used to guide clinical trials development and allow for more robust epidemiological pain studies.

This systematic review highlights the lack of literature available examining in impact of pain on individuals with CF. There is a need for more high quality research into the epidemiological aspects of pain in those with CF, for investigations into appropriate pain measures for both research and clinical applications, and to develop pain interventions targeting individuals with CF in an effort to improve QOL and clinical outcomes.
Total number of abstracts identified after searching databases (PubMed, CINAHL, EMBASE) (n=3405)

Total number of duplicates removed (n=730)

Abstracts screened for eligibility (n=2666)

Abstracts excluded: (n=2590)
- Systematic Review/Opinion Article
- Case reports, letters to the editors
- Studies not including a sample of those with cystic fibrosis
- Studies not related to pain

Articles eligible for full-text review (n=76)

Excluded after full-text review: (n=52)
- No direct pain measure used or analyzed
- Published conference abstracts; no manuscript available

Final collection included studies that:
1. Used a direct pain measure and presented the analysis
2. Included a sample of individuals with a diagnosis of cystic fibrosis
3. Investigated socio-demographics and clinical outcomes associated with pain, described pain characteristics of pain, and/or investigated an intervention specific to treating pain in a cohort of individuals with cystic fibrosis (n=24)

Figure 1: Chapter 2. PRISMA flow diagram depicting search results and eligible articles
<table>
<thead>
<tr>
<th>1st Author</th>
<th>Year</th>
<th>Study Aim</th>
<th>Study Design/Pain Instrument</th>
<th>Participant Characteristics</th>
<th>Summary of Results</th>
<th>Rating</th>
<th>Limitations</th>
</tr>
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<tbody>
<tr>
<td>Abbott</td>
<td>2008</td>
<td>To determine if domains of patient reported HRQOL are able to predict survival in CF after controlling for key variables.</td>
<td>Observational: Prospective cohort SF-36</td>
<td>N= 223, 14+ years of age from multiple UK CF Centers; Mean age: 25.1 years, 54% female; Mean FEV1% predicted: 55.0 (23.5); Mean BMI: 20.8 (2.5)</td>
<td>Pain domain in SF36 had low correlations with other domains; Physical functioning (CF QOL) and pain domain (SF-36) (HR= 0.98, 95% CI 0.97 to 1.00, p=0.019) significant predictors of survival.</td>
<td>High</td>
<td>High sample inclusion/exclusion criteria poorly defined; multivariate analysis contained moderate correlates</td>
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<tr>
<td>Abbott</td>
<td>2009</td>
<td>To compare QOL between English and German adolescents with CF and to generate comparative normative values from health controls</td>
<td>Observational: Prospective cohort SF-36</td>
<td>N=208, adolescents 13-18 years of age with CF or healthy controls from multiple CF centers; Mean age: 16.6 years, 52.9% female; Mean FEV1% predicted: 76%; Mean BMI: 20.2</td>
<td>English adolescents reported greater levels of pain compared to German adolescents (F=3.6; (1, 198); p&lt;0.000). English control females reported the most pain (F=7.8; (1,199); p&lt;0.005).</td>
<td>Moderate</td>
<td>Recruitment differed between English and German participants; potential cultural bias or mistranslation of concepts in measure</td>
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<tr>
<td>Blackwell</td>
<td>2014</td>
<td>To measure pain prevalence, intensity, frequency, and location; to measure pain coping strategies; to examine relationships between pain and HRQOL</td>
<td>Observational, cross-sectional survey and subsequent 6 day online pain diary</td>
<td>N=95, adolescents ages 11-20 years at multiple CF pediatric CF care centers; Mean age: 15.8 years, 62.1% female; Mean FEV1% predicted: 80.1%; BMI percentile: 51.3</td>
<td>74.5% reported pain once or more within a 6 day period; Pain locations: 49.3% stomach, 42.3% head/neck, 36.6% chest, 52.5% more than one location. Pain descriptions: sore, aching, pounding, cramping, stiff. Pain intensity, frequency, and duration varies greatly between individuals and is significantly associated with medication adherence, depression, anxiety, and health-related quality of life (HRQOL).</td>
<td>Moderate</td>
<td>One measure only of psychological symptoms; inclusion not limited to those at respiratory baseline; pain diary comprised of other instrument’s items; large amount of missing pharmacy refill data for medication adherence.</td>
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<td>Festini</td>
<td>2003</td>
<td>To assess the prevalence of pain symptoms in adults with CF and evaluate if and to what extent pain is assessed and treated. Evaluate impact of pain on daily life.</td>
<td>Observational, Cross-Sectional Developed own survey</td>
<td>N=239, CF patients 18+ years of age ranging from 18-43 years at multiple CF care centers; Mean age: 26.1, 52.3% female; Mean FEV1% predicted: 56.71%; Mean BMI: 20.45</td>
<td>94.1% had pain in past 2 months; Locations: headache, stomach, backache, bones, muscles, joints, abdomen, chest, cervical, and other. 38.4% reported pain in more than one location, 16.8% reported three locations. Pain Intensity: 10.8 highest pain = 10, 41.4% 4-7. Joint pain occurs most frequently, back pain is most severe. Pain management strategy: 26.2% nothing, 6.6% decided on their own, 20.8% consulted relatives/friends, 42.6% consulted CF doc, 3.5% consulted PCP. Remedies: 91.5% medications, 1.8% homeopathic, 22.2% non-pharma - massage, acupuncture, herbal remedies, rest.</td>
<td>Moderate</td>
<td>Study-developed questionnaire, no validity or reliability information provided; limited sample to Italians</td>
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<tr>
<td>Author</td>
<td>Year</td>
<td>Study Objective</td>
<td>Study Design</td>
<td>Participants</td>
<td>Outcomes</td>
<td>Methodological Quality</td>
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<td>Flume</td>
<td>2009</td>
<td>To find associations between impaired sleep quality and pain in adults using self-reported sleep quality and pain measures.</td>
<td>Observational, Cross-Sectional Brief Pain Inventory</td>
<td>N=50, adults with CF ages ranged from 18-53 years at a single CF center; Mean age: 31.1, 46% female; Mean FEV1% predicted: 58.4%; Mean BMI: 21.3</td>
<td>64% reported having pain in last month. Pain Location: head (11), back (8), abdomen (6), chest (3), extremities = 2, neck =2. Patients who report pain have overall impaired sleep (global score) (p=0.006), have worse subjective sleep quality (p=0.045), have more sleep disturbances (&lt;0.001) and more daytime dysfunction (p=0.001). Strong positive correlation between global sleep score and rating of pain interfering with sleep (r =0.56, p&gt;0.0001), regression was also significant for pain predicting poor sleep and for those with low global sleep score will experience pain in the last 30 days. OR=1.27.</td>
<td>Moderate</td>
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<td>Hayes</td>
<td>2011</td>
<td>To determine the prevalence and location of pain, the effects of pain on QOL/mood and its impact on clinical outcomes including death.</td>
<td>Observational: Prospective cohort Brief Pain Inventory</td>
<td>N=83 adult patients from a single CF care center ages ranging from 19-71 years; Median age: 29.3, 56.6% female; Median FEV1% predicted: 63.6%</td>
<td>82% pain last 30 days 56% talked to their Doctor about it. 27% chronic pain and 41.9% reported moderate to severe pain. 1/3 of all participants ranked pain &gt; 4. Pain Location: 63.5% head, 54% sinuses, 50% back, 46% chest, 34% abdomen, 30% knee, 19% wrist, 5% finger. Pain not associated with age, sex, FEV1% predicted. Risk of pulmonary exacerbation in those of pain: OR = 1.65 controlling for FEV1 and age. Risk of death in those with pain: OR: 2.28. Pain is associated with worse QOL in respiratory, role, and digestion subscales.</td>
<td>High</td>
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Limited sample size; single center recruitment only
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<tr>
<th>Hubbard</th>
<th>2005</th>
<th>To evaluate the pain experiences of those patients using a web-based education program by studying pain reports, disability, and coping.</th>
<th>Observational, web-based cross-sectional survey</th>
<th>N=18 adolescents and adults from a single care center, 66.7% females</th>
<th>55.6% reported daily pain and 27.8% reported pain 1-2 x's a month. 44.4% reported pain lasts less than or equal to 2 hours. 33.3% reported pain lasts greater than or equal to 1 week. Average pain intensity was 4.17/10. Pain location: 72% chest, 61% joints. Disability/recreation 5.53/10, occupation/school 5.18, social activity 4.85, Family/home 4.88, sex life 4.88, self-care 2.94, life support 2.94 Coping: problem solving, acceptance, and self-encouragement were top three Active and accommodative coping strategies were preferred over passive coping.</th>
<th>Low</th>
<th>Small sample size with more females than males; possible selection bias due to recruitment techniques</th>
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<td>Hubert</td>
<td>2014</td>
<td>To assess the feasibility of evaluating efficacy of osteopathic manipulative treatment to treat the pain of adults with cystic fibrosis.</td>
<td>Experimental, Randomized Control Trial with Pilot Intervention</td>
<td>N=32 CF patients 18+ years of age at multiple CF care centers; Mean age: 31, 93.8% female; Mean FEV1% predicted: 53.9%; Mean BMI: 21.6</td>
<td>No difference between treatment and sham/usual care (UC) groups. Pain medication usage decreased but decrease was not statistically significant</td>
<td>Low</td>
<td>Small sample size – study not sufficiently powered to assess effect of intervention; unequal sex distribution in treatment vs. sham/UC; no feasibility assessment</td>
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<tr>
<td>Author</td>
<td>Year</td>
<td>Objective</td>
<td>Study Design</td>
<td>Sample Size</td>
<td>Findings</td>
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<td>Kelemen</td>
<td>2012</td>
<td>To determine the prevalence, severity, and location of pain in adults with CF, identify physical and psychosocial consequences of pain on HRQOL.</td>
<td>Observational, Cross-Sectional Brief Pain Inventory</td>
<td>N=77 adults 18+ years of age at a single CF care center; Mean age: 29.9, 53.8% female; Mean FEV1% predicted: 53.9%; Mean BMI: 21.2</td>
<td>89% clinically stable (CS) and 79% acutely sick (AS) reported pain in the past week; Pain location: head/neck (CS:52%, AS:50%), back/hips (CS:70%, AS:31%), chest (CS:20%, AS:35%), limbs (CS:50%, AS:47%); intensity of pain consistent between the groups, pain interferes with airway clearance in those acutely sick and exercise in those who are clinically stable; strong correlation between average pain intensity and PCS score (r=0.64, p&lt;0.001) in those clinically stable.</td>
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<td>Koch</td>
<td>2008</td>
<td>To assess rheumatic signs and symptoms in those with CF, identify associations between CF and rheumatic disorders, identify CF characteristics that predispose to rheumatic symptoms.</td>
<td>Observational, Cross-sectional Visual Analog Scale</td>
<td>N=70 pediatric and adult patients ranging from 6-61 years of age at a single CF care center and N=70 healthy controls; Mean age: 34.3, 51.4% female; Mean FEV1% predicted: 70.8%; Mean BMI: 19.5</td>
<td>Prevalence of joint pain in CF patients = 12.9% with mean duration of 7 days. None fulfilled criteria for rheumatoid arthritis or connective tissue disorder. Compared to controls, adults with CF have more non-inflammatory back pain and myalgia, have less spine mobility, and impaired life functions. Symptomatic CF patients (non-age specific) had elevated ESR and C-reactive proteins and worse PFT's compared to those with no pain. Antibodies against PsA and Aspergillus fumigatus allergen found more frequently in CF patients (no age given) with arthralgia compared to without.</td>
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| | | | | | Moderate | Possible recall bias, pain duration and frequency not captured, sample size not discussed. |

