Georgia College
Knowledge Box

Doctor of Nursing Practice (DNP) Translational and Clinical Research Projects

School of Nursing

Fall 12-8-2015

Restoring Digestive Health

Kristin M. Corbin, DNP, APRN, FNP-C
Georgia College and State University, kristin.corbin@bobcats.gcsu.edu

Follow this and additional works at: https://kb.gcsu.edu/dnp

Part of the Alternative and Complementary Medicine Commons, Digestive, Oral, and Skin Physiology Commons, Digestive System Diseases Commons, and the Family Practice Nursing Commons

Recommended Citation

Corbin, DNP, APRN, FNP-C, Kristin M., "Restoring Digestive Health" (2015). *Doctor of Nursing Practice (DNP) Translational and Clinical Research Projects*. 12.
https://kb.gcsu.edu/dnp/12

This Dissertation is brought to you for free and open access by the School of Nursing at Knowledge Box. It has been accepted for inclusion in Doctor of Nursing Practice (DNP) Translational and Clinical Research Projects by an authorized administrator of Knowledge Box.

Restoring Digestive Health with Probiotics, Digestive Enzymes, and Glutamine

Kristin M Corbin, DNP, APRN, FNP-C

Georgia College and State University

_____
Dr. Sallie Coke, PhD, APRN, C-PNP, C-FNP
Committee Chairperson

_____
Dr. Dean Baker, RN, PMHCNS-BC, PhD
Committee Member

_____
Dr. Tasneem Bhatia, MD
Committee Member

TABLE OF CONTENTS

Page

Abstract……7

List of Tables……...9

List of Figure……..10

Chapter Page

I. INTRODUCTION……...11

Understanding Functional Gastrointestinal Disorders……11

Definition……11

Prevalence……....12

Etiology……13

Brain Gut Communication……14

Genetic Factors…….……14

Infection and Intestinal Inflammation……15

Altered Gut Bacteria……..……16

Costs……16

Symptoms and Treatment…….…...17

Purpose and Clinical Questions……...17

Pre-Intervention Clinical Questions…….19

Post-Intervention Clinical Questions……...……19

Challenges……....20

II. REVIEW OF LITERATURE……..21

Probiotics……...…..21

Glutamine……25

Digestive Enzymes……...27

Age……...29

Gender……..30

Ethnicity……...31

Weight and Waist Circumference……32

Quality of Life……..33

Stress……34

Duration of Symptoms……34

Number of Attempted Treatments……...35

Theoretical Framework……36

III. PROJECT DESIGN AND METHODOLOGY……...41

Objectives……....41

Project Design and Procedures……41

Project Site……...44

Sample……..45

Inclusion Criteria……...45

Exclusion Criteria……..46

Sample Size……46

Supplements……47

Instruments……...47

Gastrointestinal Quality of Life Index……...47

Perceived Stress Scale……50

Weight……52

Waist Circumference…….53

Research Questions…….55

Pre-Intervention Questions……55

Intervention Questions……...56

Dissemination……..56

Data Analysis……...57

Analysis Plan for Research Questions……57

IV. RESULTS……62

Data……..…62

Pre-Intervention Sample Characteristics……..64

Description of Research Instruments……...65

Waist Circumference…….66

Weight……67

Perceived Stress Scale……67

Gastrointestinal Quality of Life Index……...67

Pre-Intervention Clinical Research Questions…….68

Results for Research Question 1……68

Results for Research Question 2……....70

Results for Research Question 3……71

Results for Research Question 4……73

Results for Research Question 5……....74

Results for Research Question 6……74

Post-Intervention Data……...75

Sample Characteristics……...75

Self-Reported Gastrointestinal Symptoms……..…78

Post- Intervention Description of Research……..…….79

Perceived Stress Scale……80

Gastrointestinal Quality of Life Index……..….80

Weight and Waist Circumference……..…81

Post-Intervention Clinical Questions……..…81

Results for Research Question 7……81

Results for Research Question 8……83

Results for Research Question 9……84

Results for Research Question 10……..84

Results for Research Question 11……..…85

Conclusion……..….86

V. DISCUSSION……..……88

Demographics……..88

Age……...…..88

Gender……90

Ethnicity…….91

Duration of Symptoms……...92

Number of Attempted Treatments…….93

Additional Comments……95

Instruments……..….99

Weight and Waist Circumference……..…99

Perceived Stress Scale……..…101

Gastrointestinal Quality of Life Index……...…..101

Strengths of the Study……...102

Limitation of the Study……..103

Implications for Practice……104

Implications for Theory Building……..105

Future Research……..…105

Dissemination……...……..106

Conclusion…….106

References……..…108

Appendices…….……124

Appendix A: Flow Diagram for Research Study……...124

Appendix B: Example of Recruiting Flyer……125

Appendix C: Informed Consent……..…127

Appendix D: Example of Study Checklist…….……131

Abstract

Purpose: The purpose of this translational research project was to outline the healthcare problems associated with Functional Gastrointestinal Disorders and to explore the effectiveness of a gastrointestinal protocol utilized at Atlanta Center for Holistic and Integrative Medicine. The goal of this protocol is to restore digestive health with probiotics, digestive enzymes, and glutamine.

Background: Functional Gastrointestinal Disorders affect one in every four adults in the United States. These disorders encompass a variety of symptoms including diarrhea, constipation, cramping, abdominal pain, flatulence, reflux, and bloating without an identified physiological cause. There is currently no cure for Functional Gastrointestinal Disorders and treatment focuses on symptom management. The majority of those suffering from Functional Gastrointestinal Disorders are unsatisfied with their current treatment regimen leading to physical, social, and emotional distress.

Method: This prospective cohort study examined 98 adult participants with Functional Gastrointestinal Disorders. Each participant was instructed to take probiotics, digestive enzymes, and glutamine daily for 8-weeks. The participants were evaluated by a virtual survey at baseline, weekly, and after 8-weeks of intervention. The pre and post-intervention surveys included age, gender, ethnicity, duration of symptoms, number of attempted treatments, weight, waist circumference, the Perceived Stress Scale, and the Gastrointestinal Quality of Life Index.

Results: A total of 86 participants completed the entire 8-week intervention. Based on the results of this study, there were three statistically significant predictors of lower gastrointestinal quality of life based on the Gastrointestinal Quality of Life. These three predictors include (1) minorities, (2) higher levels of stress based on the Perceived Stress Scale, and (3) greater than 3

attempted treatments. After the 8-week intervention, the participants had significant weight loss and improved gastrointestinal quality of life scores.

Discussion: This research study is the first to examine the combined benefits of probiotics, digestive enzymes, and glutamine. In this study, participants had significant improvements in weight loss and gastrointestinal quality of life indicating that this protocol can be an effective regimen for treating patients with Functional Gastrointestinal Disorders.

KEY WORDS: Functional Gastrointestinal Disorders, Perceived Stress, Gastrointestinal Quality of Life, Weight, Waist Circumference

LIST OF TABLES

Table Page

1. Pre-Intervention Demographic Characteristics of Participants……65
2. Description of Research Instruments (Pre-Intervention)…….....66
3. Pearson Correlations between the Major Variables (Pre-Intervention)……...71
4. Results of Simultaneous Regression of Predictors of Perceived Stress on Gastrointestinal Quality of Life Scores……..72
5. Examining Association of Age, Gender, Ethnicity, Duration of Symptoms, and Number of Attempted Treatments on Waist Circumference……..73
6. Results of Simultaneous Regression of Predictors for Waist Circumference……..75
7. Post-Intervention Demographic Characteristics of Participants……..76
8. Self-Reported Gastrointestinal Symptoms of Sample Completing Entire 8-Week Study…...79
9. Description of Research Instruments (Post-Intervention)……79
10. Pearson Correlations between the Major Variables (Post-Intervention)……..…82
11. Results of Simultaneous Regression of Predictors for Gastrointestinal Quality of Life…..…84
12. Paired Samples T-Test after 8-Week Intervention……..…85
13. Additional Comments Found on Weekly Surveys……..96

LIST OF FIGURES

Figures Page

1. Applying Betty Neuman's Health Systems Model……..…...40

2. Gastrointestinal Quality of Life Scores Pre- and Post- Intervention Based on Ethnicity...92

Restoring Digestive Health with Probiotics, Digestive Enzymes, and Glutamine

CHAPTER I

Introduction

Gastrointestinal disorders are highly prevalent in the United States. The majority of gastrointestinal symptoms reported to healthcare providers are functional disorders rather than disease states (Stake-Nilsson, Hultcrantz, Unge, & Wengström, 2012). Disease states are associated with a specific underlying pathology that can be identified through diagnostic testing, while functional disorders have an unknown structural or physiological abnormality (Stake-Nilsson et al., 2012). The term used to identify this syndrome is Functional Gastrointestinal Disorders. This population often experiences little to no improvement in their symptoms, leading to physical, mental, and social distress (Markert, Suarez-Hitz, Ehlert, & Nater, 2014; Spiegel et al., 2011; Stake-Nilsson et al., 2012).

Understanding Functional Gastrointestinal Disorders

Definition

The term Functional Gastrointestinal Disorders is used when the body's digestive tract seems to be functioning normally, yet it causes significant gastrointestinal symptoms in an individual's quality of life. Examples of this in the gastrointestinal system are changes in the motility of the intestines, sensitivity of the nerves in the intestines, or the way in which the brain controls the functions of the digestive tract (International Foundation of Functional Gastrointestinal Disorders [IFFGD], 2015). Despite the impaired function, healthcare providers are unable to identify a structural abnormality through diagnostic testing, such as endoscopy, colonoscopy, CT scan, x-ray, or blood tests (IFFGD, 2015). In other words, Functional Gastrointestinal Disorders are defined as chronic or recurrent gastrointestinal symptoms, such as

pain, heartburn, abdominal distention, nausea, vomiting, bloating, constipation, or diarrhea, without a known structural or biochemical abnormality (Markert et al., 2014).

Prevalence

Functional Gastrointestinal Disorders are the most common gastrointestinal disorder seen in the general public, affecting one in every four people in the United States (IFFGD, 2015). Some of the most common Functional Gastrointestinal Disorders include functional dyspepsia, irritable bowel syndrome, and functional constipation. Functional dyspepsia affects 20-30% of the general population followed by functional constipation (up to 27%) and irritable bowel syndrome (10-20%) (IFFGD, 2009). These disorders make up 41% of all gastrointestinal symptoms reported to healthcare providers and therapists (IFFGD, 2015). Functional Gastrointestinal Disorders seem to affect females more frequently than males, yet the etiology behind this remains unknown (Markert et al., 2014).

Functional Dyspepsia is defined as symptoms that originate from the upper digestive system including the stomach and small intestines without any structural or metabolic diseases known (IFFGD, 2015). This disorder is estimated to affect 30% of the general population (IFFGD, 2015). Symptoms of dyspepsia vary tremendously including burning, pressure, fullness, nausea, early satiety, belching, and bloating. This disorder is often chronic with approximately 50% of patients having symptoms of functional dyspepsia for over 5-years (IFFGD, 2015).