<p>| | | | | | High | Sample size calculations not provided for cytokine analysis; only 10 participants underwent ultrasound imaging |
| Koh | 2005 | To determine the occurrence of acute and chronic pain in children with CF, examine relationship between pain and disease severity. | Observational, Cross-Sectional | Developed own survey | N=46 children between the ages of 8-17 years at multiple CF care centers; Mean age: 12.9, 52% female; Mean FEV1% predicted: 80.2% | Pain location: 50% abdomen, 37% chest, 33% head/neck, 15% legs, 13% arms 46% experience pain at least once a week. Median pain intensity: 1.0; Frequency: 65% less than an hour. 70% reported pain causes emotional upset. No significant differences in pain intensity, frequency, duration, location or emotional upset by age or sex. Pain management: 63% rest, 41% medication, 41% relaxation, 39% heat/cold, 39% family/friends, 36% distracting activities. Pain medications: Tylenol, NSAIDS, none reported opioids. All with neck pain reported medication use. Those with chest pain significantly associated with greater perceived functional limitations due to pain. Weekly pain had significantly more functional limitations than those with less frequent pain. | Moderate | Small sample size; sample bias (39% response rate; study-designed questionnaire; inclusion criteria of respiratory baseline not stated; possible recall bias |</p>
<table>
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<tr>
<th>Lechtzin 2016</th>
<th>Observational: prospective cohort</th>
<th>N=84 adolescents at a single CF care center ranging from 12-20 years of age; Mean age: 15.6, 56.2% female; Mean FEV1% predicted: 79.3%</th>
<th>89% reported pain other than everyday kinds of pain in previous 3 months. Pain location: Abdomen: 42%, 32% head/sinus, 19% joints, 10% chest, 6% back, 3% muscles. 80% reported pain short-lived and mild to moderate in severity; 35% had pain once a week or more. No pain rating change from baseline to follow up. 19.4% report pain limits activities. Pain associated with higher scores on disability index. Higher pain scores associated with missing school. Higher baseline pain scores associated with pulmonary exacerbations adjusting for age, sex, FEV1. Pain associated with higher risk for hospitalization but not significant when controlling for age, sex or FEV1. Pain at baseline associated with lower HRQOL at 6 months. Higher pain scores associated with higher scores on PCS.</th>
<th>High</th>
<th>Single site, possible recall bias; sample size attrition from baseline to follow-up reduced sample size</th>
</tr>
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<tbody>
<tr>
<td>Lee 2009</td>
<td>Quasi-experimental</td>
<td>N=105 adults at a single CF care center; Mean age: 30.5; Mean FEV1% predicted: 48.1% predicted</td>
<td>Thoracic spine, shoulders, cervical spine, lumbar spine and chest wall - locations for pain in descending frequency. Overall, both acute pain and chronic pain groups experienced a significant decrease in pain after treatment (mean difference 1.8 cm, p&lt;0.001).</td>
<td>Low</td>
<td>Single site; convenience sample; limited sample demographics provided, VAS only pain measure used; no information regarding quality control of the intervention provided</td>
</tr>
<tr>
<td>Lin</td>
<td>2005</td>
<td>To integrate acupuncture as a complementary medical therapy in pain management for those with CF.</td>
<td>Quasi-experimental Visual Analog Scale</td>
<td>N=30 adults with CF at a single CF care center, Median age: 26.7, 70% female</td>
<td>Pain location: 38% chest pain, 21% back pain, 21% headache, 17% abdominal, 3% limb pain. Average VAS prior to treatment: 5.95 +/- 1.4; Average VAS post treatment: 2.8 +/- 1.0. Average change in pain levels: decreased by 3.2 +/- 1.1, p&lt;0.05. Average duration of effect: 3.0 +/- 1.1 days.</td>
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<td>McNamara</td>
<td>2016</td>
<td>To determine if yoga improves QOL and reduces symptoms in those with CF.</td>
<td>Quasi-experimental; feasibility pilot Additional Pain Symptoms Assessment</td>
<td>N=20 children and adults with CF at multiple CF care centers ranging from 7-20 years of age; Mean age: 11, 60% female; Mean FEV1% predicted: 86%</td>
<td>45% reported pain prior to intervention; 35% reported pain after, not significant. Joint pain was improved p=0.028 from baseline to post-intervention. No adverse events reported related to intervention.</td>
</tr>
<tr>
<td>Munck</td>
<td>2012</td>
<td>To assess the prevalence and characteristics of recurrent abdominal pain, determine their causes, evaluate anxiety, and QOL, and to provide pain management and re-assess effect at 6 months.</td>
<td>Quasi-experimental Eland pain location FACES Pain Scale - R</td>
<td>N=8 children and adolescents from a single CF care center ranging from 9-17 years of age; Mean age: 13.6, 25% female; Mean FEV1% predicted: 88.8%</td>
<td>Pain management included behavioral intervention with effective pain relief, positive impact on QOL and anxiety. Location of abdominal pain: epigastric = 5, right = 5, left = 3,</td>
</tr>
<tr>
<td>Palermo</td>
<td>2006</td>
<td>To describe the effect of recurrent pain on HRQOL of children and adolescents with CF.</td>
<td>Observational, Cross-Sectional Developed own survey</td>
<td>N=46 children at 3 CF care centers ranging from 8-18 years of age; Mean age: 12.9 years, 52% female; Mean FEV1: 80.2%</td>
<td>46% reported pain at least once a week. Pain was associated with worse HRQOL controlling for FEV1 (p=0.02)</td>
</tr>
<tr>
<td>Year</td>
<td>Study Title</td>
<td>Pain Management/Impact</td>
<td>Study Design</td>
<td>Study Population</td>
<td>Pain Characteristics</td>
</tr>
<tr>
<td>------</td>
<td>-------------</td>
<td>------------------------</td>
<td>--------------</td>
<td>------------------</td>
<td>----------------------</td>
</tr>
<tr>
<td>1996</td>
<td>Ravilly</td>
<td>To examine pain management in a sick CF population.</td>
<td>Retrospective chart review with multiple time points</td>
<td>N=78 patients total experiencing death between 1984-1993 (Group 1, N=55) and patients referred to the Pain Treatment Service (Group 2, N=23) at a single CF care center; Mean age: 23.5, 47.2% female; Mean FEV1% predicted Group 1; 27%; Mean FEV1% predicted Group 2; 58%; 84% of group I experienced chronic pain. Most common pain locations Group I: chest 64%, headache 53%, back pain 16%, limb pain 11%, abdominal pain 11%. Pain locations Group II: chest 65%, headache 61%, abdominal pain 39%, limb 26%, back 26%. Marked increase in chest and headache pain in last months of life compared to 3 years prior to death. Therapeutics: &gt;50% used non-pharm approaches: acupuncture, TENS, relaxation, biofeedback all prior to opiate therapy. Pain medications: NSAIDS, tricyclic antidepressants, thoracic epidural analgesia for broken ribs, and opioids. 10 used opioids for greater than 3 months up to 6 yrs.</td>
<td>High</td>
</tr>
<tr>
<td>2009</td>
<td>Sermet-Gaudelus</td>
<td>To assess the prevalence, characteristics, detection and treatment of pain; investigate relationship between pain and disease severity and impact on QOL.</td>
<td>Observational, Cross-Sectional Developed own survey</td>
<td>N=183 with 73 children and 110 adults with CF from a single CF care center; Mean child age: 10.2 years, 50% child females Mean child FEV1% predicted: 70%; Mean adult age: 28.5 years, 50% adult females; Mean adult FEV1% predicted: 50.0%; 59% children and 89% adults reported pain in the past month, no differences between groups in prevalence or recurrence rates, adults reported continuous pain vs. children reported paroxysmal pain with pain-free intervals, and children reported higher pain rates in abdomen compared to the back, head and chest in adults. No significant differences existed between disease severity and sex regarding pain. QOL was negatively affected in 56% of children and 70% of adults due to pain. Most common treatment was use of acetaminophen.</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

**Notes:**
- High: Pain may be misrepresented in the age group.
- Moderate: Possible recall bias, no validated measures, single site, parents completed surveys for children under 8 years old.
<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Objective</th>
<th>Study Design</th>
<th>Sample Size</th>
<th>Characteristics</th>
<th>Pain Assessment</th>
<th>Methodology</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stenekes</td>
<td>2009</td>
<td>To gather self-reported assessment and self-management of pain, dyspnea, and cough information.</td>
<td>Observational, Cross-Sectional</td>
<td>N=123 children and adults age ≥ 7 at four CF care centers in NE Canada; Mean age: 19.9 years, 58% female</td>
<td>84% reported pain in the past 30 days. Pain locations: head (50.4%), abdomen (49.6%), back (15.4%), limbs (12.2%), ear, nose and throat (8.1%). Most common treatment was use of acetaminophen.</td>
<td>Moderate</td>
<td>Possible selection bias (64% response rate), possible recall bias, use of non-validated measures.</td>
<td></td>
</tr>
<tr>
<td>Swender</td>
<td>2015</td>
<td>To determine benefits of osteo-manipulative treatment in individuals with CF</td>
<td>Randomized Control Trial Numerical Rating Scale</td>
<td>N=36 adults with CF at a single CF care center Mean age: 24.6, 47.2% female</td>
<td>No statistically significant difference in pain levels from baseline to end of treatment.</td>
<td>Low</td>
<td>Single site; variable length of treatment dependent on hospitalization; unequal representation of men in the sham group; did not report absolute changes in pain levels; disease severity not described</td>
<td></td>
</tr>
<tr>
<td>Uchmanowicz</td>
<td>2014</td>
<td>To identify differences in self-assessment of QOL depending on sex, age, and to compare QOL of individuals with CF with a control group of individuals without CF.</td>
<td>Observational, Cross-Sectional SF-36</td>
<td>N=60, 30 CF patients, and 30 healthy controls at a single center in Poland; Mean age: 24.83, 66.7% female</td>
<td>Statistically significant difference in the mean score of bodily pain in the CF group (score = 55.0) compared to the healthy controls (score = 73/2), (p=0.011).</td>
<td>Low</td>
<td>Disease severity of sample not described, single site, small sample size, possible recall bias, no prevalence data described</td>
<td></td>
</tr>
</tbody>
</table>
Chapter III: Preliminary Data

This chapter includes a manuscript summary and a paper that contributed directly to the foundational knowledge for the development of this dissertation study. The first study is a summary of a prospective cohort survey of adolescents with cystic fibrosis exploring pain, quality of life, and clinical outcomes over a six-month period conducted from 2012-2014 at the Johns Hopkins pediatric cystic fibrosis outpatient clinic. Contributions this author made to the study include primary research coordinator/regulatory management, data collection, supervision of volunteer and employed research assistants, and second author of the manuscript, which has been accepted for publication in the Journal of Pain and Symptom Management, publication date pending.

The second study is a survival analysis performed for the 624 Biostatistics methods course taken at the JHU School of Public Health from partial data that will be used for this dissertation. Dr. Chris Goss provided the data set from an analysis his team conducted on six minute walk testing. Contributions this author made to the paper include statistical analysis, interpretation, and authorship. It is currently undergoing internal review in preparation for submission.

Study #1

Title: The Association between Pain and Clinical Outcomes in Adolescents with Cystic Fibrosis

Authors: Noah Lechtzin, MD MHS; Sarah Allgood, BS RN; Gina Hong, MD; Kristin Riekert, PhD; Jennifer A. Haythornthwaite, PhD; Peter Mogayzel MD PhD MBA; Jessica Hankinson, PhD; Myron Yaster, MD

Summary: A prospective cohort study was completed at the Johns Hopkins Pediatric Cystic Fibrosis Specialty Clinic to describe pain in this adolescent CF population and to determine whether pain at baseline was associated with lower health related quality of life (HRQOL) and worse clinical outcomes at a six month follow up. The Brief Pain Inventory (BPI), Pain Catastrophizing Scale (PCS), Cystic Fibrosis Questionnaire-Revised (CFQ-R), and the Functional
Disability Index (FDI) were administered via Survey Monkey to those eligible (n=73, 86.9%). Baseline characteristics were collected from the electronic medical record and included age (mean=15.6±2.5), sex (female=56.2%), race (Caucasian=86.3%), genotype (F508 del homozygous = 56.2%), pancreatic status (94.6% insufficient), mean lung function as forced expiratory volume in 1 second (FEV<sub>1</sub>) total liters (2.38±0.95), mean FEV<sub>1</sub> percent predicted (79.3±26.0), presence of CF-related diabetes (CFRD) (14.9%), and use of prescribed antidepressants (5.5%). The survey was administered again at 6 months (n=53, 63.1%) and information regarding number of acute pulmonary exacerbations, number of times oral and intravenous antibiotics were prescribed for an exacerbation, and hospitalizations were extracted from the electronic medical record.

89.0% reported pain at baseline and of those, 80% reported the pain was short-lived and tended to be mild to moderate in severity. The most common location for pain was abdominal (42.0%) and the head/sinuses (31.9%). Individuals with higher baseline pain scores were at an increased risk for experiencing an acute pulmonary exacerbation requiring intravenous antibiotics during the 6-month follow up period (OR= 1.99; p=0.029) controlling for FEV<sub>1</sub>, age, and sex, as well as an increased risk for hospitalizations (OR=1.59, p=0.026). Increased pain was associated with higher scores on the FDI - a one quartile increase in average pain was associated with a 0.9 point increase in the FDI, (95% CI 0.02-1.79; p=0.045) and more time away from school – 36.4% of those who missed school were in the highest quartile of average pain scores compared to 15.7% who did not miss school (p=0.02). Results on the associations between pain scores and HRQOL are displayed in Table 2.
Table 2. Chapter 3 – Study #1: Associations between Pain Score and Health Related Quality of Life

<table>
<thead>
<tr>
<th>CFQ-R Domain</th>
<th>β Coefficient</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical Functioning</td>
<td>-4.44</td>
<td>-7.6 - -1.3</td>
<td>0.006</td>
</tr>
<tr>
<td>Emotional Functioning</td>
<td>-4.58</td>
<td>-7.6 - -1.6</td>
<td>0.003</td>
</tr>
<tr>
<td>Body Image</td>
<td>-7.69</td>
<td>-12.2 - -3.1</td>
<td>0.001</td>
</tr>
<tr>
<td>Respiratory Symptoms</td>
<td>-0.82</td>
<td>-4.4 - 2.7</td>
<td>0.646</td>
</tr>
<tr>
<td>Digestion Symptoms</td>
<td>-4.19</td>
<td>-8.2 - -0.14</td>
<td>0.043</td>
</tr>
<tr>
<td>Eating</td>
<td>-2.53</td>
<td>-6.2 - 1.17</td>
<td>0.18</td>
</tr>
<tr>
<td>Treatment Burden</td>
<td>-4.63</td>
<td>-10.2 - 0.90</td>
<td>0.098</td>
</tr>
<tr>
<td>Social Functioning</td>
<td>-2.69</td>
<td>-6.5 - 1.2</td>
<td>0.167</td>
</tr>
</tbody>
</table>

These are results from unadjusted linear regression measuring the association between composite pain score at baseline and the domains or symptom scales of the CFQ-R at 6-month follow-up.

The study concluded that pain is highly prevalent in this population. Though short-lived and not as severe as reported in the adult population, pain is associated with worse HRQOL and increased pulmonary exacerbations leading to more frequent hospitalizations and missed days of school.

Study #2

Title: Disease Severity, Symptom Burden, and Mental State as Predictors for Survival in a Cohort of Adolescents and Adults with Cystic Fibrosis

Author: Sarah J. Allgood, BSN, RN

Abstract: Importance: Objective measures of disease severity such as lung function, body mass index (BMI), and infection status are well-established predictors for survival in patients with cystic fibrosis. Little is known about how patient reported outcomes such as symptom burden and quality of life contribute to these predictions. Objective: The purpose of this study was to determine if patient reported outcomes contribute to our ability to predict survival, after controlling for measures of disease severity, in a cohort of adolescents and adults with CF.
Setting: A single outpatient specialty clinic within a large academic institution between June 2003 and March 2009. **Participants:** 75 patients age ≥ 14 years old with diagnosis of cystic fibrosis. Exclusion criteria: history of solid organ transplant, inability to complete self-report questionnaires. **Design:** Secondary analysis of a prospective cohort study. **Exposure:** Observation of cystic fibrosis disease progression over time. **Main Outcome and Measures:** The main outcome of the study was lung transplantation or death. Measures included collection of demographic information (age, sex, race, BMI), forced expiratory volume in 1 second percent predicted (FEV1%), total distance of the six minute walk test (6MWT), quality of life (QOL) measures and symptom burden. **Results:** Cox regression resulted in four individual covariates as significant predictors for survival: FEV1% (HR: 0.9, p<0.000, 95% CI: .87,.93), 6MWT (HR: .99, p<0.000, 95% CI: .996,.998), well-being domain of the SF-36 (HR: 1.11, p<0.000, 95% CI: 1.05,1.18), and symptom burden (HR: 1.03, p=0.001, 95% CI: 1.01,1.06). Multivariate analysis showed that higher FEV1% (HR: 0.90, p<0.000, 95% CI: 0.56,.94) and lower symptom burden (HR: 1.02, p=0.43, 95% CI: 1.00,1.05) were significant predictors for survival, whereas lower mental health concerns was not significant (HR: 1.04, p=0.15, 95% CI: 0.99,1.09), but analysis indicated inclusion improved the fit of the model. **Conclusion:** Inclusion of patient reported outcomes including symptom burden and mental health into routine clinical assessments, in addition to objective measures of disease severity, may provide valuable information in regards to prognosis and timing for lung transplantation in adolescents and adults with cystic fibrosis.