Two of the most common digestive disorders include irritable bowel syndrome and inflammatory bowel disease. These two disorders affect 16.3 million people in the United States alone (McCormick et al., 2012). Irritable bowel syndrome patients account for 3.65 million outpatient provider visits annually (IFFGD, 2009). Unlike irritable bowel syndrome, inflammatory bowel disease is a true disease state that encompasses both Ulcerative Colitis and

Crohn's Disease. With this diagnosis, there is clear evidence to support the etiology of inflammation within the digestive tract. In contrast, irritable bowel syndrome is classified as a Functional Gastrointestinal Disorder because there is no structural abnormality associated with the disorder and the etiology remains vague and inconclusive. Functional constipation is defined as difficult, infrequent, and often incomplete defecation without a known cause (IFFGD, 2015).

Etiology

Despite increasing research, the pathophysiology behind Functional Gastrointestinal Disorders remains ambiguous and treatment options are limited (Markert et al., 2014). Current evidence suggests that the etiology behind Functional Gastrointestinal Disorders is biopsychosocial in nature (Markert et al., 2014). Over the past two decades, specific organizations, such as the International Foundation of Functional Gastrointestinal Disorders (IFFGD) have discovered some possible mechanisms behind the development of Functional Gastrointestinal Disorders (IFFGD, 2009). These discoveries have found abnormalities in the brain-gut communication, genetic factors, infection, altered gut bacteria, and intestinal inflammation (IFFGD, 2009). Two thirds of these patients are thought to have an increased sensitivity to gut stimuli or "visceral hypersensitivity"; others suffer from abnormal motility that can cause a wide range of symptoms including swallowing difficulties, heartburn, diarrhea, constipation, and incontinence (IFFGD, 2009). Other researchers are questioning the association between medication use and Functional Gastrointestinal Disorders. A population-based study was conducted to determine whether proton pump inhibitors (PPI), antidepressants, and/or narcotics were contributing to the high prevalence of Functional Gastrointestinal Disorders (Choung, Locke, Schleck, Zinsmeister, & Talley, 2013). The results found that PPI use was

causing significant irritable bowel syndrome and dyspepsia symptoms, while antidepressant use was significantly associated with bloating (Choung et al., 2013).

Brain-Gut Communication. Research concerning the brain-gut connection is continually evolving. External and internal stressors may have an effect on gastrointestinal motility and sensation. For example, some individuals may experience the sensation of butterflies in their stomach when anxious or an upset stomach related to other emotions, such as sadness (IFFGD, 2009). Pain is often a subjective symptom associated with Functional Gastrointestinal Disorders. When assessing pain, it is important to evaluate how the brain is responding to the signal. Patients diagnosed with irritable bowel syndrome were shown to have more brain activation in the area responsible for afferent processing and emotional arousal compared to the control group (Tillisch & Labus, 2011). Structurally, the amount of gray matter an individual has may be a factor in chronic illnesses. For example, individuals suffering from a variety of illnesses including chronic pain, depression, and irritable bowel syndrome have been shown to have varying amounts of gray matter (Tillisch & Labus, 2011). Specifically, irritable bowel syndrome was associated with decreased gray matter density in several areas of the brain (Tillisch & Labus, 2011).

Genetic Factors. Functional Gastrointestinal Disorders have been shown to run in families (IFFGD, 2009). Research is beginning to identify genes that may predispose individuals to Functional Gastrointestinal Disorders. For example, the beta-2 adrenergic receptor (ADRB2) is an essential target for epinephrine, which is a pain signaling neurotransmitter. Evidence has found ADRB2 minor alleles at rs1042714 to be a predictor for Functional Gastrointestinal Disorders and may influence bowel symptom severity and quality of life (Kushnir et al., 2013). Another polymorphism examined is the Serotonin Transporter (SERT) role in irritable bowel

syndrome. In patients with irritable bowel syndrome, this gene has been shown to play a key role in motility-related symptoms (Wang et al., 2012).

Infection and Intestinal Inflammation. Individuals that suffer from a gastrointestinal infection have a higher risk of developing irritable bowel syndrome symptoms that can persist for months to years (IFFGD, 2009). It is hypothesized that these symptoms may be the result of persistent, low-grade inflammation (IFFGD, 2009). Current research supports that individuals suffering from functional dyspepsia and irritable bowel syndrome have a higher risk of developing bouts of infectious gastroenteritis (Simrén et al., 2013). Porter et al. (2011) conducted a study on 31,866 U.S Military personnel diagnosed with Functional Gastrointestinal Disorders to examine the association between Functional Gastrointestinal Disorders and infectious gastroenteritis. The results of this study showed a significant association between Functional Gastrointestinal Disorders and infectious gastroenteritis ($p< 0.001$) (Porter et al., 2011). The distribution is as follows: specific bacterial pathogen (1.2%), bacterial without a specific pathogen identified (38.9%), protozoal (0.7%), and viral (61.9%) (Porter et al., 2011).

In the United Kingdom, a large study was conducted to assess the association of autoimmune disease and Functional Gastrointestinal Disorders (Ford, Talley, Walker, & Jones, 2014). This study examined the prevalence of autoimmune disorders among 23,471 patients with Functional Gastrointestinal Disorders including functional diarrhea, chronic idiopathic constipation, or multiple Functional Gastrointestinal Disorders. The results of this study found that those suffering from rheumatologic autoimmune disorders had a significantly higher incidence of Functional Gastrointestinal Disorders including functional diarrhea, chronic idiopathic constipation, and multiple Functional Gastrointestinal Disorders (Ford, Talley, et al., 2014).

Altered Gut Bacteria. One of the most recent hypotheses for Functional Gastrointestinal Disorders is that an abnormal intestinal microflora can activate mucosal innate immune system responses that increase the epithelial permeability, activate nociceptive sensory pathways, and dysregulate the enteric nervous system (Simrén et al., 2013). In the human digestive tract, there are more than 500 different species with an immense variety of aerobic and anaerobic bacteria (Ringel & Ringel-Kulka, 2011). Some of these bacteria are known to be beneficial to a person's health by helping to maintain a normal functioning intestine; while other bacteria can cause infection, or inflammation. When the normal balance in the intestine between beneficial and harmful bacteria is changed, it may lead to changes in the function of the gastrointestinal tract and cause chronic gastrointestinal symptoms (IFFGD, 2009).

Costs

In the United States, gastrointestinal disorders are the leading cause of outpatient office visits (Myer et al., 2013). Unfortunately the only data available was from 2004, which indicated 72 million outpatient office visits in the United States were associated with a gastrointestinal diagnosis (Myer et al., 2013). Women had a 20% higher rate of ambulatory visits than men, with no differences observed between Caucasians and African Americans (Myer et al., 2013). It is estimated that Functional Gastrointestinal Disorders are costing our society over $30 billion annually (IFFGD, 2009). Direct costs associated with irritable bowel syndrome alone are estimated at $1.5 billion annually and as high as $10 billion in adjusted costs, excluding prescriptions and over the counter medications (IFFGD, 2009). It is estimated that indirect costs associated with irritable bowel syndrome may be as high as $20 billion annually from decreased work productivity (IFFGD, 2009).

Healthcare costs related to gastrointestinal disorders expand beyond outpatient care. In 2007, there were 15.1 million emergency room visits associated with gastrointestinal symptoms (Myer et al., 2013). The total annual charges for all Emergency Department visits with a primary gastrointestinal diagnosis was $27.9 billion with each visit averaging $2,354 (Myer et al., 2013).

Symptoms and Treatment

The symptoms associated with Functional Gastrointestinal Disorders vary greatly and in some cases the symptoms overlap. Common symptoms include abdominal pain, bloating, heartburn, nausea, constipation, diarrhea, bloating, urgency, decreased appetite, swallowing difficulties, and incontinence (IFFGD, 2009). Unfortunately, there is no cure for Functional Gastrointestinal Disorders; rather treatment focuses on symptom management and improvements in patients' overall quality of life. Current treatment modalities include antidepressants to decrease intestinal hypersensitivity, relaxation techniques, avoiding known food triggers, medications to regulate bowel function, biofeedback therapy, hypnosis, and cognitive behavior therapy to help restore a sense of control over the disorder (IFFGD, 2009). Even these treatments have limited efficacy and have potential adverse effects (Hungin et al., 2013). Further research is needed for a safe and effective long-term treatment for Functional Gastrointestinal Disorders symptoms (Waller et al., 2011).

Purpose and Clinical Question

Maintaining a normally functioning gastrointestinal tract is essential for health. The gastrointestinal tract is a large organ in the human body encompassing everything from the mouth to the anus. The intestinal mucosa is the body's primary line of defense against toxins and bacteria (Resnick, 2010). Mucosal damage and intestinal inflammation can progress to chronic disease, autoimmune responses, and systemic inflammation (Resnick, 2010). Several conditions

are associated with intestinal permeability defects including multiple organ failure, chronic fatigue syndrome, ulcerative colitis, Crohn's disease, celiac disease, irritable bowel syndrome, juvenile onset arthritis, food allergies, chronic heart failure, and psychological conditions, such as depression and anxiety (Resnick, 2010). Long-term gastrointestinal reflux disease increases the risk of esophageal strictures, esophageal ulcers, or precancerous cells, as seen in Barrett's esophagus (Mayo Clinic, n.d.). Chronic diarrhea is associated with malabsorption; this can cause complications including electrolyte imbalances, dehydration, vitamin deficiencies, diminished urine output, kidney failure, and orthostatic hypotension (Marks, 2014).

The specific aim of this project was to outline the healthcare problems associated with functional gastrointestinal disorders and to explore the effectiveness of a gastrointestinal protocol implemented at Atlanta Center for Holistic and Integrative Medicine (ACHIM). This protocol was designed to help restore digestive health. Conventional medications play a key role in improving gastrointestinal disorders outcomes; such as proton pump inhibitors and antibiotics for the treatment of H pylori. However, all medications come with potential adverse effects. For example, long term use of proton pump inhibitors is associated with pneumonia, fractures, vitamin B12 deficiencies, hypomagnesaemia, and pneumonia (Owen, Marks, & Banks, 2014).

The goal of ACHIM's gastrointestinal protocol was to naturally heal and restore a normal functioning digestive system with minimal to no adverse effects. The purpose of this project was to determine if adult patients with functional gastrointestinal disorders report improved abdominal symptoms based on the Gastrointestinal Quality of Life Index after eight weeks of probiotics, digestive enzymes, and glutamine. This translational project was designed to quantify the benefits associated with this well-established protocol. A thorough literature review and synthesis of evidence related to probiotics, digestive enzymes, and glutamine was conducted

and the pertinent results are disseminated throughout this paper. The paper concludes with a thorough discussion of the research findings. Below is a list of the clinical research questions.

Pre-Intervention Clinical Questions

1. What demographic factors (age, gender, ethnicity, duration of symptoms, and number of attempted treatments) are associated with a lower level of gastrointestinal quality of life?
2. What is the association between patients' perceived stress and gastrointestinal quality of life?
3. Controlling for demographic variables (age, gender, ethnicity, duration of symptoms, and number of attempted treatments) what is the association of perceived stress on gastrointestinal quality of life?
4. What demographic factors (age, gender, ethnicity, duration of symptoms and number of attempted treatments) are associated with an increased weight and weight circumference?
5. Controlling for demographic variables (age, gender, ethnicity, duration of symptoms, and number of attempted treatments), what is the association between perceived stress and waist circumference and weight?
6. Controlling for demographic variables (age, gender, ethnicity, duration of symptoms, and number of attempted treatments), is there an association between gastrointestinal quality of life and weight and waist circumference?

Post-Intervention Clinical Questions

7. After 8-week treatment with probiotics, digestive enzymes, and glutamine, is there an association between patients' perceived stress and gastrointestinal quality of life?
8. Controlling for demographic variables (age, gender, ethnicity, duration of symptoms, and number of attempted treatments) after 8-week treatment with probiotics, digestive

enzymes, and glutamine, what is the association of perceived stress on gastrointestinal quality of life?

9. Controlling for demographic variables (age, gender, ethnicity, duration of symptoms, and number of attempted treatments) after 8-week treatment with probiotics, digestive enzymes, and glutamine, what is the association between perceived stress and waist circumference and weight?
10. Controlling for demographic variables (age, gender, ethnicity, duration of symptoms, and number of attempted treatments) after 8-week treatment with probiotics, digestive enzymes, and glutamine, what is the association between gastrointestinal quality of life and weight and waist circumference?
11. After 8-week treatment with probiotics, digestive enzymes, and glutamine, is there a statistically significant change in the gastrointestinal quality of life, weight, waist circumference, and perceived stress?

Challenges

Integrative Medicine utilizes both conventional and alternative medicine modalities to improve the patient's overall healthcare outcomes. Since integrative medicine incorporates non-mainstream therapies, the scientific evidence is limited, making elements of the literature review challenging. Restoring digestive health is a multi-factorial concept. Several factors play a role in restoring digestive health including stress reduction, brain-gut connection, and ruling out any food intolerances and allergies. This study did not alter participants' diet or lifestyle. It primarily examined the benefits of probiotics, digestive enzymes, and glutamine on restoring digestive health.

CHAPTER II

Review of Literature

Recently, research has gained interest in the importance of gut-related health problems, such as the increasing evidence that a poor digestive tract is associated with autoimmune diseases and inflammatory processes (Ritchie & Romanuk, 2012). The restoring digestive health protocol utilized at the Atlanta Center for Holistic and Integrative Medicine is unique to the practice. Consequently, there is not any research to support the combination of probiotics, digestive enzymes, and glutamine on digestive health. Therefore, a comprehensive literature review was conducted to assess the effectiveness of probiotics, digestive enzymes, and glutamine individually. A separate literature review was conducted to find a valid and reliable instrument that measures gastrointestinal symptoms. Each literature review was conducted primarily through GALILEO and Google Scholar. All articles included in this literature review were peer-reviewed, scholarly articles.

Probiotics

The large amount of bacteria in the digestive tract is known as the intestinal microflora. In the human digestive tract, it is estimated that the intestinal microflora contains 10^{14} cells, which is thought to be ten times more than the number of cells in the entire human body (Simrén et al., 2013). The intestinal microflora has been researched heavily in recent years for its potential influence on gastrointestinal symptoms and diseases. Some of these organisms have been shown to be beneficial to one's health, while others may cause infection or inflammation (IFFGD, 2009). When the normal balance in the intestines between beneficial and harmful bacteria changes, it may lead to negative results in the function of the gastrointestinal tract (IFFGD, 2009).

The beneficial bacteria for the digestive tract are known as probiotics. The term probiotic is derived from the Latin words “pro” and “bios” meaning “for life” (Castellazzi et al., 2013). Eli Metchnikoff first coined the term *probiotic* in 1907 (Castellazzi et al., 2013). He was the first man to propose the notion that consuming live microorganisms may have potentially beneficial effects on human’s overall health (Castellazzi et al., 2013). Probiotics can be supplemented or naturally found in foods, such as yogurt, kefir, miso, tempeh, and teas like Kombucha. Basically, probiotics are live microorganisms that help maintain and restore beneficial intestinal microflora that have the ability to prevent or treat gastrointestinal disorders and other related systemic conditions (Resnick, 2010). Restoring the normal flora in the digestive tract is crucial for digestive health, because probiotics can act as an intestinal barrier to pathogen causing microorganisms (Rao & Samak, 2013).

In the United States, there has been an overall improvement in hygiene and nutrition that has resulted in a significant reduction in overall bacteria exposure, including beneficial bacteria (Ritchie & Romanuk, 2012). Through experimentation, it is known that gut microflora is essential to the normal development of the immune system, growth and development (Hickson, 2013). Probiotics have been shown to be beneficial for cytoprotection, cell proliferation, cell migration, resistance to apoptosis, and synthesis of proteins and gene expression (Rao & Samak, 2013). The beneficial properties of probiotics include protective barriers, enhancing immune responses, and clearing pathogens in the gastrointestinal tract (Ritchie & Romanuk, 2012).

One study found that supplementing probiotics significantly helped treat inflammatory bowel disease (Cary & Boullata, 2010). Other symptom improvements seen with probiotics include a reduction in abdominal pain and bloating (Jafari, Vahedi, Merat, Momtahen, & Riahi, 2014; Rogha, Esfahani, & Zargarzadeh, 2014). Probiotics have the ability to significantly

improve whole gut transit time by up to 12.4 hours, improve stool consistency, and increase stool frequency by 1.3 bowel movements per week in patients with constipation (Dimidi, Christodoulides, Fragkos, Scott, & Whelan, 2014).

Probiotics can be bacteria or yeast. The most common bacterial probiotics include *Lactobacillus* and *Bifidobacterium* groups. These include a number of different strains including *L. rhamonusus, L. bulgaricus, L. salivarius, L. plantarum, L. casei, B. infantis,* and *B. longum*. The most common beneficial yeast is *Saccharomyces boulardii*. In order for probiotics to be effective, they must be able to adhere to the gut epithelium cells, eliminate or reduce pathogenic adherence, produce and multiply acids, such as, hydrogen peroxide, which will ultimately protect the digestive tract against pathogen growth (Castellazzi et al., 2013).

Research on the benefit of probiotic supplementation is often strain specific (Waller et al., 2011). For example, *L. rhamnosus GG* is a specific strain that has been shown to be beneficial in antibiotic-associated diarrhea (Hickson, 2013; McFarland, 2008; Suardi, Crippa, & Monforte, 2013). This is important because in the United States, it is estimated that 258 million course of antibiotics were prescribed in 2010; that is 833 antibiotic prescriptions per 1,000 people (Hickson, 2013). The incidence of antibiotic associated diarrhea is estimated to affect up to 30% of adults prescribed antibiotics (McFarland, 2008). Probiotics can be recommended prophylactically to prevent antibiotic associated diarrhea. Individuals that supplement probiotics containing S. boulardii while taking an antibiotic have half the risk of getting antibiotic associated diarrhea compared to those not taking this yeast (Hickson, 2013).

Bifidobacterium lactic HN019 is a probiotic strain for which many health benefits have been established, primarily related to immune enhancement (Waller et al., 2011). Dietary consumption of the probiotic *B. lactis HN019* is well tolerated, decreases whole gut transit time

in a dose-dependent manner, and reduces the frequency of functional gastrointestinal symptoms in adults (Waller et al., 2011).

According to the Natural Medicines database, the level of evidence associated with probiotics is a grade A (strong scientific evidence) for acute diarrhea and atopic dermatitis and a grade B (good scientific evidence) for cirrhosis, dental caries, growth, immune enhancement, irritable bowel syndrome, sinusitis, and ulcerative colitis (Natural Standards, 2015c). Natural Medicines is an international research database that maintains up to date, comprehensive systematic reviews on complementary and alternative medicine. It adheres to the most recent recommendations of the Institute of Medicine for all systematic reviews and clinical practice guidelines. The editorial board performs multiple rounds of blinded multidisciplinary peer review methodologies to ensure the accuracy of the information.

Probiotics have been shown to be safe with minimal adverse effects. Consumers can easily find probiotics in natural food sources, such as kefir, yogurt, or Kombucha. Probiotics can also be found in the form of a supplement over the counter at grocery stores or health food stores. A meta-analysis of 28 randomized controlled studies found probiotics to be safe with no adverse effects reported in any of the 28 studies (Hungin et al., 2013). Probiotics are not metabolized through the CYP 450 system; therefore they do not interact with other medications that are metabolized through the CYP 450 system. The therapeutic dose of probiotics is important, however the ideal recommended dose remains unclear (Hickson, 2013). There are currently no clinical guidelines for the recommendation of probiotics in the outpatient setting. Although there is an abundant amount of evidence to support probiotics, the specific strains, dose, and duration vary depending on the study conducted. Therefore, future research is needed to assess what strains, specific doses, and duration are the most beneficial. At Atlanta Center for

Holistic and Integrative Medicine the protocol for restoring digestive utilizes multi-strain probiotics with at least 20 billion CFUs.

Glutamine

Glutamine is a functional amino acid that has several beneficial properties in the digestive tract (Wang et al., 2014). In healthy individuals, glutamine is the most abundant amino acid in muscles and plasma; however, after injuries, surgeries, or infection, glutamine concentration significantly decreases (Mochiki et al., 2011). Glutamine is naturally found in several foods including grass-fed beef, bison, chicken, eggs, whey protein, and certain cheeses. Health food stores sell glutamine over the counter as a supplement in the form of a capsule or powder. Glutamine is often added to protein powders or other nutritional shakes. L-glutamine has been shown to help maintain the intestinal barrier function and help fight off foreign microorganisms including bacteria, viruses, and funguses (Resnick, 2010). In recent years, glutamine has been researched for its role in gut mucosal turnover and function (Mochiki et al., 2011). Supplementing glutamine for gastrointestinal discomfort has been shown to improve the intestinal mucosal barrier by regulating the expression of genes and proteins that are involved in cell proliferation, differentiation, and apoptosis, protein turnover, anti-oxidative property, and immunity responses (Wang et al., 2014).

Glutamine is required for the normal production of immunoglobulin A in the intestines, which is a key factor in immune support (Resnick, 2010). Glutamine has been shown to have anti-inflammatory benefits in the intestinal tract (Ren et al., 2013) and can regulate the metabolism of intestinal bacteria in the digestive tract (Wang et al., 2014). LDH or Lactate Dehydrogenase is an enzyme that is released when tissues are damaged. LDH activity was

significantly decreased ($p < 0.05$) when participants were given antioxidants and glutamine (Ziegler, Seddiki, Marion-Letellier, Lavoinne, & Déchelotte, 2011).