**Background and Significance:** Cystic Fibrosis (CF) is a life-limiting autosomal disease affecting approximately 40,000 people in the United States and 70,000 people worldwide. The disease is characterized by recurrent respiratory infections, pancreatic insufficiency, diabetes mellitus, sinus disease, and other complications such as male infertility. Twenty years ago the average life expectancy for a person with CF was 18 years old. Advancements in disease management have increased the predicted life expectancy to 38 years old and, for the first time in history, the CF population has more adults than pediatric patients. Despite these advances, patients suffer from a
heavy symptom burden including cough, dyspnea, fatigue, pain, anxiety, and depression, as well as functional limitations due to decreased lung capacity and frequent hospitalizations to treat acute pulmonary exacerbations. The most common cause of death in CF is respiratory failure.

Individuals with CF typically attend an outpatient specialty clinic quarterly to assess their disease progression and may be referred for lung transplant evaluation when forced expiratory volume in 1 second (FEV1) is approximately 30% of the predicted value or if they have multiple acute exacerbations in one year, and their symptom burden is high. Timely identification for those at increased risk for mortality is of great importance to give both the patient and the health care team adequate time for transplant consultation, transplant listing, symptom management care plans, and advanced end of life planning.

Lung function (FEV1%), body mass index (BMI) as an indicator for nutritional status, and functional capacity, measured here as the six minute walk distance, are known predictors for survival in those with CF.\textsuperscript{3,5} Patient-reported outcomes such as quality of life and symptom burden have been associated with poorer health outcomes and mortality.\textsuperscript{6,7} Little is known, however, about their role and influence with other objective measures on survival over time. The purpose of this study was to determine if patient reported outcomes contribute to our ability to predict survival, after controlling for measures of disease severity, in a cohort of adolescents and adults with CF.

**Methods:** All patients aged 14 and older attending an outpatient CF specialty clinic with a confirmed diagnosis of CF (sweat chloride testing > 60 mlEq/L or via genetic mutation identification) were eligible for inclusion. Exclusion criteria were: a history of solid organ transplantation or inability to read/speak English or complete self-reported questionnaires independently. Patients were recruited from Seattle Children’s Hospital and the University of Washington CF clinics and enrolled in the study between June 2003 and December 2006. Seattle Children’s institutional review board approved the study (IRB #11447).

This study was a prospective longitudinal cohort study designed to assess quality of life and physical functioning in adolescents and adults. Patients were followed from time of enrollment
to a censored date of March 2009 or until the outcome of interest – bilateral lung transplantation or death – occurred. This paper is to report on a secondary analysis of the existing data with the intended purpose as stated in the introduction.

**Outcome Measures:**

The St. George’s Respiratory Questionnaire (SGRQ) was developed for patients with chronic obstructive pulmonary disease and assesses symptoms in the form of cough, sputum production, wheeze, and breathlessness. It also assesses activity level and the impact on daily life. This questionnaire has been found to be valid and reliable in a number of chronic respiratory disease patient populations. A higher score on this questionnaire indicates a higher symptom burden. The questionnaire has seventy-six items, is self-administered, and takes up to ten minutes to complete.

The Medical Outcome Study Short Form 36 (SF-36) assesses functioning (physical, role, and social which is analyzed together as the physical component score) and well-being (which is analyzed together as the mental component score). It has been used widely in a number of chronic respiratory diseases and has well-demonstrated reliability and validity. Higher scores within each domain and on the total questionnaire indicates higher disabilities, thus, lower physical functioning, lower mental health, and lower quality of life. The questionnaire has twenty to thirty-six items, is self-administered, and takes up to five minutes to complete.

Demographic data including age at time of enrollment (years), sex, and race, anthropometric measures including height (cm), weight (kg), and BMI, total distance completed in the six minute walk test (6MWT), and lung function testing (FEV1%) were collected at Visit 1 (day of enrollment). Study questionnaires were also administered at this time. Participants were then followed for lung transplant and/or death, or were censored March 9th, 2009 if no outcome was observed.

All statistical analyses were performed using Stata V.13 and approved by the course instructors. Age, BMI, FEV1%, and sex were compared between those in whom the outcomes
was observed and in those who were censored. Two-tailed T-tests were performed on continuous variables and Chi-square performed on the dichotomous sex variable to assess for statistically significant differences between the two groups. Single cox regression modeling was used on each variable of interest to test for significance. Those that were significant alone were then placed into a multivariate cox regression. The Akaike information criterion test was then performed to determine the best model fit. A test of non-zero slope using a log of the survival time to account for changes in variables over time was implemented to test the proportional-hazards assumption. A $P$-value of $\leq 0.05$ was considered statistically significant.

**Results:** A total of 75 participants completed the surveys and follow-up observation period. There were no missing data. 30 participants (40.0%) had a transplant or died during the study period. Sample baseline characteristics are presented in Table 3. The physical domain of the SF-36 was found to be collinear via the variance inflation factor and was not included in the cox regression. Single cox regression hazard ratios for FEV1%, 6MWT, total symptom score, well-being domain of the SF-36, and the total score of the SF-36 are presented in Table 4.

All variables were significant predictors for survival in simple cox regression analyses, with the exception of BMI ($P=.081$) and the total SF-36 score ($P = 0.740$). These two were excluded from the multivariate model. A stepwise model selection was applied which resulted in FEV1% (HR: 0.897, SE: 0.020, 95% CI: (0.869, 0.937), $P = 0.00$), total symptom score (HR: 1.024, SE: 0.012, 95% CI: (1.001, 1.047), $P = 0.043$) and the well-being domain on the SF-36 (HR: 1.03, SE: 0.027, 95% CI: (0.986, 1.093), $P = 0.150$). Testing of the proportional hazards assumption resulted in failing to accept the hypothesis that the proportions are equal ($P = 0.033$). Application of a time interaction to the variables did not change the hazards ratio, but did allow for the assumption of proportional hazards to be met ($P = 0.128$).
Comment:

This analysis provides insight into the role of patient reported outcomes such as mental well-being and symptom burden on survival in adolescents and adults with CF. Previous studies have reported that FEV1% is a major indicator for survival \(^3\)\(^-\)\(^5\) and this analysis provides further evidence supporting FEV1% as an indicator in determining health outcomes in those with CF. BMI did not contribute significantly when analyzed alone or when included in the multivariate model. Nutritional status has long been associated with outcomes in CF and treatments designed to target weight gain and adequate vitamin levels have been recently developed to address this deficiency. It is possible that BMI may no longer play as significant role in survival as it has in the past or that this sample was too small to detect significant differences. Further longitudinal observations are needed to determine whether this is a trend, or whether this is a finding that is unique to this cohort.

Likewise, in the multivariate model, the well-being domain was no longer significant controlling for FEV1% and symptoms, but its inclusion improves the fit of the model. Mental health disorders such as anxiety and depression are evident in CF patients at rates three times those of otherwise healthy people, \(^1\)\(^1\) so its inclusion here highlights the importance of adequate mental health screening as part of routine clinical care. Future studies should include measures to assess anxiety, depression, and other mental health considerations such as hope and optimism to further explore how mental health and well-being contribute to survival.

There have been no other studies that included the impact of symptom burden on survival in this population. The role of symptoms and how they contribute to health outcomes is well studied in cancer, and the use of aggressive symptom management through palliative care specialists to address physical, psychosocial and spiritual symptoms has been shown to not only improve quality of life, but extend life as well.\(^1\(^2\)\) Research is needed to develop effective symptom management strategies tailored to the specific needs of those with CF.
This study has several limitations. The sample size is small and data collection was limited to one large academic site and limited to those over the age of fourteen. These factors may prevent the results from being generalizable to the whole CF patient population.

In conclusion, the addition of mental health well-being assessments and symptom burden into routine clinical care along with physical measures of lung function will help healthcare providers and patients reassess prognosis and aid in timely lung transplantation referrals or advanced care planning.

**Author Contributions:**

*Study concept and design:* Dr. Christopher Goss, MD, MSc, FCCP

*Acquisition of data:* Dr. Christopher Goss, MD, MSc, FCCP

*Analysis and interpretation of data:* Sarah J Allgood, BSN, RN

*Critical revision of the manuscript for important intellectual content:* Sarah J Allgood, BSN, RN

*Statistical analysis:* Sarah J Allgood, BSN, RN

*Obtained funding:* Dr. Christopher Goss, MD, MSc, FCCP

*Administrative, technical, or material support:* None

*Study supervision:* Dr. Noah Lechtzin, MD, MHS

**Conflict of Interest Disclosures:** None

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**Role of the Sponsor:** Pre-doctoral support

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Fibrosis Foundation Therapeutics, the CFF Leroy Matthew’s Physician Scientist Award and the CFF Research Development Program at the University of Washington.

Previous Presentations: None

Table 3. Chapter 3 – Study #2: Baseline Characteristics

<table>
<thead>
<tr>
<th>Baseline Characteristic</th>
<th>Median Age (years)</th>
<th>Sex (% female)</th>
<th>Median FEV1% (%)</th>
<th>Median 6MWT total distance (m)</th>
<th>Median BMI (kg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>22.73 (14.35 – 54.75)</td>
<td>50.67</td>
<td>41.0 (15.0 – 122.0)</td>
<td>1535 (392 – 2140)</td>
<td>19.70 (14.80 – 31.21)</td>
</tr>
</tbody>
</table>

Table 4. Chapter 3 – Study #2: Single cox regression on variables of interest

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio (SE)</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1%</td>
<td>0.90 (0.0168)</td>
<td>.86-.93</td>
<td>P &lt; 0.000*</td>
</tr>
<tr>
<td>6MWT</td>
<td>0.9979 (0.0005)</td>
<td>0.9970 – 0.9987</td>
<td>P &lt; 0.000*</td>
</tr>
<tr>
<td>BMI</td>
<td>0.865 (0.072)</td>
<td>0.736 – 1.02</td>
<td>P = 0.081</td>
</tr>
<tr>
<td>Total score on SGRQ</td>
<td>1.045 (0.0117)</td>
<td>1.022 – 1.068</td>
<td>P &lt; 0.000*</td>
</tr>
<tr>
<td>Well-being domain on SF-36</td>
<td>1.113 (0.316)</td>
<td>1.053 – 1.177</td>
<td>P &lt; 0.000*</td>
</tr>
<tr>
<td>Total score SF-36</td>
<td>0.991 (0.028)</td>
<td>0.0937 – 1.048</td>
<td>P = 0.740</td>
</tr>
</tbody>
</table>

* Statistically significant and included in the multivariate analysis
Chapter IV: Dissertation Methodology

This dissertation contains is a multi-method dissertation comprising of two independent studies. The quantitative study is a secondary analysis of an existing study: Quality of Life in Adults and Adolescents with Severe Cystic Fibrosis. Data from the parent study were used to identify associations with pain and the effects on mortality. The qualitative study is comprised of primary data collected at Johns Hopkins University to describe how this population experiences pain. Both study’s methodology are presented here. The quantitative study’s results are presented in Chapter 5 and the qualitative study’s results are presented in Chapter 6.

Conceptual Framework

Conceptual Model: A bio-psycho-social model of pain in individuals with cystic fibrosis, created for this dissertation, is presented below in Figure 1 and illustrates the steps undertaken to explore pain in individuals with cystic fibrosis and the need to develop pain interventions that address the functional and emotional effects of pain. The greyed out rectangles within the framework emphasize how the concepts were measured in this dissertation as well as the plans moving forward for the development of an intervention. The model incorporates some concepts from the middle range nursing theory, The Comfort Theory\textsuperscript{12}, and diagrams the influence of psychological, biological and situational factors on the development of pain, with solid lines indicating direct associations on the pain experience, and dotted lines indicating moderating contributors. The model explains the effects of functional limitations and emotional burden on how individuals seek relief from their pain. There is further need to understand the relationships that exist between pain, the CF disease process, mental health, and situational factors that contribute toward the negative effects of pain on quality of life before we can begin to develop pain interventions. There is also a need to explore the effects of pain on emotions and functionality, and how that contributes to clinical outcomes. The goal is to add to the existing literature and develop a holistic pain intervention that addresses both the functional limitations and the emotional burden of pain.
can lead to effective treatment of chronic pain and ultimately, improve clinical outcomes for individuals with CF.

Figure 2: Chapter 4. Conceptual Model of Pain in CF

**Quantitative Study: Secondary Analysis Methods**

**Parent Study Design.** The parent study was a prospective cohort study of individuals with severe CF to advance the state of the art in the measurement of health related quality of life (HRQOL) in adolescents and adults. The research was supported in part by the National Heart, Lung and Blood Institute (K23 HL72017), the National Institute of Health (RR-00037-39), the National Heart, Lung and Blood Institute Respiratory Research Training Grant (HL007287), the Cystic Fibrosis Foundation Therapeutics, the CFF Leroy Matthew’s Physician Scientist Award and the CFF Research Development Program at the University of Washington.
The study includes aims designed to identify clinical predictors of HRQOL, to compare the performance of two generic measures of HRQOL, to assess longitudinal change in HRQOL, and to assess the long term stability of HRQOL and its relationship to lung function decline.\textsuperscript{13}

Patients were recruited from Seattle Children’s Hospital and the University of Washington, CF clinics and enrolled in the study between June 2003 and December 2006. Seattle Children’s institutional review board approved the study (IRB #11447). All patients aged 14 and older attending an outpatient CF specialty clinic with a confirmed diagnosis of CF (sweat chloride testing $> 60$ mEq/L or via genetic mutation identification) were eligible for inclusion. Initial inclusion criterion also limited FEV1\% to less than 50\% predicted, but by February 2006, lung function limitations were removed in order to meet enrollment goals for the study. Exclusion criteria included inability to read/speak English or complete self-reported questionnaires independently.

Participants were administered questionnaires (described below) and underwent pulmonary function testing quarterly until either death or a censored date of March 1\textsuperscript{st}, 2009. Baseline demographics including age, sex, and BMI were also collected.