Intestinal permeability and morphology was significantly improved with glutamine supplementation (Benjamin et al., 2012). Glutamine significantly improved motor activity in the duodenum after gastric surgery (Mochiki et al., 2011). When used at the right dose, glutamine can be protective and prevent the increasing intestinal permeability seen in patients that are chronically ill (De-Souza & Greene, 2005; Sevastiadou et al., 2011). The therapeutic dose varies greatly across each research study; however, the ACHIM's protocol for restoring digestive health utilizes 2-3 grams. In practice, this has seemed to be the most beneficial at improving gastrointestinal symptoms while scientific evidence varies. By decreasing the intestinal permeability, glutamine can reduce the frequency of infections and reduce the translocation of intestinal bacteria and toxins (Camilleri, Madsen, Spiller, Van Meerveld, & Verne, 2012; De-Souza & Greene, 2005).

When intestinal permeability is improved, intestinal absorption is improved (Leite et al., 2013). This is an important concept to understand when treating individuals with diarrhea. Diarrhea can cause decreased absorption of vitamins and minerals because the total transit time is increased. One study found that in patients with diarrhea, absorption was significantly improved with glutamine supplementation (Leite et al., 2013). Glutamine has the power to improve patients overall gastrointestinal function and health (Camilleri et al., 2012). Therefore, it is a key component of the restoring digestive health protocol.

The FDA is heavily researching glutamine, with 174 studies being conducted regarding the effectiveness and safety of glutamine (Clinical Trials, n.d). Glutamine is shown to be safe with minimal to no risk factors even in studies conducted on premature infants (Sevastiadou et

al., 2011). Glutamine is not metabolized through the CYP 450 system; therefore it does not interact with medications that are metabolized in the CYP 450 system. According to Natural Medicines' database, glutamine's level of evidence is a grade A (strong scientific evidence) for burns and a grade B (good scientific evidence) for total parenteral nutrition during trauma or post-surgery and grade C (unclear or conflicting scientific evidence) for the critically ill, inflammatory bowel conditions, mood, malnutrition, septicemia, transplants, and supplementation in preterm and very low birth weight infants (Natural Standards, 2015a).

Digestive Enzymes

The concept of supplementing digestive enzymes is not new. For over seventy years scientist have been researching the benefits of digestive enzymes (Stout, 2013). As individuals age, the amount of digestive enzymes produced by the body declines. Supplementing digestive enzymes can improve digestion, reduce abdominal distress, and result in a greater assimilation of vital nutrients like vitamins K, D, and omega-3 and omega-6 (Stout, 2013). Protease helps the body breakdown protein and absorbs the essential nutrients in proteins (amino acids) (Stout, 2013; Whitcomb & Lowe, 2007). Lipase helps the body breakdown fatty acids, which is essential for the absorption of fat-soluble vitamins, such as, vitamin A, E, D, and K (Stout, 2013; Whitcomb & Lowe, 2007). Digestive enzymes allow the digestive tract to rest and recover.

Adequate digestion is required for gastrointestinal health; inadequate digestive enzymes are correlated with malabsorption, food intolerance, food allergy, autoimmune, bacterial overgrowth, and gastrointestinal discomfort (Resnick, 2010). In the small intestine, there are digestive enzymes that are produced by the pancreas for the hydrolysis of complex nutrients (Kaur & Sekhon, 2012; Whitcomb & Lowe, 2007). The main digestive enzymes that the body uses include protease, amylase, sucrase, lipase, lactase, and maltase (Kaur & Sekhon, 2012).

Digestive enzymes can be supplemented or found naturally in foods. Food enzymes are produced externally and are derived solely from raw foods like animal or plant products and supplements. Protease, lipase, amylase, bromelain, and cellulose are plant based while pepsin, is an animal based enzyme (Kaur & Sekhon, 2012). Naturally occurring food enzymes are found in bananas, papaya, kiwi, bee pollen, raw honey, avocado, grapes, pineapple, extra virgin olive oil, dates, and certain raw oils and sprouts (Kaur & Sekhon, 2012). Digestive enzymes particularly protease, bromelain, and lipase can be extremely beneficial in reducing symptoms and restoring a balanced digestive tract (Kaur & Sekhon, 2012).

Pancreatic enzyme products contain the active ingredient pancrelipase, a mixture of the digestive enzymes amylase, lipase, and protease (Kaur & Sekhon, 2012). Cellulase and protease have been shown to be beneficial in controlling candida overgrowth (Kaur & Sekhon, 2012). Cellulase enzyme breaks down fiber and it is the only digestive enzyme the body does not make (Kaur & Sekhon, 2012). The enzyme protease has the ability to hydrolyze protein. Protease has been used in clinics all over the world to break down Candida and prevent its overgrowth (Kaur & Sekhon, 2012). Lactase supplements are used to help treat lactose intolerance. Lactase chewable tablets consists of an enzyme that helps consume dairy foods without producing gas, cramps, bloating, or diarrhea in the patient (Kaur & Sekhon, 2012). Digestive enzymes are supplemented in combination with lipase to digest fat, amylase to digest starchy carbohydrates, and protease to digest protein.

Digestive enzymes as supplements along with meals share the workload of body's own pancreatic enzymes for digestion (Kaur & Sekhon, 2012). Pancreatic enzyme replacement therapy is currently the mainstay of treatment for nutrient malabsorption, secondary pancreatic insufficiency, cystic fibrosis, chronic pancreatitis, pancreatic and periampullary cancer (Kaur &

Sekhon, 2012). Reported data demonstrated efficacy in reducing steatorrhea and fat malabsorption (Kaur & Sekhon, 2012).

Digestive enzymes as supplements may bring improvement in health problems such as heartburn, indigestion, gastrointestinal reflux disease, diarrhea, constipation, diabetes, bloating, and host of other health problems (Kaur & Sekhon, 2012). Supplemental proteolytic enzymes are derived from plant and animal sources. Common proteases include bromelain from pineapple, papain and chymopapain from papaya (Kaur & Sekhon, 2012). The fungal protease from the Aspergillus oryzae fungi and the trypsin, chymotrypsin, and pancreatin usually from porcine or bovine origin (Kaur & Sekhon, 2012)

The FDA currently has 3677 studies regarding the effectiveness and safety of digestive enzymes (Clinical Trials, n.d). According Natural Medicines' database, digestive enzyme's level of evidence is a grade C (unclear or conflicting scientific evidence) for digestive enzyme insufficiency, hiatal hernias, and recovery from surgery (pancreatic, gastrectomy) (Natural Standards, 2015c). At Atlanta Center for Holistic and Integrative Medicine the most common digestive enzymes utilized in the restoring digestive health protocol are called GFCF Similase. This digestive enzymes is a purely plant based product that consists of protease I, II, III, IV, V, amylase, lipase I, II, phytase, lactase I, II, cellulose I, II, and sucrase. However, there are several other digestive enzymes available on the market including bromelain sources or betaine HCL. The specific digestive enzymes used in this study are not metabolized by the CYP 450 system; therefore they do not interact with medications that are metabolized by the CYP 450 system.

Age

Patient age range most affected by Functional Gastrointestinal Disorders remains vague and inconsistent. Research studies have found a wide-range of ages affected from childhood to

adulthood. A case-control study of 23,471 diagnosed with Functional Gastrointestinal Disorders was conducted in the United Kingdom. The mean age for this study was 51.4 years old (Ford et al., 2014). A study examined the prevalence of Functional Gastrointestinal Disorders among 3,976 adolescents (10-17 years old) from 40 different schools. The study found that 552 students met the criteria for Functional Gastrointestinal Disorders. Although this study was conducted on adolescents, the results showed that the prevalence of Functional Gastrointestinal Disorders significantly increased as the adolescents aged (Sagawa et al., 2013). A European study examined 199 patients with Functional Gastrointestinal Disorders and found the mean age to be 50 years old, ranging from 21-85 years old (Lahner et al., 2013). Another study examined 3,600 individuals with Functional Gastrointestinal Disorders (Ford et al., 2014). The mean age for irritable bowel syndrome, functional diarrhea, and chronic idiopathic constipation was 38-42 years old, 48 years old, and 52 years old respectively (Ford et al., 2014). Other studies have found that individuals younger than 50 years old are affected by irritable bowel syndrome more frequently (Scalera & Loguercio, 2012). As evident by the supporting studies, Functional Gastrointestinal Disorders do not discriminate, affecting all ages.

Gender

Functional Gastrointestinal Disorders affect females more frequently than males, yet the etiology behind this remains unknown (Markert et al., 2014). Possible theories for the female predominance include hormonal variations and perceived stress. Ford et al. (2014) found females to suffer more frequently from Functional Gastrointestinal Disorders including irritable bowel syndrome, functional dyspepsia, and chronic idiopathic constipation. In Western countries, irritable bowel syndrome is more common in females with a one to three ratio of males to females (Scalera & Loguercio, 2012). One study found women to have a 20% higher rate of

ambulatory visits related to gastrointestinal symptoms than men (Myer et al., 2013). A study conducted on adolescent found females to have a significantly higher prevalence of Functional Gastrointestinal Disorders compared to male students (Sagawa et al., 2013).

In contrast, an epidemiological study was conducted in Mexico to determine the prevalence of Functional Gastrointestinal Disorders. This study found that all Functional Gastrointestinal Disorders were equally prevalent among both genders except for irritable bowel syndrome and functional constipation which were found to be more prevalent in women (López-Colombo et al., 2012). A large Internet survey was conducted in Japan to evaluate the lifestyle of individuals suffering with Functional Gastrointestinal Disorders (Miwa, 2012). The results of this study showed that the prevalence of functional dyspepsia and irritable bowel syndrome were significantly higher in women than males (Miwa, 2012). A study conducted on 31,866 U.S military personnel diagnosed with Functional Gastrointestinal Disorders found an overall higher incidence of Functional Gastrointestinal Disorders among females compared to males (Porter et al., 2011). Specifically, this study found a seven-fold higher rate of functional constipation among females compared to males (Porter et al., 2011). The case-control study conducted in the United Kingdom found a higher prevalence of females diagnosed with Functional Gastrointestinal Disorders (66.1%) (Ford et al., 2014). Another study conducted in Europe, found a female predominance (75.9%) when assessing 199 individuals with Functional Gastrointestinal Disorders (Lahner et al., 2013).

Ethnicity

There are limited studies assessing the role ethnicity plays on Functional Gastrointestinal Disorders. One study found that there were not any significant differences in ambulatory visits related to gastrointestinal symptoms between Caucasians and African Americans (Myer et al.,

2013). Ford et al. (2014) found the majority of irritable bowel syndrome (87.4%) and chronic idiopathic constipation (88.9%) patients to be Caucasians.

Weight and Waist Circumference

The majority of the studies related to Functional Gastrointestinal Disorders, found that individuals that are overweight or obese suffer from Functional Gastrointestinal Disorders symptoms more frequently. A study was conducted on 450 children with 42% overweight or obese and 58% normal weight (Phatak & Pashankar, 2014). The results of this study found that in children, obese and overweight participants (47%) had a higher prevalence of Functional Gastrointestinal Disorders than normal-weight children (27%) (Phatak & Pashankar, 2014). A study conducted on 199 European adults diagnosed with Functional Gastrointestinal Disorders found the average body mass index to be 39.2, which is considered class II obesity (Lahner et al., 2013).