**Dissertation Study Design.** The quantitative component of this dissertation was a secondary analysis of a prospective cohort study to examine the associations with pain and to determine if pain is associated with mortality. Study variables were selected from the parent study based on relevance to what is known about the cystic fibrosis disease process and associated factors. Inclusion and exclusion criteria for this dissertation study were the same as for the parent study, with the addition of one exclusion criterion: history of solid organ transplant. The sample size for this study was 75 individuals.

**Study Aims.**

**AIM 1: To identify the physiologic, psychological, and social factors that are associated with pain**

$H_{1.1}$: Lung function is not associated with pain.
Lower Forced expiratory volume in 1-second percent predicted (FEV1%) and shorter total distance on the six-minute walk test (6MWT) will not be associated with higher reports of pain

H1.2: Respiratory symptoms are associated with pain.

Higher scores on the St. Georges Respiratory Questionnaire (SGRQ) and the Cystic Fibrosis Questionnaire-Revised (CFQ-R) Respiratory Symptom domain indicating a high respiratory symptom severity will be associated with higher reports of pain

H1.3: Physical quality of life (QOL) is related to pain

Lower scores on the Physical QOL Domain of the CFQ-R indicating lower quality of life related to physical functioning will be associated with higher reports of pain

H1.4: Mental well-being is associated with pain.

Higher scores on the Mental Component Scale of the Medical Outcomes Study Short Form 36 (SF-36) indicating lower quality of life related to mental well-being will be associated with higher reports of pain

H1.5: Socio-economic status (SES) is associated with pain

Lower socio-economic status as determined by the demographic information provided on the CFQ-R will be associated with higher reports of pain.

AIM 2: To determine the characteristics of individuals with CF that are associated with worse clinical outcomes

H2.1: Pain is associated with worse clinical outcomes

The presence of pain as indicated on the Pain Domain of the SF-36 will be associated with higher risk for mortality

H2.2: Lung function is associated with worse clinical outcomes

Lower FEV1% and shorter total distance on the 6MWT will be associated with a higher risk for mortality

H2.3: Respiratory symptoms are associated with worse clinical outcomes
Higher scores on the SGRQ and the Respiratory Symptoms Domain of the CFQ-R, indicating a high respiratory symptom severity, will be associated with higher risk for mortality.

H2.4 Worse mental well-being is associated with worse clinical outcomes.

Higher scores on the Mental Component Scale of the SF-36 indicating lower quality of life related to mental well-being will be associated with higher risk for mortality.
Table 5: Chapter 4 – Methods: Study Variables and Instruments

<table>
<thead>
<tr>
<th>Variable</th>
<th>Instrument</th>
<th>Description</th>
<th>Type of Variable</th>
<th>Cronbach’s α</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td>Age at enrollment in years</td>
<td>Continuous</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td>Male/Female</td>
<td>Dichotomous</td>
<td></td>
</tr>
<tr>
<td>FEV1%</td>
<td>Lung function testing (%)</td>
<td>Forced expiratory volume in 1 second percent predicted</td>
<td>Continuous</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>Body Mass Index (kg/m²)</td>
<td>Indicator of nutritional status</td>
<td>Continuous</td>
<td></td>
</tr>
<tr>
<td>Bodily pain</td>
<td>Medical Outcomes Study Short Form 36</td>
<td>Amount of pain and level of interference on life in the past 4 weeks</td>
<td>Dichotomous</td>
<td></td>
</tr>
<tr>
<td>Respiratory Symptoms</td>
<td>St. George’s Respiratory Symptom Questionnaire</td>
<td>Assesses respiratory symptoms and level of interference with 1, 3, and 12 month recall</td>
<td>Continuous</td>
<td>0.88-0.90</td>
</tr>
<tr>
<td></td>
<td>CFQ-R Respiratory Symptom Domain</td>
<td>Assesses respiratory symptoms within the past two weeks</td>
<td>Continuous</td>
<td>0.84</td>
</tr>
<tr>
<td>Physical Quality of Life</td>
<td>Cystic Fibrosis Questionnaire – Revised</td>
<td>Assesses impact of CF on patient reported physical functioning</td>
<td>Continuous</td>
<td>0.94</td>
</tr>
<tr>
<td>Mental Component Scale</td>
<td>Medical Outcomes Study Short Form 36</td>
<td>Assesses emotional well-being</td>
<td>Continuous</td>
<td>0.90</td>
</tr>
<tr>
<td>Depression</td>
<td>Center for Epidemiological Studies Depression (CESD)</td>
<td>A screening test for depression and depressive disorder</td>
<td>Continuous</td>
<td>0.90</td>
</tr>
<tr>
<td>Socio-Economic Status (SES)</td>
<td>Cystic Fibrosis Questionnaire – Revised</td>
<td>Highest degree earned</td>
<td>Categorical</td>
<td></td>
</tr>
</tbody>
</table>

**Age.** CF is a life-limiting disease with a slow decline over time coupled with acute events that contribute to worsening health outcomes. Controlling for age to determine independent associations of other variables is essential, as is determining differences in symptoms and outcomes across the lifespan.
Sex. Females with CF have a 2.7 year less average life expectancy compared to males and experience increased acute pulmonary events and more co-morbidities than males.\textsuperscript{14} Differences in pain and symptoms between sexes will be explored.

**FEV1%**. Forced Expiratory Volume in 1 second percent predicted is a component of lung function routinely measured in individuals with CF. The percent is based on the volume of air in liters that is expelled within one second and then applied to an algorithm to determine how much lung function an individual has compared to a healthy person of the same age, race, and height.\textsuperscript{15} Individuals with an FEV1% of less than 40% are considered to be in the severe stages of CF. FEV1% is perhaps the most common endpoint for randomized controlled trials investigating the effectiveness of drugs or other interventions on CF, is a known indicator for prognosis,\textsuperscript{16} and is used clinically to identify acute pulmonary exacerbations and treatment effectiveness.

**BMI**. Body mass index is a measure of tissue mass that quantifies nutritional status of an individual as underweight, normal weight, overweight, or obese. It is routinely tracked in individuals with CF during quarterly clinic visits and is considered a proxy for nutritional status. Low BMI is associated with worse clinical outcomes and is a component of the Liou 5-year survival model used clinically to predict readiness for lung transplantation.\textsuperscript{16}

**Medical Outcomes Study Short Form 36**.\textsuperscript{17} The Medical Outcome Study Short Form 36 (SF-36) assesses functioning (physical, pain, role, and social which is analyzed together as the physical component score) and well-being (which is analyzed together as the mental component score). The individual domains can also be assessed individually. The bodily pain domain consists of two questions, item 21 and 22 on the questionnaire, with a Likert response scale:
21. How much bodily pain have you had during the past 4 weeks?

(Circle One Number)

None 1
Very Mild 2
Mild 3
Moderate 4
Severe 5
Very Severe 6

22. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

(Circle One Number)

Not at all 1
A little bit 2
Moderately 3
Quite a bit 4
Extremely 5

Scoring includes recoding the Likert-scale response to a number out of 100 and averaging the two scores with lower scores indicating higher pain severity:

Table 6. Chapter 4 – Methods: Pain items scores

<table>
<thead>
<tr>
<th>Item Number</th>
<th>Original Response Category</th>
<th>Change to Recorded Value of:</th>
</tr>
</thead>
<tbody>
<tr>
<td>21</td>
<td>1</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>22</td>
<td>1</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>75</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>0</td>
</tr>
</tbody>
</table>

The mental component scale consists of five Likert-response questions and is scores similar to the pain domain. The SF-36 has been used widely in a number of chronic respiratory diseases and has well-demonstrated reliability and validity. Lower scores within each domain and on the total
questionnaire indicate worse states of health and lower quality of life. The questionnaire has twenty to thirty-six items, is self-administered, and takes up to five minutes to complete.

**St. George’s Respiratory Questionnaire.** The St. George’s Respiratory Questionnaire (SGRQ) was developed for patients with COPD and assesses symptoms in the form of cough, sputum production, wheeze, and breathlessness. It also assesses activity level and the impact on daily life. This questionnaire has been found to be valid and reliable in a number of obstructive respiratory disease patient populations. A higher score on this questionnaire indicates a higher symptom burden. The questionnaire has seventy-six items, is self-administered, and takes up to ten minutes to complete.

**Cystic Fibrosis Questionnaire – Revised.** The Cystic Fibrosis Questionnaire (CFQ-R) is a disease-specific self-report questionnaire designed specifically for individuals with cystic fibrosis. Versions of the questionnaire exist for ages six through adulthood. It contains nine domains of quality of life: physical, role/school, vitality, emotion, social, body image, eating, treatment burden, and health perceptions. It also includes three symptom scales: weight, respiratory, and digestion. Each domain/symptom scale can be scored individually, or all can be combined to assess for total QOL. The respiratory symptom domain is commonly used as an endpoint in randomized controlled trials in individuals with CF. A higher score on the questionnaire indicates a higher overall quality of life. The questionnaire is self-administered for those age fourteen and up, it has 50 items and takes up to fifteen minutes to complete.

**CESD.** The CESD is a screening tool for depression and depressive disorders that has been in use both clinically and in research since 1977. It is used in the National Health and Nutrition Examination surveys for assessment of depression epidemiology in the United States is within the public domain. It is a 20 item test that can be administered in person, over the phone, or can be self-administered. Higher scores on the CESD indicate a higher risk for depression.

**SES.** Socio-economic status has been linked to worse outcomes and an increased risk for mortality in individuals with CF. Level of education attained has been used in previous studies as an
indicator for SES in CF along with other indicators such as type of insurance. The sample for this dissertation contained individuals who are too young to have obtained a degree, and parent information was not provided. Logistic regression using the highest level of schooling attained as a proxy for socioeconomic status did not provide any significant associations with pain. 28% of this sample had not attained a high school diploma at the time of enrollment. Likewise, 24% were under the age of 19 years old at the time of enrollment. Given the high prevalence of school-age patients in this sample, it is impossible to draw any conclusions about the association of pain and SES. A different indicator for SES is needed to further explore this relationship.

The CFQ-R is arguably the most commonly used measure of self-reported outcomes in CF research and its strength lies in that it was developed specifically for assessment of HRQOL issues related to cystic fibrosis. The SF-36, though not disease specific, has been used in multiple CF studies prior to the development of the CFQ-R, and was the comparison questionnaire for validity testing of the CFQ-R.\textsuperscript{19} The CFQ-R does not contain a pain domain, making the SF-36 questionnaire a more appropriate tool for this dissertation’s purpose. The SGRQ is also a more general pulmonary symptom instrument that has been used for several years in pulmonary and cardiac research. Use of this measure in this dissertation in conjunction with the respiratory domain of the CFQ-R will eliminate a possible mono-method bias and strengthen the analysis.

**Data Collection Procedures.** No additional data were collected for this study. All data was obtained from the parent study’s Principle Investigator and has been de-identified. This study does not meet the requirements for human subjects research, and submission to the Johns Hopkins Medicine IRB is not required (per Johns Hopkins Medicine IRB – see Appendix A). This dissertation author has been added to the Seattle Children’s active IRB application.

**Data Analysis Plan**

**Descriptive and Exploratory Statistics.** Baseline demographic data and measurement scores were used for the analysis of the aims and hypotheses. Continuous variables were summarized using
mean and standard deviations (SD) and medians with interquartile ranges (IQR). Categorical variables were summarized using frequencies and percentages. Demographics of the sample are presented including mean age, % female, mean BMI and mean FEV1%.

**AIM 1: Identify the physiologic, psychological, and social factors that are associated with pain**

The pain domain of the SF-36 has been used by several studies in CF exploring associations with clinical outcomes and survival predictors.\(^8,22\) Exploratory analysis showed considerable skewness in this domain that was not able to be normalized with log transformations. For this reason, pain was dichotomized to those who experienced pain equal to or less than that of the general population\(^{23}\) (a score of ≥75/100 on the pain domain of the SF-36) and those who experienced pain greater than that of the general population (a score of <75/100 on the pain domain of the SF-36).

Pearson’s correlation coefficient and Spearman rank correlation coefficient testing was performed on all variables as applicable. Univariate logistic regression was performed on each variable. Variables with a p-value of ≤0.10 were included in a multivariate logistic regression model with the exception of the working/attending school status variable. Those variables with a moderate to strong correlation coefficient (>4.0) were not included in the same multivariate model. A p-value of ≤0.05 was considered significant. Odds ratios are presented with 95% CIs. Statistical analyses were performed with Stata statistical software, release 13 (StataCorp; College Station, Texas).

**AIM 2: To determine how pain and respiratory symptoms contribute to predictions for survival**

Univariate cox regression was performed on each variable. Variables with a p-value of ≤0.10 were included in a multivariate cox regression model with the exception of the working/attending school status variable. Those variables with a moderate to strong correlation coefficient (>4.0) were not included in the same multivariate model. A p-value of ≤0.05 was
considered significant. Hazards ratios are presented with 95% CIs. Statistical analyses were performed with Stata statistical software, release 13 (StataCorp; College Station, Texas).

Qualitative Study Methods

Study Design. An exploratory descriptive design was used to gain first-hand knowledge of individual experiences with pain.

Study Aim:

AIM 3: To explore and describe ways adolescents and adults with CF experience pain.

The goal of this study was to explore how adolescents and adults with self-reported moderate to severe pain perceive their pain, its effects on their social, physical, emotional, and work lives, and how their healthcare team addresses pain.

Recruitment and Sampling. Study participants were recruited from the Johns Hopkins Hospital CF Center pediatric and adult outpatient specialty clinics. The center is composed of a pediatric clinic and an adult clinic that sees approximately 550 CF patients per year. Eligible participants were identified through a positive response to the presence of moderate to severe pain occurring at least once a week for a period of at least once a month on the Brief Pain Inventory during previous participation in a self-reported pain survey.

A purposive sample of 10 participants were enrolled into the study. Other inclusion criteria were that the participants had a diagnosis of CF and could understand English in order to provide informed consent. Participants who had undergone a solid organ transplant were excluded from the study to explicitly explore pre-transplant pain experiences. All participants who were invited agreed to participate; however, one participant was withdrawn as the person underwent a lung transplant between the time of enrollment and the scheduled interview. Sample characteristics are summarized in Table 1. A wide range of ages, stages of disease severity, and co-morbidities were represented by the sample and females comprised 50% of the participants.

The Johns Hopkins Medicine Institutional Review Board (IRB00033661/NA_00027981) approved the study. A written informed consent was obtained from adult participants, and written
parental consent with adolescent assent was obtained from adolescent participants per the institution’s IRB requirements. Informed consent was obtained at outpatient clinic visits and individual in-depth telephone or face-to-face interviews were scheduled for each participant depending on participant availability and clinic space. Demographic data and participant characteristics were collected from electronic medical records.

Data Collection. A semi-structured interview guide was developed by the study team through formative exploration of the available literature, clinical experiences, and informal discussions with providers and patients. The characterization of pain, the effect of pain on quality of life, productivity, and relationships, were identified as gaps in the current CF literature that could be addressed by this study. Additionally, patients and CF nurses expressed the need to explore how pain is assessed, addressed, and treated by CF healthcare providers. Both the adolescents and adults received the same questions with school life being inserted in place of work life where applicable. The domains and questions are displayed in Table 1.

Audio-recorded telephone or face-to-face interviews were conducted by two different interviewers relative to their adolescent and adult group specific experience. Data collection occurred over an eight month period. Each audio-recorded interview was transcribed verbatim, crosschecked for accuracy, and then transcripts were de-identified prior to analysis. Participants received a parking voucher as a reimbursement for their participation.

Data Analysis. The collected data were analyzed via a conventional content analysis and managed using the NVivo qualitative research software package, Version 10.2.1. Transcripts were first read independently by each team member several times to allow for general impressions of the content to develop into categories and preliminary codes. The team then met to discuss the independently coded content. Discrepancies were reconciled through team consensus for each emergent code. Previously coded transcripts were compared to each newly coded transcript to ensure consistency in code assessment. Peer review of the analysis was performed by CF clinical and research experts at conclusion to ensure trustworthiness.
Chapter V: Quantitative Study Results

It is the author’s intent to submit this paper the Journal of Cystic Fibrosis. There is no required format for submission other than consistency with the citations. The word limit for original research is 3000, 150 word limit for the abstract and the citations cannot exceed 30.

ASSOCIATIONS WITH PAIN AND ITS IMPACT ON OUTCOMES IN INDIVIDUALS WITH MODERATE TO SEVERE CYSTIC FIBROSIS

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Figures: 0 Tables: 3 Word Count: Body: 2894 Abstract: 150
Conflict of Interest: No conflicts of interest exist for any of the authors
Abstract

**Background:** The purpose of this cohort study was to explore the relationship between pain, quality of life (QOL), and depression in individuals with moderate to severe cystic fibrosis (CF).

**Methods:** n=75; Logistic regression was used to assess pain and associations with baseline data and cox regression was used to evaluate the impact of pain and other variables on risk of mortality.

**Results:** Pain was associated with physical function (OR: 0.97; p=0.002; 95% CI: [0.95-0.99]), mental well-being (OR: 0.94; p=0.015; 95% CI: [0.90-0.99] depression (OR: 1.10; p=0.003; 95% CI: [1.03-1.17], and respiratory symptoms (OR: 0.98; p=0.045, 95% CI: [0.96-1.00]). Pain was associated with an increased risk of mortality (HR: 5.83; p=0.001; 95% CI: [1.82, 18.67]). Women with pain are at a higher risk of mortality (HR: 5.35; p<0.000; 95% CI: [2.59-11.10]).

**Conclusion:** Pain was associated with worse QOL, depression, and overall mental well-being, as well as contributing to risk of mortality.
1. Background

Cystic fibrosis (CF), an autosomal recessive disease caused by a mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, is a life-limiting disease affecting approximately 70,000 people worldwide (1). This multi-system disease is primarily characterized by thick respiratory secretions causing chronic lung infections, but can also cause pancreatic insufficiency, sinus disease, liver disease, CF-related diabetes, osteoporosis, and infertility in males (2). Therapeutic advances have increased the life expectancy of this once terminal childhood disease to approximately 41 years (1), but despite these new treatments, individuals with cystic fibrosis experience a multitude of symptoms such as cough, fatigue, and dyspnea that negatively impact quality of life (QOL) and health outcomes (3,4).

Though not typically considered a painful disease, studies indicate the prevalence of pain in those with CF is as high as 94% in adults (5-7) and 89% in children (6-8). Additionally, chronic pain is estimated to occur at rates more than double that of the general population (9, 10). These studies have shown an association between pain and depression, reduced QOL, an increased risk of pulmonary exacerbations requiring hospitalizations, and an increased risk of mortality (6,7). These associations occur independent of age and forced expiratory volume in 1 second percent predicted (FEV1%), a value resulting from spirometry lung function testing routinely used to measure lung health. There are still considerable gaps in the literature, especially surrounding pain in those with moderate to severe lung function. The purpose of this cohort study was to explore the relationship between pain, sex, functional status, respiratory symptoms, and mental health status in a cohort of individuals with moderate to severe CF lung disease.

2. Methods

2.1 Sample

This study was a prospective longitudinal cohort study designed to assess quality of life and physical functioning in adolescents and adults with moderate to severe lung disease as a result of CF. Patients were recruited from Seattle Children’s Hospital and the University of Washington,
Seattle CF clinics and enrolled in the study between June 2003 and December 2006. Seattle Children’s institutional review board approved the study (IRB #11447). All patients >14 years of age attending an outpatient CF specialty clinic with a confirmed diagnosis of CF (sweat chloride testing > 60 mlEq/L or via genetic mutation identification) were eligible for inclusion. Initial inclusion criterion also limited FEV1% predicted to < 50% predicted, but by February, 2006, lung function limitations were removed in order to meet enrollment goals for the study. Exclusion criteria included inability to read/speak English and/or complete self-reported questionnaires independently and history of solid organ transplant. Patients were followed from enrollment until the outcome of interest occurred - bilateral lung transplantation or death – or the censored date of March 2009.

2.2 Data Collection

Baseline data including age, sex, current work/school status, FEV1% predicted, and BMI, were collected at the time of enrollment. A comprehensive questionnaire consisting of the Medical Outcomes Scale Short Form (SF-36) (11), the CF Questionnaire-Revised (CFQ-R) (12), the St. George’s Respiratory Questionnaire (SGRQ) (13), and the Center for Epidemiologic Studies Depression Scale-Revised (CESD-R) (14) was administered.

The SF-36 assesses QOL in domains including physical functioning, pain, and well-being. It has been widely used in a number of chronic respiratory diseases and has well-demonstrated reliability and validity (11). Lower scores within each domain and on the total questionnaire indicates higher disabilities. SF-36 includes 20-36 items, is self-administered, and takes up to five minutes to complete. We report the mental component summary score in the analysis as it is a global self-report assessment of general mental well-being. The SF-36 pain domain has been used by several studies in CF exploring associations with clinical outcomes and survival predictors (15, 16). Exploratory analysis showed considerable skewness in this domain that was not able to be normalized with log transformations. For this reason, pain was dichotomized to those who experienced pain equal to or less than that of the general population (17) (a score of ≥75/100 on
the SF-36 pain domain) and those who experienced pain greater than that of the general population (a score of <75/100 on the SF-36 pain domain).

The CFQ-R is a disease-specific self-report QOL questionnaire designed specifically for individuals with cystic fibrosis (12). Age-appropriate versions of the questionnaire exist for patients >6 years of age. It assesses various quality of life indicators such as role functioning, physical functioning, and treatment burden. A higher score on the questionnaire indicates a higher overall quality of life. The questionnaire is self-administered in those >14 years of age, has 50 items and takes up to 10 minutes to complete. The respiratory symptom domain was included as it is a widely used outcome measure for CF clinical trials and it, along with the physical function domain, was designed specifically to assess individuals with CF.

The SGRQ was developed for patients with COPD to assess multiple domains of health status including symptoms, disease activity, and disability (13). This questionnaire has been found to be valid and reliable in a multitude of chronic respiratory disease patient populations (13). A higher score on this questionnaire indicates a higher respiratory disease burden. The questionnaire has 76 items, is self-administered, and takes up to ten minutes to complete. The symptom score was included in this analysis to further explore the relationship between pain and symptoms.

The CESD is a screening test for depression and depressive disorder (14). The CESD measures symptoms defined by the American Psychiatric Association' Diagnostic and Statistical Manual (DSM-V) for a major depressive episode (14). The scale assesses possible symptoms of depression over the previous 2 weeks, which mirrors the recall time of the SF-36. The total score of this instrument was used in the analysis. This measure was included to further explore the relationship between pain and depression in a cohort with more severe CF disease compared to cohorts represented in the existing literature.

2.3 Data Analysis

Descriptive statistics were used to summarize demographic data and are presented as mean +standard deviation (SD) or median with interquartile (IQR) range. Pearson’s correlation
coefficient and Spearman rank correlation coefficient testing was performed on all variables as applicable. Univariate logistic regression and cox regression modeling was performed on each variable. Variables with a p-value of ≤0.10 were included in a multivariate logistic regression model and a cox regression model with the exception of the working/attending school status variable. Those variables with a moderate to strong correlation coefficient (>4.0) were not included in the same multivariate model. A p-value of ≤0.05 was considered significant. Hazard ratios and ORs are presented with 95% CIs. Statistical analyses were performed with Stata statistical software, release 13 (StataCorp; College Station, Texas).

3. Results

3.1 Baseline Characteristics

The study sample included 75 participants. Baseline demographic characteristics are shown in Table 1. The median age of patients in this study was 23.8 years, with a range of 14.6 to 54.8 years. A total of 53.3% (n=40) reported pain levels over the past 2 weeks greater than that of the general population with 50.0% of those being female (n=20). The median FEV1% predicted for this study was 41.0% predicted with a mean of 47.34% predicted + a standard deviation (SD) of 23.8% predicted. We were unable to find any associations between baseline characteristics and pain in the univariate analysis with the exception of work status. Those who were not working or attending school due to their health status had more than 4.5 times higher odds for having pain than those who worked or attended school (OR: 4.57; p=0.016; 95% CI: [1.33, 15.73]). (Table 2)

3.2 Mental Health, Function and Symptoms

There was a significant association between all of the self-report questionnaire domains and pain with the exception of the SGRQ symptom scale (OR: 1.01; p= 0.119; 95% CI: [0.996-1.04]) (Table 2). For every 1 point increase in the mental component summary score (better mental wellbeing), the odds of having pain decreased by 6% (OR: 0.94; p=0.015; 95% CI: [0.90-0.99]). This association remained significant when controlling for physical function (OR: 0.94; p=0.025; CI: [0.90-0.99]). Similarly, decreased depression scores on the CESD were associated with
increased odds for pain (OR: 1.10; p=0.003; 95% CI: [1.03-1.17]), and remained significant when controlling for physical function (OR: 1.08; p=0.015; 95% CI: [1.01-1.16]). The odds of having pain decreased by 3% for every 1 point increase in physical function (OR: 0.97; p=0.002; 95% CI: [0.95-0.99]) and remained significant when controlling for depression (OR: 0.98; p=0.027; 95% CI: [0.95-0.99]) and overall mental well-being (OR: 0.98; p=0.004; 95% CI: [0.95-0.99]). The respiratory domain of the CFQ-R was associated with pain in the univariate analysis (OR: 0.98; p=0.045; 95% CI: ([0.96-1.00]), but was no longer significant when controlling for depression, physical function, or mental well-being.

3.3 Outcomes

Total analysis time was 76711 days (mean: 1022; SD±540 days), and 40% (n=30) experienced the outcome of death or transplant. Significant predictors of survival in the univariate analyses included the SF-36 pain domain (HR: 6.05; p=0.001; 95% CI: [2.10-17.47]), and the CFQ-R physical function domain (HR: 0.985; p=0.021; 95% CI: [0.97, 0.998]). Other variables included in the multivariate analysis were sex (HR: 2.00; p=0.064; 95% CI: [0.96, 4.16]) and the SF-36 MCS (HR: 0.973; p=0.098; 95% CI: [0.94, 1.01]). In the multivariate model, the pain domain was the only variable independently associated with an increased risk of mortality (HR: 5.83; p=0.001; 95% CI: [1.82, 18.67]). Sex approached significance for an increased risk of mortality in females when controlling for pain, physical function, and MCS (HR: 2.17; p=0.053, 95% CI: [0.99, 4.78]). Further exploration into the role of pain and sex revealed that females in pain have more than 5 times a greater risk of meeting the outcome of death or transplant compared to males with or without pain and females without pain (HR: 5.35; p<0.000; 95% CI: [2.59-11.10]).

4. Conclusions

This study is consistent with previous findings demonstrating pain is associated with depression, physical function, mental well-being, and is significantly associated with worse health outcomes in individuals with CF.
The cohort in this study displayed a median lung function of FEV1 41% predicted and mean of FEV1 47.34% predicted which meets the criterion for severe lung disease (18). There are no published guidelines for when to refer a patient for a bilateral lung transplant, but objective measures such as lung function, the number of hospitalizations for pulmonary exacerbations, and infection status have long been used as suggestive indicators for when the conversation regarding transplant and subsequent referral for transplant should begin. A recent study by Sole et al. used the CFQ-R along with measures including resting heart rate and FEV1% predicted to determine a predictive model for mortality (19). They found that the best predictive model included FEV1% predicted and the physical function domain of the CFQ-R. Pain was not measured in the study. We did not include FEV1% predicted in the multivariate regressions in this study as there was no association between lung function and pain in the univariate logistic regression and no significant hazard ratio for FEV1% predicted being predictive of survival in the univariate cox regression. Additionally, there was a moderate to high correlation between the physical function domain of the CFQ-R and FEV1% predicted (Spearman’s Rho = 0.65, p<0.000) within our data. Our findings do support the findings of a study by Abbot et al. that used the SF-36 to assess predictors of survival. Their study found that pain and the physical function domain had the strongest statistical associations with survival; however our study showed physical function becomes less significant when controlling for pain and sex. The sample size in our study was less than half that of the Sole study (n=152) and much less than the Abbott study (n=223), another study looking at predictors of mortality using the SF-36 (15), but both studies had cohorts with lung function indicating moderate lung disease (Sole et al. median FEV1% predicted: 56.3%, mean: 60.7%; Abbott et al. mean: 55%). It is possible that the effect of lung function diminishes in sicker populations. These studies suggest that patient-reported measures including pain and physical function status should be considered in addition to objective clinical measures when determining the timing of transplant referral.
Mental health disorders such as anxiety and depression occur in CF patients at rates 3 times compared to otherwise healthy people (20). Recent guidelines established by the Cystic Fibrosis Foundation have recommended annual mental health screening for all patients with CF and their caregivers (20). Pain is a complex and highly subjective experience that is known to affect multiple psychosocial aspects of life as well as physical function and activities of daily living. Unpublished qualitative data from this study team have found that individuals with chronic pain and CF consider the emotional pain from having CF to be as debilitating as the toll of their physical pains. Untangling the relationships between emotional and physical pain goes far beyond the ability of this study, but our findings do highlight the association between mental health well-being, depression and pain, suggesting that mental health and pain should be assessed in tandem. The SF-36 pain domain is general in its assessment of pain but still seems to be quite sensitive in determining the effects of pain on quality of life in those with CF. The addition of 2 or 3 general pain questions into the annual mental health assessment could at least identify those individuals at a greater risk for worse mental health outcomes due to their pain status or vice versa.