An increased weight circumference is associated with an increased risk of irritable bowel syndrome (Lee et al., 2015). A descriptive study was conducted in Turkey to evaluate how obesity affects gastrointestinal quality of life (Yilmaz, 2013). The results of this study found that obese patients suffer from gastrointestinal symptoms more frequently and have a decreased quality of life based on the Gastrointestinal Quality of Life Index (Yilmaz, 2013).

A prospective cohort study examined 35,447 adults to examine the relationship between BMI and Functional Gastrointestinal Disorders (Le Pluart et al., 2015). This study found that females with a high BMI had a significantly increased risk for functional diarrhea; however both high and low BMIs were shown to have an increased risk for functional dyspepsia (Le Pluart et al., 2015). In men, those with a lower BMI were found to have a greater risk for irritable bowel syndrome (Le Pluart et al., 2015). A smaller case-controlled study with 336 individuals found

that overall BMI was not a good predictor for irritable bowel syndrome; yet, abdominal fat and an increased waist circumference were better predictors of irritable bowel syndrome, specifically irritable bowel syndrome with diarrhea (Lee et al., 2015).

Quality of Life

Several studies have been conducted to examine the correlation of Functional Gastrointestinal Disorders symptoms and quality of life. Adolescents suffering from Functional Gastrointestinal Disorders had a significantly lower quality of life score (Sagawa et al., 2013). Individuals suffering from Functional Gastrointestinal Disorders were shown to have impairments in sleep, eating habits, diet, exercise, and feelings of excessive stress (Miwa, 2012). A random sample of 1,001 Swedish adults was conducted to assess the impact functional dyspepsia has on quality of life (Aro et al., 2011). This study used the Short Form-36 questionnaire to assess eight domains related to quality of life including physical, mental, and social aspects (Aro et al., 2011). The results of this study found a statistically significant impact on health-related quality of life ($p < .05$) in all the Short Form-36 domains except for Role Emotional (Aro et al., 2011).

Singh et al. (2012) conducted a study to examine the prevalence of somatic and psychiatric co-morbidities seen in patients with irritable bowel syndrome and how the disorder affects the participants' quality of life. The study evaluated 184 participants diagnosed with irritable bowel syndrome and 198 controlled participants. Major depressive disorders, somatoform disorders, and panic disorders were more common in patients suffering from irritable bowel syndrome than in the controls (Singh et al., 2012). Quality of life was significantly lower in patients with irritable bowel syndrome when compared to the control group based on the World Health Organization (WHO) QOL-BREF (Singh et al., 2012).

Lackner et al. (2014) conducted a study with 234 individuals with irritable bowel syndrome to determine what factors reduced the individual's quality of life. The results of this study found that fear of gastrointestinal symptoms related to irritable bowel syndrome was the most strongly associated with reduced quality of life (Lackner et al., 2010; Lackner et al., 2014). This factor was shown to triumph other factors, such as symptom severity, personality, sociodemographics, and overall emotional wellbeing (Lackner et al., 2010.; Lackner et al., 2014).

Stress

Those suffering from Functional Gastrointestinal Disorders are thought to have higher stress levels. Markert et al. (2014) conducted a study on two different universities in Switzerland to evaluate the association between stress and digestive symptoms. A total of 1901 participants completed the survey online with 1857 participants included in the study. Of the sample, 62.78% met the criteria for at least one Functional Gastrointestinal Disorders. The results of this study found that those with higher levels of self-reported stress had worse symptoms (Markert et al., 2014).

Another study was conducted on 105 patients diagnosed with irritable bowel syndrome to examine the association between social support and the severity of irritable bowel syndrome (Lackner et al., 2010). The Perceived Stress Scale was used to measure how the participants appraised the amount of stress in their life. This study found that perceived stress significantly predicted pain severity ($p < 0.05$) (Lackner et al., 2010).

Duration of Symptoms

When conducting the literature review, minimal information was obtained regarding the mean duration of Functional Gastrointestinal Disorder symptoms. However, the majority of the

studies used the diagnosis of Functional Gastrointestinal Disorders as having experienced functional symptoms involving the upper and/or lower gastrointestinal tract over the past 6 months at least one time per week (Lahner et al., 2013).

Number of Attempted Treatments

Conventional or standard treatment for functional gastrointestinal disorders is symptom management through laxatives, antidiarrheal, antispasmodics, or antidepressants. It is estimated that less than 50% of patients with irritable bowel syndrome are satisfied with their treatment plan (Aucoin, 2014). Therefore, 21-51% of irritable bowel syndrome patients are seeking complementary and alternative modalities (Aucoin, 2014). Historically, treatment of Functional Gastrointestinal Disorders focused on symptom relief through conventional medications. However, symptom control has not been effective means for managing the symptoms associated with Functional Gastrointestinal Disorders (Lahner et al., 2013).

Failure of conventional therapy may be related to the poorly understood pathology and the vast psychological factors associated with Functional Gastrointestinal Disorders (Lahner et al., 2013). Due to the lack of success with conventional therapy, individuals suffering from Functional Gastrointestinal Disorders are beginning to try complementary and alternative medicine therapies. A study was conducted on 199 patients diagnosed with Functional Gastrointestinal Disorders to examine patients' current treatment modalities for the management of Functional Gastrointestinal Disorders (Lahner et al., 2013). The results show that roughly half of the patients in the study used some sort of CAM (48.7%) including herbal medicine (36.7%) and homeopathy therapy (17.1%) (Lahner et al., 2013). Natural remedies include a dietary approach (64.3%), exclusion diets (39.7%), probiotics (31.7%), and prebiotics (22.6%). Two-thirds of the patients used more than one treatment option for the management of symptoms:

34.7% conventional medications, CAM, and dietary supplements, 17.1% conventional medications and dietary supplements, 10.1% diet and CAM, and 5% conventional medications and CAM (Lahner et al., 2013). When examining conventional medications, the largest drug class utilized includes proton pump inhibitors (42.2%), antispasmodics (34.2%), anti-acids (29.1%), and prokinetics (29.1%) (Lahner et al., 2013).

Theoretical Framework

Betty Neuman's Healthcare System Model

Understanding the basic assumptions of Betty Neuman's Healthcare System Model is important when restoring digestive health. Betty Neuman's Healthcare System Model stresses the fact that each client's system is unique; therefore, no two patients are created equal. Within each system there are known, unknown, and universal stressors that occur within each client's life (Neuman, 1989). These stressors have the ability to disturb the client's stability. The term "wellness" can be thought of as a continuum with optimal wellness on one side and illness on the other side. When caring for patients with functional gastrointestinal disorders, the goal is optimizing their wellness and reducing their gastrointestinal symptoms. Individuals are continuously shifting along the continuum depending on internal and external stressors. Examples of internal stressors include anxiety and depression. External stressors include job stress, family stress, and social stress. At times, food sensitivities or environmental triggers could be aggravating gastrointestinal symptoms. Reducing known and unknown stressors can ultimately improve the patient's symptoms and healthcare outcomes.

Major concepts and terms explained in this theory include content, basic structure or central core, degree to reaction, entropy, negentropy, open systems, stability, and stressors. *Content* is the variables within each person's interaction with the internal and external

environment that comprise the whole person's system (Neuman, 1989). In patients with Functional Gastrointestinal Disorders, stress may be a variable that is compromising the whole person's system. The *basic structure* or *central core* is made up of the basic survival factors, such as, temperature and genetic structures (Neuman, 1989). Patients with digestive dysfunction have basic structures or survival factors embedded in their system to help overcome illnesses. For example, if patients are exposed to bacteria via ingestion, the body's natural mechanism is to speed up motility to eliminate the bacteria. This can cause diarrhea or loose stools. *Stability* or *homeostasis* is achieved when the energy that is available exceeds that being used by the system (Neuman, 1989). This process is constantly changing to maintain a state of balance with input, output, feedback, and compensation (Neuman, 1989). Stability or homeostasis is achieved in patients with Functional Gastrointestinal Disorders when there is resolution of gastrointestinal symptoms and balance is achieved. The *degree to reaction* is the amount of each system that is unstable due to the negative impact of stressors (Neuman, 1989). In patients with Functional Gastrointestinal Disorders the higher the degree of reaction, or the negative factors that cause the system to become unstable, the worse the gastrointestinal symptoms become. *Entropy* is the process of energy depletion and disorganization that ultimately moves the system towards illness or in this case functional gastrointestinal disorder symptoms (Neuman, 1989). *Negentropy* is the process of energy conservation that increases the organization and complexity of the system (Neuman, 1989). This makes the system more stable allowing the body to achieve a higher degree of wellness.

Neuman's model relies heavily on the concept of an open system. An *open system* is where all systems are in continuous interaction with each other and the environment (Neuman, 1989). In the human body, the digestive system interacts with numerous other systems including

the pancreas, gallbladder, and liver. The term *reconstitution* is used when the system has returned and maintained stability. Betty Neuman believes reconstitution is possible. Reconstitution typically occurs after an individual has defined and reduced his or her individual stressor. The end goal of Betty Neuman's Theory is stability, which is a state of balance and harmony. This is achieved when the patient adequately copes with stressors and maintains an optimal level of health and wellness. Overtime, this preserves the systems overall integrity.

When considering Betty Neuman's Healthcare System Model, it is important to remember that each client's system is in a state of dynamic and constant energy exchange with the environment. Research suggests that internal and external stressors can worsen gastrointestinal symptoms. As previously stated, internal stressors could be anxiety, emotional stress, or physical illness. There is clear evidence that anxiety and depression are positively correlated with abdominal pain (Walter et al., 2013). External stressors may be family illnesses, job deadlines, or schoolwork. There are several promising treatment options for reducing these stressors, such as mindfulness programs and cognitive behavior therapy. Studies have found that mindfulness programs can improve irritable bowel syndrome symptoms (Kearney, McDermott, Martinez, & Simpson, 2011). Mindfulness programs have the power to reduce the negative effects of external and internal stressors. GI-specific anxiety has been used to describe thoughts, emotions, and behaviors that revolve around the fear of developing gastrointestinal symptoms (Kearney et al., 2011). This is an endogenous stressor that can worsen intestinal function and cause visceral pain (Kearney et al., 2011). Research suggests that mindfulness training has been shown to significantly reduce bowel symptom severity, improve health-related quality of life, and reduce distress (Gaylord et al., 2011). The results found in this study showed that the positive benefits persisted for 3 months after treatment with mindfulness training (Gaylord et al.,

2011). Therefore, this is a cost-effective treatment with long lasting impact in the patients overall health. Another study found that increased perception of social support improved irritable bowel syndrome symptoms, specifically abdominal pain (Lackner et al., 2010). The social support seemed to reduce stress levels and ultimately improve irritable bowel syndrome symptoms (Lackner et al., 2010).

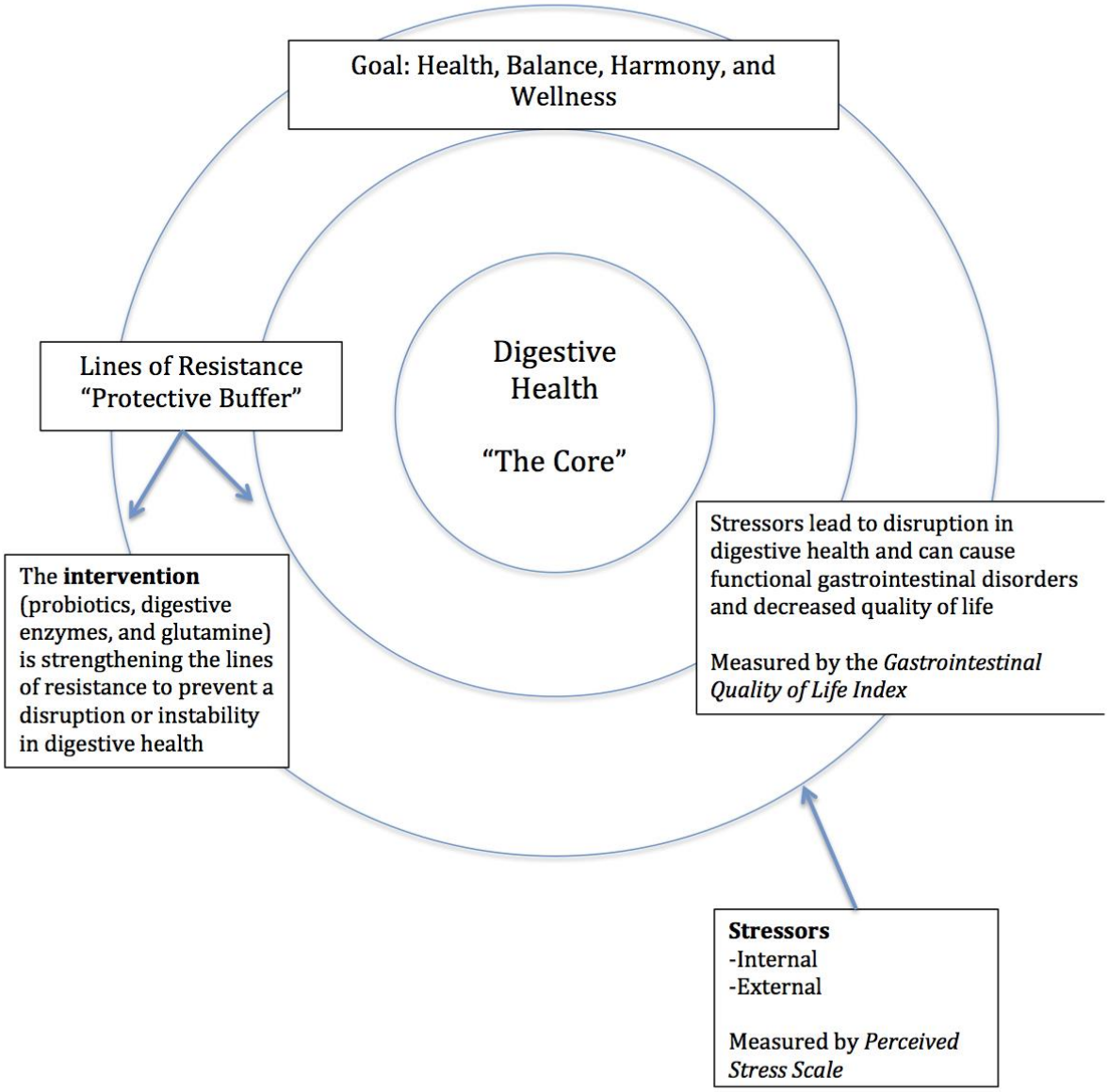

Figure 1. Applying Betty Neuman's Health Systems Model. Adapted from Neuman (1989).

CHAPTER III

Project Description and Methodology

Objectives

The specific aim of this project was to outline the healthcare problems associated with Functional Gastrointestinal Disorders and to explore the effectiveness of a gastrointestinal protocol implemented at Atlanta Center for Holistic and Integrative Medicine. This protocol was designed to help restore digestive health.

The purpose of the proposed translational research project was to determine if adult patients with Functional Gastrointestinal Disorders would report improved symptoms based on the Gastrointestinal Quality of Life Index after eight weeks of probiotics, digestive enzymes, and glutamine. Each one of the components of this intervention served a unique purpose. The probiotics were used to help improve the bacterial gut morphology. The digestive enzymes helped facilitate digestion and absorption of nutrients from food, which allowed the digestive tract time to rest and heal. Glutamine was used to calm inflammation, improve intestinal permeability, and heal the intestinal lining. The primary objective of this research project was to quantify a well-established protocol utilized at the Atlanta Center for Holistic and Integrative Medicine. This practice's protocol focuses heavily on restoring digestive function, since a normally functioning digestive tract is essential for overall health and wellbeing.

Project Design and Procedures

The design for this translational research project was a prospective cohort study. The subjects in this study were examined at baseline, weekly, and after eight weeks of intervention with probiotics, digestive enzymes, and glutamine. This design was appropriate to examine the effectiveness of the restoring digestive health protocol in adults with gastrointestinal symptoms.

Below is a brief overview of the project design. Each component will be further discussed in the following sections. A flow diagram for the research study can be found under Appendix A.

Consent from Atlanta Center for Holistic and Integrative Medicine and Georgia College and State University Institutional Review Board was obtained prior to beginning the recruitment of participants for this study. After receiving IRB approval, the researcher enrolled subjects that met the inclusion criteria. Recruitment was initiated in May 2015 from Atlanta Center for Holistic and Integrative Medicine. The subjects were virtually recruited through ACHIM's newsletters and Facebook wall. An example of the flyer used in the newsletter and on Facebook can be found under Appendix B. Participants that expressed interest in participating in the research study received a detailed informed consent to his or her email. An example of the informed consent can be found in Appendix C.

If the participants would like to participate after reading the full informed consent, the consent was signed and either faxed or scanned directly to the researcher. The researcher reviewed each informed consent to ensure the participant answered "no" to the alarming symptoms based on the Rome III criteria. If a participant answered "yes" to any of the exclusion criteria, they were not allowed to participant in the study. Once the informed consent was signed and received by the researcher, the qualified participants received a welcome email with detailed instructions for the research study. Each subject voluntarily participated with the ability to cancel his or her participation at any time during the study without reason. Participants that lived close to ACHIM had the option to personally pick up the supplements (probiotics, digestive enzymes, and glutamine) and those that did not live close had the supplements mailed directly to his or her house at the researcher's expense.

The welcome email included links to an introduction video, a video demonstrating how to accurately measure weight and waist circumference, baseline questionnaires administered through survey monkey and a study checklist. The introduction video clearly outlined the purpose of the research study and an official thank you for his or her time and participation. The video explained the expected time commitment, his or her rights to withdraw at any time, the confidentiality in data collection, analysis and reporting of findings. The next video explained to each participant the importance of consistency for weekly weigh-ins and waist circumference measurements. The video outlined (step by step) how to accurately measure his or her waist circumference and weight. An identification number was assigned to each participant prior to starting data collection. All participants were prompted to put in their unique identification number on each electronic questionnaire and weekly update. Only the principal investigator had access to the participant's identity and identification number. All information obtained was encrypted and password protected on a secure network. The initial assessment questionnaire included demographic data (age, gender, and ethnicity), duration of symptoms, number of attempted treatments, waist circumference, weight, Perceived Stress Scale, and the Gastrointestinal Quality of Life Index. The baseline questionnaire was completed prior to starting the intervention of probiotics, digestive enzymes, and glutamine. The study checklist could have been printed and kept as a reminder for each step during the research study. An example of the study checklist can be found under Appendix D.

To enhance compliance and active involvement, each participant received a weekly email through survey monkey. Survey monkey was used to collect the data because it has the ability to automatically sync with SPSS version 22.0. The weekly questionnaire would prompt individuals to enter their unique identification number prior to answering the four questions: (1) how many

supplements did you miss in the previous week; (2) what is your current weight; (3) what is your current waist circumference; and (4) any additional comments at this time. The purpose of the weekly weight and waist circumference was to determine the timing of significant change, minimize missed supplements, and encourage active participation. If participants missed more than 2 weekly entries, their data was excluded. However, if a participant missed a Wednesday survey the researcher sent two additional reminders to their email 24 hours apart. No participant was penalized for missing supplements because research shows even individuals on crucial medications can occasionally forget their daily dose. A study was conducted to assess how often individuals with epilepsy forgot their medication (Paschal, Rush, & Sadler, 2014). The results of the study found that 66% of the 180 subjects reported not taking their medication on a monthly basis due to "forgetfulness" (Paschal et al., 2014).

After the 8-week intervention of probiotics, digestive enzymes, and glutamine, a post-intervention questionnaire was administered through the participants preferred email. This email included the Perceived Stress Scale, Gastrointestinal Quality of Life Index, waist circumference, and weight. All data collected was analyzed to answer each specific research question and the results were disseminated at the Georgia Nursing Leadership Coalition's Doctorate Symposium in November of 2015. All data was reported in aggregate to keep patient confidentiality. Collected data will be kept on a secure network for five years.

Project Site

The researcher for this project is a Family Nurse Practitioner at Atlanta Center for Holistic and Integrative Medicine, located in Atlanta, Georgia. This practice is a unique fee-for-service practice with three physicians, two nurse practitioners, a registered dietician, a nutritionist, an acupuncturist and an Ayurveda therapist. The primary focus of the practice is to

integrate both mainstream conventional medicine and alternative therapies to heal the whole person and uncover the root cause of patients' symptoms.

The Founder of the Center, Dr. Tasneem Bhatia was a committee member for this translational research project. Letters of Support and the Statement of Mutual Agreement were obtained from Atlanta Center for Holistic and Integrative Medicine prior to beginning the study.

Sample

From May to June 2015, a convenience sample was obtained from the Atlanta Center for Holistic and Integrative Medicine (ACHIM). This practice sends out a virtual newsletter to over 5,000 people and it has a Facebook group with over 20,000 followers. Both the virtual newsletter and Facebook group were used to recruit subjects. While the primary researcher of this project works at ACHIM, she did not personally recruit patients to ensure participants did not feel coerced to participate. All subjects voluntarily enrolled in the study. Approval from the Institutional Review Board was obtained prior to recruiting subjects. Informed consent was obtained from each participant prior to data collection.

Inclusion Criteria. Adult patients (males and females) 18 to 65 years old with current complaints of gastrointestinal symptoms including, but not limited to constipation, abdominal pain, diarrhea, reflux, or bloating. Digestive symptoms had to be functional without a known organic cause. Each participant was required to have a physical exam within the 12 months of the research study. Participants must have been proficient in English and have access to email, a scale, and a tape measure (in centimeters). Each participant had to be able to follow directions. Participants who were willing and able to participate in the full course of the study signed the informed consent.