The literature supports our findings that women are at an increased risk of mortality when compared to men. Multiple studies focusing on survival in individuals with CF have found evidence of this “Gender gap” using patient registry data from across the globe. (21) In 2014, a study compiling the U.S. CF patient registry data from 1995 to 2007 concluded that the average life expectancy for men was 38.7 years compared to 36.0 years controlling for key CF-related co-morbidities. No one factor has been found to be responsible for this difference in outcomes, but studies suggest estrogen, specifically estrogen 17β-estradiol (E2) as a potential candidate (21). The field of pain research recognizes that there are several ways in which men and women differ in their pain experiences. Men and women perceive pain differently, have different coping strategies, and women are more likely than men to experience physical disability from the same pain condition, especially in chronic pain conditions (22). Our study demonstrates that women with pain have a much higher risk of mortality compared to both women without pain and men in either
pain category. More research is needed to determine both the physiological factors as well as behavioral and social factors that contribute to this CF gender gap.

Despite the existing literature that highlights the high prevalence of pain and its impact on clinical outcomes, there have been no large-scale clinical trials on pain interventions targeting CF patients, and there are no established clinical guidelines on how pain should be assessed and approached. It is possible that both the patient and CF care providers do not consider pain to be a symptom that needs to be addressed in CF specialized clinics. Research needs to be conducted exploring the CF care providers’ knowledge of pain in those with CF, their own attitudes surrounding pain, and their comfort in pain assessment and treatment. Additionally, further research into the interplay of pain, emotional stress, coping, and the additive burden of functional limitations is needed to help guide pain interventions that will address the complexity involved in successful pain treatments. This will help contribute to the development of patient education and clinical guidelines to address and treat pain with the goal of optimizing health outcomes for those with CF.

There are several limitations in this study. The sample size, though well represented within the CF community, is small. It is possible that a larger representative sample of patients with more severe CF lung disease would provide stronger evidence of the relationships we sought to examine. Also, we did not include co-morbidities such as diabetes as variables in this study. A 2015 study by Hayes et al found that the presence of diabetes mellitus significantly increased the risk for death in patients with CF on the transplant wait list (23). Finally, we did not include infection status in this study. Chronic infections with Pseudomonas aeruginosa and Burkholderia cepacia are known contributors to worse clinical outcomes in patients with CF (24).

Despite the existing literature that highlights the high prevalence of pain and its impact on clinical outcomes, there have been no large-scale clinical trials on pain interventions targeting CF patients, and there are no established clinical guidelines on how pain should be assessed and approached. It is possible that both the patient and CF care providers do not consider pain to be a
symptom that needs to be addressed in the CF specialty clinic. Research needs to be conducted exploring the CF care providers’ knowledge of pain in those with CF, their own attitudes surrounding pain, and their comfort in pain assessment and treatment. Additionally, further research into the interplay of pain, emotional stress, coping, and the additive burden of functional limitations is needed to help guide pain interventions that will address the complexity involved in successful pain treatments. This will help contribute to the development of patient education and clinical guidelines for addressing pain clinically with the goal of optimizing health outcomes for those with CF.
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (n=75)</th>
<th>Pain ≤ General Population (n=35)</th>
<th>Pain &gt; General Population (n=40)</th>
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<tr>
<td>Age, median (IQR), y</td>
<td>23.8 (19.9-30.3)</td>
<td>23.6 (18.5-28.7)</td>
<td>23.8 (21.1-36.2)</td>
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<tr>
<td>Sex (Female)</td>
<td>48.0%</td>
<td>45.7%</td>
<td>50.0%</td>
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<tr>
<td>BMI, median (IQR)</td>
<td>19.5 (18.1-21.5)</td>
<td>20.2 (18.4-21.8)</td>
<td>19.1 (18.1-21.0)</td>
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<td>FEV1 % (IQR)</td>
<td>41.0 (30.0-60.0)</td>
<td>42.0 (30.0-65.0)</td>
<td>38.0 (30.0-56.0)</td>
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<td>Current work status:</td>
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<td>Working/attending school</td>
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<td>85.7%</td>
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<td>24.0%</td>
<td>11.4%</td>
<td>35.0%</td>
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<tr>
<td>Not working for other reasons</td>
<td>5.3%</td>
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Table 8: Chapter 5: Univariate Logistic Regression

<table>
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<th>Variable</th>
<th>Odds Ratio [95% CI]</th>
<th>P-value</th>
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<tbody>
<tr>
<td>Age</td>
<td>1.05 [0.99-1.11]</td>
<td>0.113</td>
</tr>
<tr>
<td>Sex</td>
<td>1.19 [0.48-2.95]</td>
<td>0.711</td>
</tr>
<tr>
<td>BMI</td>
<td>0.97 [0.81-1.17]</td>
<td>0.776</td>
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<tr>
<td>FEV₁, %</td>
<td>1.00 [0.98-1.01]</td>
<td>0.642</td>
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<tr>
<td>No work/school due to health</td>
<td>4.56 [1.33-15.73]</td>
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</tr>
<tr>
<td>CESD Total Score</td>
<td>1.10 [1.03-1.17]</td>
<td>0.003*</td>
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<tr>
<td>SF-36 Mental Component Summary</td>
<td>0.94 [0.90-0.99]</td>
<td>0.015*</td>
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<tr>
<td>CFQ-R Physical Function Domain</td>
<td>0.97 [0.95-0.99]</td>
<td>0.002*</td>
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<tr>
<td>CFQ-R Respiratory Symptom Domain</td>
<td>0.98 [0.96-1.00]</td>
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<td>SGRQ Symptom Domain</td>
<td>1.01 [1.00-1.04]</td>
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Table 9: Chapter 5: Cox Regression

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<th>Variable</th>
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<th>P-value</th>
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<td>Sex (female)</td>
<td>2.00 (0.96-4.16)</td>
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<td>FEV1% Predicted</td>
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<tr>
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<tr>
<td>CESD Total Score</td>
<td>1.03 (0.99-1.06)</td>
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<tr>
<td>SF-36 MCS</td>
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<td>0.098*</td>
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<td>SF-36 Pain Domain</td>
<td>6.05 (2.10-17.47)</td>
<td>0.001**</td>
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<tr>
<td>CFQ-R Physical Function</td>
<td>0.99 (0.97-0.998)</td>
<td>0.021**</td>
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<td>CFQ-R Respiratory</td>
<td>1.00 (0.983-1.011)</td>
<td>0.667</td>
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<tr>
<td>SGRQ Symptoms</td>
<td>1.01 (0.99-1.02)</td>
<td>0.261</td>
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<td><strong>Multivariate model:</strong></td>
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<tr>
<td>Pain</td>
<td>5.83 (1.82-18.67)</td>
<td>0.003**</td>
</tr>
<tr>
<td>Sex</td>
<td>2.18 (0.99-4.78)</td>
<td>0.053</td>
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<tr>
<td>CFQ-R Physical</td>
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<tr>
<td>SF-36 MCS</td>
<td>1.00 (0.97-1.03)</td>
<td>0.970</td>
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</table>
Chapter VI: Qualitative Study Results

It is the author’s intent to submit this paper the Journal of Pain and Symptom Management. There is no required format for submission other than consistency with the citations. The word limit for original research is 3500 and a 250 word limit for the abstract.

DESCRIPTIONS OF THE PAIN EXPERIENCE IN ADULTS AND ADOLESCENTS WITH CYSTIC FIBROSIS

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Figures: 0   Tables: 2   Word Count: Body: 3361   Abstract: 247

Conflict of Interest: No conflicts exist for any of the authors
Abstract:

Context: People living with cystic fibrosis (CF) experience pain that is associated with decreased quality of life (QOL), poorer health outcomes, and increased mortality. It is one of the most prevalent symptoms associated with CF, however, it is currently unknown how persons describe their pain experiences or the ways those experiences impact their lives.

Objectives: To explore and describe ways adolescents and adults with CF experience pain.

Methods: Used an exploratory descriptive design to perform semi-structured interviews with 10 CF individuals, exploring their pain experiences within 5 domains: Pain Characteristics, Activities, Relationships, Work/School Life, and Healthcare Team. Transcribed interviews underwent a content analysis with team-based constant comparisons.

Results: Individuals with CF identify CF as being a painful disease, express how pain negatively affects all aspects of their lives, including loss of functionality and productivity, and are able to disclose their pain to those with whom they have relationships. Adolescents feel an emotional toll from the loss of socialization due to pain and feel their healthcare team adequately supports their pain. Adults express that emotional pain due to CF is as damaging as physical pain and feel stigmatized and unsupported by their healthcare team when asking for pain management solutions.

Conclusion: There are differences in how pain is perceived by adolescents and adults with CF that have otherwise not been demonstrated in the current literature. Further explorations of pain across the lifespan and with CF healthcare providers are needed to guide the development of effective pain management interventions for those with CF.

Key words: cystic fibrosis, pain, content analysis, exploratory descriptive, qualitative
Introduction

Pain is a complex, multi-dimensional process that negatively affects physical and mental functioning, clinical outcomes, quality of life, and productivity. (1) The prevalence of pain in the general population is widespread and can be accounted for up to 80% of all general practitioner visits. (2) The effective treatment of chronic pain - defined as persistent unpleasant sensory and emotional experience lasting more than six months and without an anticipated or predictable end (3) – is a public health concern that is associated with loss of productivity, loss of functionality, increased risk for mental health conditions, with significant costs to the healthcare system. (4)

Cystic fibrosis (CF) is a life-limiting autosomal recessive disease affecting approximately 30,000 people in the United States and 60,000 people worldwide. (5) The disease is characterized by recurrent respiratory infections, pancreatic insufficiency, CF-related diabetes, sinus disease, and other complications such as absence of the vasa deferens in males. (6) No longer considered a childhood terminal disease, advances in treatments and a greater understanding of the underlying genetic mutations responsible for CF have increased the life expectancy from an average age of 6 months in 1938 (6) to a current average age of 41 years. (5) Despite these advances, individuals with CF still experience considerable physical (e.g., pain, cough, dyspnea, fatigue) (7) and psychological symptoms (e.g., depression, and anxiety) (8) that are associated with increased disease severity and decreased quality of life (QOL). (8-11)

Symptom management in CF largely focuses on the treatment of the underlying pathology as opposed to direct symptom-managing interventions. In one study, 94% of surveyed CF patients reported a pain event within a two-month period with one third of those reporting it as moderate to severe. (10) However, there are no standard assessments, measures, nor treatments for pain in this population. (11) Although multiple retrospective studies have reported on the location, duration, and severity of pain in both adolescents and adults with CF and its negative relationship to health-related quality of life and disease outcomes (12-20), the role of pain in CF, its effect on daily life, and how the impact of pain changes across the lifespan is poorly understood. Understanding
patient pain characterization and the consequential limitations the pain experience has on CF individuals is essential to developing a standard, clinical approach to CF pain management and treatment. The purpose of this study was to explore patient-reported descriptions of the pain experience among adolescents and adults with CF.

**Methods**

**Design:**

An exploratory descriptive design was used to gain first-hand knowledge of individual experiences with pain. (22)

**Setting and Sample:**

Study participants were recruited from a nationally accredited Cystic Fibrosis Care Center within a large teaching hospital’s outpatient specialty clinics. The center is composed of a pediatric clinic and an adult clinic that sees approximately 550 CF patients per year. Eligible participants were identified through a positive response to the presence of moderate to severe pain occurring at least once a week for a period of at least once a month on the Brief Pain Inventory during previous participation in a self-reported pain survey.

A purposive sample of 10 participants were enrolled into the study. Other inclusion criteria were that the participants had a diagnosis of CF and could understand English in order to provide informed consent. Participants who had undergone a solid organ transplant were excluded from the study to explicitly explore pre-transplant pain experiences. All participants who were invited agreed to participate; however, one participant was withdrawn as the person underwent a lung transplant between the time of enrollment and the scheduled interview. Sample characteristics are summarized in Table 1. A wide range of ages, stages of disease severity, and co-morbidities were represented by the sample and females comprised 50% of the participants.

**Procedures**

The Johns Hopkins Medicine Institutional Review Board (IRB00033661/NA_00027981) approved the study. A written informed consent was obtained from adult participants, and written
parental consent with adolescent assent was obtained from adolescent participants per the institution’s IRB requirements. Informed consent was obtained at outpatient clinic visits and individual in-depth telephone or face-to-face interviews were scheduled for each participant depending on participant availability and clinic space. Demographic data and participant characteristics were collected from electronic medical records.

A semi-structured interview guide was developed by the study team through formative exploration of the available literature, clinical experiences, and informal discussions with providers and patients. The characterization of pain, the effect of pain on quality of life, productivity, and relationships, were identified as gaps in the current CF literature that could be addressed by this study. Additionally, patients and CF nurses expressed the need to explore how pain is assessed, addressed, and treated by CF healthcare providers. Both the adolescents and adults received the same questions with school life being inserted in place of work life where applicable. The domains and questions are displayed in Table 1.

Audio-recorded telephone or face-to-face interviews were conducted by two different interviewers relative to their adolescent and adult group specific experience. Data collection occurred over an eight month period. Each audio-recorded interview was transcribed verbatim, crosschecked for accuracy, and then transcripts were de-identified prior to analysis. Participants received a parking voucher as a reimbursement for their participation.

Data Analysis

The collected data were analyzed via a conventional content analysis (22) and managed using the NVivo qualitative research software package, Version 10.2.1. Transcripts were first read independently by each team member several times to allow for general impressions of the content to develop into categories and preliminary codes. The team then met to discuss the independently coded content. Discrepancies were reconciled through team consensus for each emergent code. Previously coded transcripts were compared to each newly coded transcript to ensure consistency.
in code assessment (23). Peer review of the analysis was performed by CF clinical and research experts at conclusion to ensure trustworthiness. (24, 25)

Results

Participant demographic data including age, sex, and disease severity – represented as forced expiratory volume in 1 second percent predicted (FEV1%), and accompanying comorbidities commonly associated with CF were collected (Table 2.) The age of participants ranged from 13–46 years with 50% of the participants being female. Forced expiratory volume in 1 second percent predicted (FEV1%), a value typically indicative of obstructive pulmonary disease severity, ranged from 23.5% to 102.0%, with the adult FEV1% trending more severe compared to the adolescent FEV%1 range. Pain location was reported by participants as occurring in the lungs, head, sinuses, abdomen, back, ribcage joints, and the whole body.