Exclusion Criteria. Exclusion criteria included patients younger than 18 years old or older than 65 years old, pregnant or nursing women, and any symptoms which may indicate significant health related problems based on the alarming symptoms in the Rome III Criteria. The primary researcher screened all participants based on the Rome III Criteria for alarming symptoms. The alarming symptoms used from the Rome III Criteria include: blood in stool, black stools, vomiting blood, anemia unrelated to menstrual cycle, fever, unintentional weight loss of greater than 10 pounds, over the age of 50 with a major change in bowel movements, persistent or worsening hoarseness of the voice, worsening throat pain over the past 3 months, chest pain on exertion, and difficulty swallowing. Participants under 18 years old were excluded from the study to avoid having to take into account growth and developmental factors. All participants diagnosed with an organic gastrointestinal disease were excluded including peptic ulcers, Crohn's disease, ulcerative colitis, or gastrointestinal tumors. Any participants that self-reported diseases that alter the function of the liver or kidney were excluded from the study including hepatitis, cirrhosis, non-alcoholic fatty liver disease, kidney disease, or organ transplants.

Sample size. The sample size was determined based on Warner's decision rule for calculating sample sizes with a power of 0.80 and an alpha of 0.05 (Warner, 2008) to test significance with R^2 with a medium effect (*F*2-0.15) the total N required was 80 + k where k was the number of independent variables. In this study, sample size was based on 10 independent variables. Based on Warner's formula, the sample size needed is 90 adult subjects with functional gastrointestinal symptoms. This study had 98 enroll in the study and 86 complete the entire 8-week intervention.

Supplements

The specific brands used in the restoring digestive health protocol at Atlanta Center for Holistic and Integrative Medicine include Metagenics, Integrative Therapeutics, and Orthomolecular. The same brands were used for this study for a number of reasons including the following: (a) to replicate the protocol as closely as possible; (b) to keep consistency among each participant; (c) to ensure the high quality supplements were used. The following products were donated for the research study: Glutagenics by Metagenics (glutamine powder), Orthobiotic by Orthomolecular (probiotic), GFCF Similase by Integrative Therapeutics (digestive enzymes). Since the products were donated, the study was free for participants. The researcher received no compensation by the companies and does not promote specific brands.

Instruments

The instruments utilized in this study include the Gastrointestinal Quality of Life Index, the Perceived Stress Scale, weight, and waist circumference. The following section discusses these instruments.

Gastrointestinal Quality of Life Index. Defining distress is often difficult because it is a subjective term. Researchers often validate distress by quantifying and measuring the patients' quality of life through appropriate instruments, such as the Gastrointestinal Quality of Life Index (GQOLI) as used in this study. It is evident that there is a direct correlation between gastrointestinal symptoms and quality of life (Naliboff et al., 2012; Tielemans et al., 2013). Unfortunately, there is limited research investigating the impact of subjective distress and Functional Gastrointestinal Disorders (Markert et al., 2014). The instrument utilized in this translation research project was the Gastrointestinal Quality of Life Index (Eypasch et al., 1995). Prior to using this tool, permission was obtained via email from the instrument's designer. The

Gastrointestinal Quality of Life Index was developed in 1995 by 4 surgeons and 3 methodologists (Eypasch et al., 1995). This instrument was developed to help healthcare providers better measure quality of life specific for the gastrointestinal tract. The GIQLI is a 36-Likert item GI-specific Health Related Quality of Life (HRQL) instrument designed to assess HRQL in clinical practice and clinical trials of patients with gastrointestinal disorders (Eypasch et al., 1995). The GIQLI has five sub scales (Gastrointestinal symptoms, Emotion, Physical Function, Social Function, and Medical Treatment) as well as a total score (Eypasch et al., 1995). Each of the items was scored on a five point Likert scale with a range from 0 (most negative) to 4 (most positive). Possible total scores ranged from 0-144 points (Eypasch et al., 1995). The Intraclass Correlation Coefficient (ICC) was .92 which denotes a high level of reliability and the internal consistency based on Cronbach's Alpha ranged from .90 to .93 (Eypasch et al., 1995). This instrument has been used and validated in a variety of cultures.

In the United States, a study was conducted to evaluate gastrointestinal symptoms in liver transplant patients after the conversion from mycophenolate mofetil to enteric-coated mycophenolate sodium (Toledo et al., 2012). The GIQLI was administered to the participants at baseline and three months later. The instrument was able to capture significant improvements from baseline to three months in gastrointestinal quality of life ($p < .05$) (Toledo et al., 2012). However, this article did not report the internal consistency.

A pilot study was conducted in the United States to assess the quality of life in pediatric patients after a laproscopic cholecystectomy for biliary dyskinesia (Maxwell, Thompson, Richmond, McCagg, & Ubert, 2012). This study administered the GIQLI to both the parents and children. The results were similar between the parents and the children indicating homogeneity (*r*

= .93) (Maxwell et al., 2012). The study found those patients suffering from long-term symptoms have lower quality of life than those with symptom resolution (Maxwell et al., 2012).

Machnicki et al. (2008) conducted a longitudinal, observational study involving five South American centers. The purpose of this study was to evaluate the reliability and validity of two different GI-specific outcome measures (Gastrointestinal Symptom Rating Scale (GSRS) and Gastrointestinal Quality of Life Index) in renal transplant patients. Each participant completed the GSRS, GIQLI, and Psychological General Well-Being Index at baseline and at 4 – 6 weeks. The GIQLI total and sub scale scores demonstrated excellent internal consistency reliability (.78 - .96) (Machnicki et al., 2008).

Borgaonkar & Irvine (2000) conducted a thorough literature review to evaluate ways to reliably measure quality of life as it relates to gastrointestinal and liver disorders. The results of the literature review found the GIQLI to be both valid and reliable. Construct validity was supported by demonstrating a reasonable correlation with the Spitzer quality of life index (r = .53) and the Bradburn aVect balance scale (r = .42) in 204 German patients with a variety of GI illnesses (Borgaonkar & Irvine, 2000). The test-retest reliability was found to be excellent with an ICC of .92 as was internal consistency ($\alpha > .90$) (Borgaonkar & Irvine, 2000).

A study was conducted in the Netherlands to validate the GIQLI for patients with periampullary tumors (van Dijkum et al., 2000). The GIQLI has been shown to be valid and reliable based on the Cronbach's alpha of each sub-score including, total score (.93), physical well-being (.91), gastrointestinal digestion (.83), gastrointestinal defecation (.75), and mental well-being (.87) (van Dijkum et al., 2000).

Sandblom et al. (2009) validated a Swedish version of the GIQLI in patients with gallstones. The purpose of this study was to evaluate the sensitivity to change, internal

consistency, and test–retest stability of the instrument on 187 consecutive patients who underwent planned cholecystectomy (Sandblom et al., 2009). Construct validity was assessed by comparing the GIQLI score with the SF-36 in a separate group of patients. The intraclass correlation was .85 (95% CI [.73–.92]) for the global score, .87 (95% CI [.76–.93]) for symptoms, .83 (95% CI [.70–.91]) for physical dysfunction, .68 (95% CI [.46–.81]) for emotional dysfunction, .63 (95% CI [.40–.79]) for social dysfunction, and .62 (95% CI [.38–.78]) for effect of medical treatment (Sandblom et al., 2009). The Cronbach's alpha was .92 for the global score, .89 for symptoms, .84 for physical dysfunction, .83 for emotional dysfunction, and .77 for social dysfunction (Sandblom et al., 2009). Therefore, the Swedish version of the GIQLI was shown to be valid, reliable, and sensitive enough to yield significant results ($p < .05$) (Sandblom et al., 2009).

Chen et al. (2005) conducted a study to evaluate the quality of life in patients who underwent laparoscopic versus open cholecystectomy. Each participant completed the GQLI preoperatively and at 2, 5, 10, and 16 weeks postoperatively (Chen et al., 2005). This instrument was shown to be a valid and reliable way to detect significant changes ($p < 0.05$) in gastrointestinal-specific quality of life after surgery (Chen et al., 2005).

Perceived Stress Scale. The Perceived Stress Scale (PSS) is a self-reported questionnaire designed to measure the degree to which a person perceives a given situation as markedly stressful compared to the individual's ability to cope (Cohen, Kamarck, & Mermelstein, 1983). The primary goal of the instrument is to provide a global and subjective way to measure perceived stress (Cohen et al., 1983) and to assess the general predisposition an individual may have to experience stress (Morgan, Umberson, & Hertzog, 2014). This instrument has been described as the most popular measure for perceived stress (Karam et al., 2012). The PSS has

been translated into over twenty-five languages including Arabic, Swedish, Spanish, Chinese, Japanese and Turkish versions (Andreou et al., 2011; Taylor, 2014). Currently, there are three versions of the PSS: the original 14-item scale (PSS-14), the 10-item scale (PSS-10), and the 4-item scale (PSS-4) (Taylor, 2014).

In previous studies, the PSS-14 was shown to have good internal consistency with a Cronbach alpha of .86 (Cohen et al., 1983). Through further investigating, the developers of the PSS-14 found four of the items to be poor indicators of perceived stress and created the more widely used and researched PSS-10 (Taylor, 2014). The PSS-10 is a 10-item Likert-type scale with answers ranging from 0 - 4 (0 = never, 1 = almost never, 2 = sometimes, 3 = fairly often, 4 = very often) (Barbosa-Leiker et al., 2013; Taylor, 2014). Number 4, 5, 7, and 8 are reverse-scoring items (Taylor, 2014). Total scores are calculated after reversing positive items scores ranging from 0 - 40, with higher scores indicating greater perceived stress.

The scale was first shown to be reliable when it was tested on a sample of college students in comparison to the life-event scores (Cohen et al., 1983). The results presented showed that the PSS was a better predictor of the outcomes related to stress than the life-event scores (Cohen et al., 1983). The results of the PSS were further strengthened with the correlation of elevated cortisol levels with higher PSS scores (Ezzati, 2013). Through the initial testing of the PSS, the internal consistency reliability coefficients for the negative subscale of PSS-14, PSS-10, and PSS-4 were .83, .83, and .67, respectively and the positive subscales of PSS-14, PSS-10, and PSS-4 were .86, .81, and .71, respectively. The total scores of the PSS-14 and PSS-10 had similar internal consistencies with a Cronbach's alpha of .83 and .82 respectively, however the PSS-4 was not found to be reliable with a Cronbach's alpha of .68 (Andreou et al., 2011; Cohen et al., 1983).

The scale was further assessed on healthy adults and found an adequate reliability with Cronbach's alpha of .78 (Barbosa-Leiker et al., 2013). Another study found the PSS-10 to be a reliable tool when measuring perceived stress in pregnant women taking anti-depressants with a Cronbach's alpha of .90 (Karam et al., 2012). Another study was seeking to validate the Swedish version of the PSS-10; the results showed that the PSS-10 presents normally distributed data, good internal reliability (α = .84), and good construct validity with anxiety (r = .68), depression (r = .57), and mental and physical exhaustion (r = .71) (Nordin, 2013). Being that Nordin (2013) studied the reliability and validity of the PSS-10 twenty-five years after its development and with a different culture and still found comparable results, indicates that the PSS-10 is not culture-sensitive rather it assesses the basic human reaction to stressful life events (Nordin, 2013). This instrument is broad and can be applied to a platitude of situations. It has been used as both an outcome variable and a predictor variable (Morgan et al., 2014).