Concordant and discordant themes between the adolescents and adults emerged from within the explored domains. The adolescents discussed the effects of pain on their social lives, and overall felt supported by their healthcare team in terms of pain management. The adults discussed the pervasive nature of their pain, the emotional pain associated with CF, and the barriers within the healthcare system that contribute to poor pain management. All participant quotes have been ascribed to a pseudonym.

CF is a Pain

The ability to differentiate between CF-specific pain and other, more typical sources of pain, for example, a strained muscle after a strenuous workout, emerged as a strong concordant theme between the two groups. The participants clearly distinguished the pain they associate with their CF as a separate and unique pain:

“I also have kind of like CF-related pain too” (Don, 13 years)

“...yeah, I think it’s...definitely a different pain” (Roy, 32 years)
When asked about the quality and locations of the pain they experience, adolescent participants reported experiencing pain in episodes and were not able to verbalize pain duration, but were able to attribute their pain more to a specific event:

“*It’s usually in my stomach because I forget my enzymes.*” (Josh, 15 years)

“*You know my back pain they have said that it’s just from coughing.*” (Susan, 19 years)

“Aching,” “shooting,” “stabbing,” and “constricting” were the terms used to describe the quality of their pain.

Adult participants reported experiencing pain that is pervasive in duration:

“*I would say 3 or 4 years now*” (Tom, 30 years)

It was more difficult for the adult participants to find single descriptive words for the quality of their pain compared to the adolescent group:

“*It’s just a consistent, almost like tightness umm it-at any given point it’s not overwhelming or stabbing or sharp or anything like that, it’s just a consistent um I always have trouble describing it—like a tightness um sometimes it feels almost like somebody’s reaching up under my ribcage and pulling outwards.*” (Paul, 34 years)

A sub-theme, *Emotions are a Pain*, emerged within the adult group. Adult participants experience more than physical pain, and discussed how depression and emotional pain is a significant aspect of their CF disease:

“*Emotionally…is equal to the physical pain, and often is much more harming or hurtful,*” (Molly, 46 years)

“*It’s an emotional rollercoaster.*” (Joan, 34 years)

”*It’s a big part of CF is emotional pain, and depression.*” (Roy, 32 years)

Pain Restricts Life

The negative impact of how pain restricts daily living, reactional and work-related aspects of life was shared among all participants. Participants described how pain limits their ability to function and perform typical activities of daily living, revealing how on some days their pain is so severe it prevents them from getting out of bed:
“Once I wake up the first hour I just sit on the couch...just wait until I feel better.” (Tim, 30 years)

“Especially some days because the pain gets really bad it just-I just on really bad days I can’t get out of bed.” (Terry, 16 years)

“I don’t feel well enough to get up and move around. Sometimes I can’t even get out of bed.” (Molly, 46 years)

Participants also shared how pain restricts their ability to participate in social and family recreational activities. Family vacations, hobbies, and planned social events have to be modified or cancelled due to the limiting effects pain has on their ability to participate and enjoy in these activities:

“I left my sophomore homecoming because I didn’t feel good... being on my feet and stuff like that was like really hurting me. So my mom um um, my mom came and picked me up from the dance and I just didn’t really do anything, I just came home and my friends went out afterwards and hung out together and whatever...” (Monica, 19 years)

Additionally, participants described how pain impacts their ability to keep up with their workload from a functional perspective, but also from the effects of absenteeism: “I usually have tests like every other day...and I remember, ‘oh wait, I’m going to have to catch up on everything’ and I’m like ‘Blergh!’” (Donny, 13 years)

“I usually just work like 2 days a week, 6 hours each day. That’s just because anything else will wear me out really.” (Paul, 34 years)

A subtheme, Social Life and Emotional Toll emerged from the adolescents we interviewed. There is an emotional toll from missed sporting events, social activities, and school functions that is otherwise not shared by the adults we interviewed:

“I was pretty bummed out.” (Josh, 15 years)

“...I try and understand it, but it’s kind of upsetting sometimes”. (Sue, 14 years)
Sharing the Pain

The willingness to disclose pain to family, friends, and people at work/school was shared by the participants. They reported that families and close friends are supportive and understanding of how pain affects and limits their ability to function in day to day life:

“I can pretty much talk to him about anything, whether it’s pain, or CF-related…” (Molly, 46)

“Most of my friends, like, they understand.” (Donny, 13)

“For a while I was like, No, I don’t need anybody, I don’t need anybody to talk to, I don’t need anybody to talk about my pain and now, it’s like I want to tell everybody!” (Moncia, 19)

All participants discussed that they disclose their pain to bosses and teachers, though one adult says he volunteers the information with hesitation mostly due to internal fear of job loss:

“You’re scared that you’ll lose your job…in general no one has ever made me feel like I have to hide it. It comes from me mostly.” (Roy, 32)

Supported and Treated

All participants spoke to the fact that they do discuss their pain with their CF healthcare providers, but there were stark differences in the perceptions of how pain is addressed and treated between the groups. Adolescent participants had a strong belief that their HCP’s are open to hearing about their pain, are helpful in finding treatment options, and expressed feeling supported and satisfied with the relationship:

“They always want to know my side of the story…they know how to handle (it) in my view at least.” (Terry, 16)

“What they’re doing is pretty good.” (Josh, 15)

Disbelieved and Stigmatized

The adult participants expressed feeling that their CF HCP’s don’t always believe in their CF- specific pain, don’t feel that their pain needs are being met, and feel stigmatized when asking for pain medications:
“They weren’t 100% sure um, that what I was describing was, you know, actual physical pain, um it took a lot, took a little bit for them to come around and realize it.” (Tim, 30)

“But it kind of made me feel really bad about myself…I was like a wimp and I should be sucking it up and handling it because I was a CF patient, and we’re not supposed to have pain…you feel like going to the doctors asking for pain meds, you feel like you’re like a druggy ‘cause you’re like, ‘no that doesn’t work anymore’.” (Molly, 46)

Discussion

The participants were very forthcoming in their discussions around pain and many expressed thanks and relief in having a voice for their pain and how it affects their lives. They provided rich insights into their pain experiences, illustrating how pain is burdensome on emotional, social, and functional levels. In particular, the ability of individuals with CF to differentiate “normal pain” from CF-specific pain has not before been reported. Some of the descriptive phrases the participants used when discussing their physical pain including “stabbing”, “constricting” and “pulling outwards”, provide vivid details into the experience of pain that is otherwise not captured by quantitative studies. CF is a multi-system disease that can be responsible for painful inflammatory and endocrine responses such as bone loss in osteoporosis or pancreatitis due to pancreatic insufficiency. (5) The pain experienced by those with CF is not limited to one specific body system, which suggests that multiple mechanisms of action are responsible for their pain.

Studies by Hayes et al, and Lechtzin et al, have associated pain with worse clinical outcomes in CF patients, including more hospitalizations and increased risk for mortality. (19, 20) This is not surprising given the bi-directional relationship between pain and immune function. (26) These findings indicate that patients perceive a pain that is uniquely specific to their CF disease process suggesting that pain should be assessed, addressed, and treated not as an independent entity, but as a symptom or comorbidity of CF.

The negative association of pain on QOL has been well documented in cohort studies of CF patients (11), and both adolescent and adult participants in this study endorsed the disabling effects
of pain on function, including performing activities of daily living. What has not been previously
documented however, is the debilitating influence pain has on all aspects of their lives. Our study
revealed specific ways and areas in which individuals with CF are restricted by their pain.
Participants described how work and school became a challenge if not impossible, recreational
activities were put on hold or avoided, and when the pain was at its worst, they were bed bound
and unable to ambulate. Despite the Supported and Treated theme that emerged among the
adolescent participants, the loss of functional ability that was revealed suggests that this may not
be the case. There are currently no standards of care specifically for pain management in this
population. Episodic pain, such as abdominal pain due to non-adherence to pancreatic enzymes, or
a headache due to sinusitis, can be well managed through treatment of the underlying cause. Hot
packs and Tylenol are routinely ordered when patients are hospitalized, but the amount and depth
of education received for self-management of pain at home is unknown. Pervasive pain, as
discussed by the adults, is more difficult to manage. The experiences of participants feeling
stigmatized by seeking pain relief, healthcare provider disbelief of the presence of physical pain,
and uncertainty in how pain should be addressed in patients with CF demonstrates the lack of
knowledge of pain management options within the healthcare system. These findings warrant
immediate attention to increasing pain management competencies within CF healthcare providers,
and to explore the use of integrated symptom management specialists into CF standards of care.

The subtheme emergence of the Social Life and Emotional Toll theme from the adolescent
participants is consistent with the developmental stage of this age group. (27) Peer groups and
social events are the focus of an adolescent’s life. The episodic and unpredictable nature of their
pain (14, 16, 18, 20) may place these participants at a greater risk for compromised social
functioning. Provider and patient education regarding strategies for self-management is needed to
help alleviate pain as it is occurring and before it becomes a hindrance to activities.

Both adolescents and adults expressed an openness and willingness to disclose pain to those
in most aspects of their lives, including their families, friends, peers, and professional colleagues.
A 2010 study by Modi et al found that 94% of adults with CF are comfortable disclosing their CF status to relatives, 81% to close friends and 51% to bosses and teachers (28). The theme of *Sharing the Pain* in our study is consistent with these findings given that the participants we interviewed consider pain to be a part of their CF disease.

The subtheme of *Emotions are a Pain* that emerged from the adult interviews is not surprising given recent data on the prevalence of anxiety and depression in the CF patient population (29) and the known association between pain and depression/anxiety (19). The discussion of emotional pain also suggests that there is a psychosocial health need in the adult population that is not being met by current standards of care. The CF Foundation recently released a clinical care guideline recommending the use of depression and anxiety screening tools as a standard of care for CF patients (30) in an effort to help identify those who may be experiencing emotional distress or have a mental health disease. Qualitative studies exploring the sources and perceptions of emotional pain should be undertaken to guide the implementation of clinical interventions.

The adult participants also noted that they did not feel supported in their attempts to discuss their pain nor did they receive treatment or adequate treatment from their CF healthcare provider. These findings bring to light the general stigma that exists in the health care community around pain treatments and drug seeking behavior (31) as well as the importance of implementing multi-disciplinary teams in the treatment of life-limiting chronic diseases. Future qualitative studies of CF care provider beliefs, management practices, and understanding of pain are needed. This information could be used to guide the development of educational programs geared toward CF health care providers.

**Limitations**

The limited sample size and divergent themes that emerged between adolescent and adult participants did not allow for data saturation. Larger samples within each age groups are needed to fully explore how pain develops and is experienced across the lifespan of those with CF.
Conclusion

This study provided much needed insight into the pain experiences of adolescents and adults with CF. CF pain is perceived to be different from other types of pain, the impact on all aspects of life is severe enough to inhibit activities of daily living, and CF patients are willing to talk to others about their pain. Adolescents experience episodic pain, feel supported in their pain management and are at risk for impaired social functioning due to the emotional impact of missed social events. Adults experience persistent pain, recognize a distinct emotional pain associated with CF, and feel stigmatized and unsupported by their attempts to seek pain treatments. A larger qualitative study of pain in persons with CF as well as studies exploring the beliefs, knowledge, and competencies of pain management in CF healthcare providers are warranted to provide much needed insight into the impact of pain during key developmental stages and to help guide the development of education and treatment interventions for pain management in this population.
Table 10: Chapter 6: Interview Questions

<table>
<thead>
<tr>
<th>Question Domain</th>
<th>Questions</th>
</tr>
</thead>
</table>
| Pain Characteristics     | Are you currently having any pain?  
                            | Usually, where is your pain located?  
                            | How would you describe the pain (for example, stabbing, dull, throbbing etc.)?  
                            | How long have you been experiencing this particular pain?  
                            | Do you currently take any medications or undergo any therapies to help alleviate your pain? If yes, please explain and rate effectiveness.  
                            | If drug/alcohol use is endorsed by participants freely then follow up questions regarding effectiveness may be pursued.               |
| Activities               | Can you tell me a little bit about your home life (living arrangements, family, etc.)?  
                            | What kinds of things do you like doing for fun?  
                            | How does pain affect your ability to do those things?  
                            | Tell me about a time that pain has prevented you from doing something you wanted to do.  
                            | How does pain, if at all, limit your ability to perform your activities of daily living (brushing teeth, CF treatments, eating, etc.). |
| Relationships            | Tell me about your friends/family and your comfort discussing your illness with them.  
                            | Describe how you talk about your pain with your family/friends  
                            | Tell me about a time your family/friends responded (can be negatively or positive through support) to a situation where your pain limited you from doing something with them |
| Work/School Life         | Describe your work/school life (If currently not working, explore if illness/pain is the reason why and discuss previous work experiences and how CF and pain affected performance)  
                            | How comfortable are you discussing your illness and pain with people at work?  
                            | Tell me about a time pain affected your ability to work and how your work responded.  
                            | Describe to me your level of comfort in telling your work about your CF and your pain |
| Healthcare Team          | How comfortable are you discussing your pain with your healthcare team?  
                            | Describe to me how your pain is addressed/treated in clinic  
                            | Have you had any experience as an inpatient? If yes, describe your experiences with the inpatient team and how your pain is addressed |
Table 11: Chapter 6: Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Adolescents, n=5</th>
<th>Adults, n=5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (range)</td>
<td>13-19 years</td>
<td>30-46 years</td>
</tr>
<tr>
<td>Sex (female)</td>
<td>3 (60%)</td>
<td>2 (40%)</td>
</tr>
<tr>
<td>FEV1(% Predicted range)</td>
<td>53.0% - 102.0%</td>
<td>23.5% - 82.3%</td>
</tr>
<tr>
<td>Pancreatic insufficient (%)</td>
<td>5 (100%)</td>
<td>5 (100%)</td>
</tr>
<tr>
<td>Cystic fibrosis related diabetes (%)</td>
<td>2 (40%)</td>
<td>1 (20%)</td>
</tr>
<tr>
<td>Osteopenia/osteoporosis (%)</td>
<td>1 (20%)</td>
<td>4 (80%)</td>
</tr>
<tr>
<td>Sinus disease (%)</td>
<td>2 (40%)</td>
<td>3 (60%)</td>
</tr>
<tr>
<td>Depression (%)</td>
<td>0 (0%)</td>
<td>2 (40%)</td>
</tr>
<tr>
<td>Anxiety (%)</td>
<td>0 (0%)</td>
<td>1 (20%)</td>
</tr>
</tbody>
</table>
Chapter VII: Conclusions and Implications

This dissertation provides two different stories of pain in individuals with CF, but both speak to the negative implications of an untreated symptom in a patient population already at risk for poor health outcomes. In those patients with moderate to severe lung disease, pain is associated with worse mental well-being, depression, and worse physical function. In those with moderate to severe pain, quality of life suffers, activities of daily living become impossible, and in adults, patients feel stigmatized by their efforts to seek relief. The outcomes research presented here paints an even grimmer picture for women in pain, with the risk for mortality increasing dramatically compared to their counterparts. The co-morbidities of CF – such as pancreatitis, sinusitis, coughing – can be painful, but pain can also exist independent of the disease such as in lower back pain from simply getting old. Regardless of the cause, the implications of having pain and having CF are the same. Pain affects how those with CF can live, and it may affect how they die.

The findings of this dissertation, and other studies, indicate the need for clinical guidelines to identify, describe, assess, and ultimately effectively treat CF-specific pain. Research needs to focus on several avenues to allow this to happen. We need to further investigate patient attitudes and experiences with pain in the healthcare setting, but we also need to learn how they attempt to relive pain at home, if complementary modalities are used, and if they seek pain relief from sources such as spiritual or social support. We need to investigate the attitudes of our CF health care providers surrounding pain and pain treatment and their own knowledge of how best to treat pain in those with chronic diseases. There also needs to be large-scale studies to allow for a global assessment of the impact and trends of pain in this population. This can easily be achieved by the insertion of pain measures into the Cystic Fibrosis Foundation (CFF) Patient Registry. This registry collects data on every person in the United States with CF that attends a CF care center. It collects information such as age of diagnosis, types of medications, and bacterial infections, and has been a rich source of epidemiological and clinical data for many years. The 2015 CFF Patient
Registry Annual Data Report includes zero mentioning of pain, yet ‘outcomes’ are mentioned over twenty times. By including a few questions regarding pain, above and beyond the one question of “On a scale of zero to ten, are you in any pain” that everyone is asked at routine clinic visits, and requiring those responses to be entered into the registry, we can begin to truly see the landscape of this symptom in CF over time. And finally, we need to look beyond the CF world and tap into research from other diseases to assess what treatment options work best for those with a life-limiting disease who also have pain, with the overarching goal of developing CF-specific, patient-centered interventions to alleviate this symptom and improve outcomes for this population.
Appendix: Email correspondence from the JHU Medicine IRB regarding IRB application requirements for secondary analysis

To: Gayle Page  
Tue 9/22/2015 11:25 AM  
Thank you for taking the initiative to check on this…An email to save…  
Best regards,  
gayle  
Gayle G. Page | Professor

Independence Foundation Chair  
Johns Hopkins School of Nursing  
525 N Wolfe Street, Room 533  
Baltimore, MD 21205  
P. 410-502-3692 | E. gpage1@jhu.edu  
http://nursing.jhu.edu

From: Sarah Allgood  
Tue 9/22/2015 11:23 AM  
To: Gayle Page;  
FYI re: no IRB app required for secondary data analysis. The official word is that we can submit a non-human subjects research application if we really want to, but it’s not required. I wasn’t sure if the SON had any requirements above and beyond the IRB?? I also figured it was best to have a paper trail in case anyone questions it.  
Thanks!  
Sarah  
Sarah J. Allgood, BSN, RN  
PhD Student  
Robert Wood Johnson Foundation Future of Nursing Scholar  
Johns Hopkins University, School of Nursing

Research Nurse  
Johns Hopkins University, School of Medicine  
Division of Pulmonary and Critical Care  
(410) 614-4411, phone  
(240)446-0024, cell  
(410) 502-7048, fax  
From: Clemence Miller  
To: Sarah Allgood  
Mon 9/21/2015 9:24 AM  
Hi Sarah –  
I left you a voicemail with my advice. Call if you need more info. Basically, no submission is required if the data will be totally de-identified and you will have no access to links. Please listen to the message and let me know if you have additional questions.  
Thanks,  
Clemmie  
From: Sarah Allgood  
To: Clemence Miller
I am a second year PhD student at the school of nursing and will be using an existing de-identified data set from an investigator at the University of Washington for my dissertation work. That investigator has added me onto the University of Washington IRB that approved and still oversees the conduction of the study. Do I need to submit a separate protocol/IRB application to Hopkins IRB to perform this secondary analysis and utilize the information gathered from that analysis? I spoke to a few people about this. One person said absolutely, one person said no as the University of Washington was overseeing the project, and lots of other people just didn’t know! Letrice Gant suggested I check in with both of you for clarification.

Thanks so much for any help in this matter!

Sarah
Sarah J. Allgood, BSN, RN
PhD Student
Robert Wood Johnson Foundation Future of Nursing Scholar
Johns Hopkins University, School of Nursing

Research Nurse
Johns Hopkins University, School of Medicine
Division of Pulmonary and Critical Care

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References
Chapter I & IV References


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21 Taylor-Robinson D, Schechter MS. Health inequalities and cystic fibrosis. BMJ 2011;23:343

22 Uchamnowitz I, Janjowska-Polanska B, Wleklik M, Rosinczuk-Tonderus J, Debska G. Health-related quality of life of patients with cystic fibrosis assessed by the SF-36 questionnaire. Pneumonol Alergol Pol 2014;82(1):10-17


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Chapter II References


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Chapter III References


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Chapter V References


Chapter VI References


Curriculum Vitae

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1830 E. Monument St, Suite 500
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Phone: 410-614-4411
Email: sallgoo1@jhmi.edu

Hospital Affiliation:
Johns Hopkins Hospital
1800 Orleans Street
Baltimore, MD 21287

Education and Training

2014  PhD Candidate, Johns Hopkins University, School of Nursing, Baltimore, MD, Final Defense Date: June 16th, 2017, Graduation: August, 2017

2011  Clinical Research Nurse Med-Surg Internship, National Institutes of Health Clinical Center, Bethesda, MD

2009  Bachelor of Science, Nursing (BSN), Johns Hopkins University, School of Nursing, Baltimore, MD

2000  Associates of Science (A.S.) Animal Health Technology, Mesa College, San Diego, CA

Licensor:
Maryland State Board of Nursing
License #: R186724, Expires: 08/2019
Registered Nurse, active since 2009

Certificates/Training:

- Medical/Surgical Clinical Research Nurse Internship, NIH, 2011
- HIPAA and Human Subjects Research certification, JHU, 2017, renewed annually
- Electronic Institutional Review Board (eIRB) training course, JHU, 2011
- CPR for Health Care Providers, JHU, Expires July 2017
- End of Life Nurses Education Consortium, Train the trainer course, 2016
Research and clinical experience

06/2011 to Present

Research Nurse

Johns Hopkins University, School of Medicine, Pulmonary and Critical Care

- Study Manager: Responsible for protocol development, sponsor consultation/liaison, supporting research operations; study team training/education, data management, analysis, and dissemination of findings
  - eICE: Early Intervention in Cystic Fibrosis Exacerbation; supervised and supported research and protocol operations at 13 national cystic fibrosis centers (currently undergoing analysis)
  - Pain in Adults with Cystic Fibrosis – Qualitative Interviews (completed)
  - Cystic Fibrosis Remote Monitoring System to Support Resource-Limited Communities (completed)
  - Detection and Significance of Fungal Respiratory Infection in Cystic Fibrosis Patients (completed)
  - Assessment of Pain in Individuals with CF (completed)
- Site Coordinator/Research Nurse: Responsible for feasibility assessment, budget development, all regulatory documents management including IRB applications, ancillary support training/coordination, participant recruitment, study operationalization, data management
  - The IGNITE Study: Phase II (enrolling)
  - Investigation of CF Sputum Microbiologic Characteristics (enrolling)
  - Standardized Treatment of Pulmonary Exacerbations II (enrolling)
  - VX-440 Combination Therapy, Phase 2 (enrolling)
  - Development of wearable chloride sweat sensor for diagnosis and clinical management (enrolling)
  - Nasal Collection of Cells for CFTR analysis (enrolling)
  - Use of High Flow Nasal Insufflation in Children and Adults with CF (enrolling)
  - Association of Uric Acid with Health Outcomes Among Patients with CF (approved for enrollment)
  - The Galapagos Study (in start-up)
  - The Use of Biomarkers to Guide Management of Pulmonary Exacerbations (completed)

08/2009 to 06/2011

Clinical Research Nurse, III

National Institutes of Health, Clinical Center, General Medicine
• Provided direct patient medical/surgical care in endocrine, genetic disease, respiratory, and gastrointestinal in-patient populations
• Performed charge nurse duties to a 32 bed unit
• Protocol liaison: communicated to PI protocol status, and conducted in-service training to staff nurses and unit personnel
• Provided education regarding health status and protocol participation to study volunteers
• Collected samples, interpreted results, and communicated findings as indicated per protocol requirements and best practice guidelines

01/2008-05/2009  Lab Technician/Student Researcher  
*JHU, School of Nursing, Lab of Dr. Gayle G. Page*
• Performed surgery and administered inhalation anesthesia in a rat model
• Performed ELISA testing for cytokines and corticosterone levels
• Administered Von Frey hair stimuli and scored pain response in a rat model
• Collected and processed samples for storage and testing
• Evaluated, interpreted, and presented study results

03/2008-05/2009  Research Assistant  
*JHU, School of Nursing, Center for Collaborative Intervention Research*
• Supported and participated in project development of pilot studies
• Developed study tools utilizing the Teleform computer program
• Maintained department budget and conference reports
• Organized and marketed conferences and seminars

---

**Teaching Experience**

08/2016 to current  Teaching Assistant  
*Johns Hopkins University, School of Nursing*
• Providing IRB protocol development evaluation and consultation to PhD students
• Instructing master’s entry nursing students in pathophysiology
• Developing reviews and tutoring sessions for exam preparation through in-person and online teaching modalities
• Evaluating case reports and nursing implication assignments
08/2012 to 12/2012  **Clinical Instructor**  
*Johns Hopkins University, School of Nursing*
- Instructed baccalaureate nursing students in entry-level clinical care procedures including aseptic technique, wound care, mobility, medication administration, dosage calculations, fluid therapy, first aid, catheter placement and care, and general patient assessment
- Assessed student’s ability to demonstrate patient-centered care, use of evidence-based guidelines, quality improvement, safety, and informatics in performing nursing skills

08/2005- 06/2007  **Guest Lecturer**  
*Fairmont State University*
- Instructed baccalaureate students in equine healthcare and veterinary medicine

**Mentoring:**

- **10/2013 to 06/2014**  
  Michelle Beccio, JHU SON baccalaureate candidate, Alumni-Student Mentorship Program

- **09/2013 to 06/2014**  
  Co-Mentor with Dr. Sharon Kozachik; Marcos Vera, JHU SON baccalaureate candidate, Research Honors Program

**Awards and Honors**

**Scholarships:**
- **2014 – 2017**  
  Future of Nursing Scholar, The Robert Wood Johnson Foundation

**Grants:**
- **2009**  
  The Minority Global Health Disparities International Research Training Program Grant,

  National Center on Minority Health and Health Disparities (NCMHD) and Fogarty International Center (FIC), University of Newcastle, Australia

**Awards:**
- **2009**  
  Research Award (for demonstrating intellectual curiosity and creativity in nursing), Johns Hopkins University, School of Nursing

- **2009**  
  Graduated with Honors, Johns Hopkins University, School of Nursing

- **2008**  
  Research Honors Program, mentored by Dr. Gayle Page, DNSc, RN, FAAN, Johns Hopkins University, School of Nursing
Publications


Lechtzin N, West N, Allgood S, Wilhelm E, Khan U, Mayer-Hamblett N, Atken ML, Ramsey BW, Boyle MP, Mogayzel PJ, Goss CH. 2013. Rationale and design of a randomized trial of home electronic symptom and lung function monitoring to detect cystic fibrosis pulmonary exacerbations: The early intervention in cystic fibrosis (eICE) trial. Contemporary Clinical Trials. 2:460-469

Posters/Presentations


05/20/2014 The Association between Pain and Depression in Adolescents with Cystic Fibrosis. Hong G, Allgood S, Riekert K, Hankinson J, Rivera T, Mogayzel P, Yaster M, Lechtzin N. American Thoracic Society Conference 2014; San Diego, CA,

10/16/2013 Did We Have You At Hello? Recruitment strategies for CF research. North American Cystic Fibrosis Conference, Salt Lake City, UT
10/11-14/2012  Phase 1 Pharmacokinetic and safety study of intravenous Ganite™ (Gallium nitrate) in CF. Goss, Christopher H.; Hornick, Douglas B.; Aitken, Moira L.; Anderson, Gail; Caldwell, Ellen; Lechtzin, Noah; Wilhelm, Ellen; Wolfstone, Alycia; Allgood, Sarah; Teresi, Mary; Singh, Pradeep K. North American Cystic Fibrosis Conference, Orlando, FL

11/02/2011  Introduction to eICE: Early Intervention in Cystic Fibrosis Exacerbation, North American Cystic Fibrosis Conference, Anaheim CA

05/06/2011  Effective Orientation Strategies for Use in Clinical Research, United States Public Service Nurse Recognition Day, Bethesda, MD

02/13/2010  It’s Not in her Head: An Insulinoma Case Study, NIH Clinical Center, Bethesda, MD

07/23/2009  Infection, anxiety and sex: Perinatal determinates of later life behavior. School of Psychology Colloquium, University of Newcastle, Australia

05/08/2009  Effects of indomethacin on cytokine and corticosteroid production in postsurgical rats. Johns Hopkins School of Nursing, Baltimore, MD

__________________________________________

**Organization Memberships**

2016-Present  Hospice and Palliative Nurses Society

2016-Present  American Pain Society

2009-Present  Sigma Theta Tau Nursing Honors Society

2009-Present  Johns Hopkins University Alumni Association

2006-2008  American Association of Equine Veterinary Technicians
  - 2006 Continuing Education Chair
  - 2006 Executive Organizing Committee