For the purpose of this study, the PSS-10 was used. As outlined, this instrument has been shown to be reliable and valid. It has been heavily researched in many different cultures and has few limitations. One identified limitation, which would be true to all instruments that measure stress is the gender bias. Females have been shown to have an overall higher level of stress than males, which may skew the results (Taylor, 2014).

Weight. Each subject was required to have access to a scale and was asked to use that same scale over the eight-week period. Weights were recorded at baseline, weekly, and post-intervention. Since each participant was weighing him or herself on a weekly basis, each scale was not calibrated. To enhance validity each participant received detailed instructions on how to accurately measure his or her weight. The most important factor when gathering accurate weight measurements was consistency. Therefore, each participant weighed his or herself on

Wednesday with the same scale, without clothing, and at the same time of the day. Wednesdays were chosen to prevent fluctuations in weight from the weekend.

Jerome et al. (2014) conducted a longitudinal study to assess the accuracy of web-based self-reported weights. Each participant in the study received a digital scale for home use and instructions to weight themselves at the same time of day, in the same clothing, and with the same scale. The results of this study found that weight was significantly underestimated from 6 months to 24 months (Jerome et al., 2014).

Another study was conducted to validate self-reported weights and heights in avoiding diabetes after pregnancy (Paez, Griffey, Thompson, & Gillman, 2014). Each participant was mailed a digital scale with spare batteries and a printed protocol with weighing instructions. The women were instructed to weigh themselves in the morning before eating, drinking, or dressing. Scales were to be placed on a hard surface and calibrated by stepping on the scale and waiting for it to blink three times (Paez et al., 2014). The results found that the women under-reported their weight (Paez et al., 2014).

Waist Circumference. Waist circumference was self-reported at baseline, weekly, and post-intervention. Each participant was required to watch the instructional video on how to accurately measure waist circumference prior to starting the study. For the purpose of the study, each waist circumference was measured (in centimeters) in line with the umbilicus and parallel to the floor. Participants were instructed to take two measurements back to back and report the average. Measurements were taken flush against bare skin, at the same time of the day, every Wednesday over the course of the study. Wednesdays were chosen to prevent fluctuations in weight from the weekend.

A study was conducted to assess the validity of self-reported waist circumference measurements in Thai adults (Lim, Seubsman, Sleigh, & Bain, 2012). The results of the study found self-reported waist circumference to be similar to the technicians waist circumference measurement with a concordance correlation coefficient from .84 to .90 (Lim et al., 2012). This study had subjects measure their waist circumference at the umbilicus with light clothing on (Lim et al., 2012).

Another study was conducted to assess the validity of self-measured waist circumference in adults at risk of type 2 diabetes and cardiovascular disease (Ayala, Nijpels, & Lakerveld, 2014). In this study, each participant received mailed instructions and a measuring tape. The instructions specified that the waist circumference should be taken around a bare belly just above the navel (Ayala et al., 2014). The results of this study found that participants on average over-estimated their waist circumference (Ayala et al., 2014).

Dekkers, van Wier, Hendriksen, Twisk, and van Mechelen (2008) conducted a study to assess the accuracy of self-reported body weight, height, and waist circumference in a Dutch overweight working population. The instructions were mailed to each participant along with a questionnaire. Participants were instructed to use a non-stretchable paper measuring tape to measure their waist circumference in centimeters. Subjects were instructed to measure their waist circumference at the mid-point between the lower border of the ribs and the upper border of their pelvis. Participants were advised to measure against bare skin during exhalation with feet 25-30 cm apart. Subjects were to take two measurements back to back and report the average value (Dekkers et al., 2008). Waist circumference was significantly over-reported by an average of 1.1 cm (Dekkers et al., 2008).

Research Questions

The specific aim of this project was to determine if adult patients suffering from Functional Gastrointestinal Disorders would report improved symptoms based on the Gastrointestinal Quality of Life Index after 8 weeks of probiotics, digestive enzymes, and glutamine. This specific gastrointestinal protocol is heavily used at Atlanta Center for Holistic and Integrative Medicine. Below is a list of the clinical questions examined.

Pre-Intervention Clinical Questions

1. What demographic factors (age, gender, ethnicity, duration of symptoms, and number of attempted treatments) are associated with a lower level of gastrointestinal quality of life?
2. What is the association between patients' perceived stress and gastrointestinal quality of life?
3. Controlling for demographic variables (age, gender, ethnicity, duration of symptoms, and number of attempted treatments) what is the association of perceived stress on gastrointestinal quality of life?
4. What demographic factors (age, gender, ethnicity, duration of symptoms and number of attempted treatments) are associated with an increased weight and weight circumference?
5. Controlling for demographic variables (age, gender, ethnicity, duration of symptoms, and number of attempted treatments), what is the association between perceived stress and waist circumference and weight?
6. Controlling for demographic variables (age, gender, ethnicity, duration of symptoms, and number of attempted treatments), is there an association between gastrointestinal quality of life and weight and waist circumference?

Post-Intervention Clinical Questions

7. After 8-week treatment with probiotics, digestive enzymes, and glutamine, is there an association between patients' perceived stress and gastrointestinal quality of life?
8. Controlling for demographic variables (age, gender, ethnicity, duration of symptoms, and number of attempted treatments) after 8-week treatment with probiotics, digestive enzymes, and glutamine what is the association of perceived stress on gastrointestinal quality of life?
9. Controlling for demographic variables (age, gender, ethnicity, duration of symptoms, and number of attempted treatments) after 8-week treatment with probiotics, digestive enzymes, and glutamine, what is the association between perceived stress and waist circumference and weight?
10. Controlling for demographic variables (age, gender, ethnicity, duration of symptoms, and number of attempted treatments) after 8-week treatment with probiotics, digestive enzymes, and glutamine, what is the association between gastrointestinal quality of life and weight and waist circumference?
11. After 8-week treatment with probiotics, digestive enzymes, and glutamine, is there a statistically significant change in the gastrointestinal quality of life, weight, waist circumference, and perceived stress?

Dissemination

The author of this research study disseminated the findings with a podium presentation at a conference at West Georgia College in November 2015. Understanding the importance of dissemination, the author of this research study plans to apply for publication in a variety of medical journals.

Data Analysis

The collected data was analyzed using Statistical Package for the Social Sciences (SPSS) software version 22.0. Data analysis began with an examination of missing data and standard data cleaning. Internal consistency reliability of all the instruments was determined for this sample. All interval/ratio variables were assessed for normality and measures of central tendency. Descriptive statistics were used to describe the demographics of the sample. Any instrument that was not completed fully by the participant was not used in the final analysis if greater than 20% of the data was missing. If less than 20% of the data on a single scale was missing, the mean sample replacement was used to replace the missing data. Statistical assumptions for all statistical tests were examined prior to addressing the research questions.

Analysis Plan for Research Questions

Research Question One: What demographic factors (age, gender, ethnicity, duration of symptoms, and number of attempted treatments) are associated with a lower level of gastrointestinal quality of life?

Approach: Appropriate statistical analysis was selected depending on the level and normality of the data. Both age and gastrointestinal quality of life scores were normally distributed and interval/ratio level data, therefore Pearson's correlational analysis was used to evaluate whether age was associated with a lower level of gastrointestinal quality of life. An independent samples t-test was used to test the association between gender, ethnicity, duration of symptoms, and number of attempted treatments and gastrointestinal quality of life.

Research Question Two: What is the association between participants' perceived stress and gastrointestinal quality of life?

Approach: Perceived stress was measured by the Perceived Stress Scale and gastrointestinal quality of life was measured by the Gastrointestinal Quality of Life Index. Both of these instruments were interval/ratio level data and normally distributed. Therefore, Pearson's correlational coefficient was used to determine if there was an association between participants' perceived stress and gastrointestinal quality of life.

Research Question Three: Controlling for demographic variables (age, gender, ethnicity, duration of symptoms, and number of attempted treatments) what is the association of perceived stress on gastrointestinal quality of life?

Approach: A simultaneous multiple linear regression was conducted to test the relationship between age, gender, ethnicity, duration of symptoms, number of attempted treatments, and perceived stress on gastrointestinal quality of life after controlling for the independent variables.

Research Question Four: What demographic factors (age, gender, ethnicity, duration of symptoms and number of attempted treatments) are associated with an increased weight and weight circumference?

Approach: Appropriate statistical analysis was selected depending on the normality and level of data. Initially, all of the interval/ratio level data was normally distributed except for weight. After conducting a logarithm transformation, weight was normally distributed based on Fisher's measure of skewness and kurtosis. Therefore, the association between age on weight and waist circumference was examined with Pearson's correlational coefficient. Ethnicity, duration of symptoms, and number of attempted treatments was grouped and coded dichotomously. Therefore, the association between gender, ethnicity, duration of symptoms, and number of attempted treatments on waist circumference/weight was tested with an independent t-test. The

association between duration of symptoms and number of attempted treatments on weight and waist circumference was verified with a one-way ANOVA.

Research Question Five: Controlling for demographic variables (age, gender, ethnicity, duration of symptoms, and number of attempted treatments), what is the association between perceived stress and waist circumference and weight?

Approach: A simultaneous multiple linear regression was conducted to test the relationship between age, gender, ethnicity, duration of symptoms, and number of attempted treatment on perceived stress and waist circumference/weight after controlling for the independent variables.

Research Question Six: Controlling for demographic variables (age, gender, ethnicity, duration of symptoms, and number of attempted treatments), is there an association between gastrointestinal quality of life and weight and waist circumference?

Approach: A simultaneous multiple linear regression was conducted to test the relationship between age, gender, ethnicity, duration of symptoms, and number of attempted treatments on gastrointestinal quality of life and waist circumference/weight after controlling for the independent variables.

Research Question Seven: After 8-week treatment with probiotics, digestive enzymes, and glutamine, is there an association between perceived stress and gastrointestinal quality of life?

Approach: Perceived stress was measured with the Perceived Stress Scale and gastrointestinal quality of life was measured with the Gastrointestinal Quality of Life Index. Both of these instruments were interval/ratio level data and normally distributed. Therefore, Pearson correlational coefficient was used to determine if there was an association between participants' perceived stress and gastrointestinal quality of life.

Research Question Eight: Controlling for demographic variables (age, gender, ethnicity, duration of symptoms, and number of attempted treatments) after 8-week treatment with probiotics, digestive enzymes, and glutamine, is there an association between perceived stress and gastrointestinal quality of life?

Approach: A simultaneous multiple linear regression was conducted to test the relationship between age, gender, ethnicity, duration of symptoms, number of attempted treatments, and perceived stress on gastrointestinal quality of life after controlling for the independent variables.

Research Question Nine: Controlling for demographic variables (age, gender, ethnicity, duration of symptoms, and number of attempted treatments) after 8-week treatment with probiotics, digestive enzymes, and glutamine, what is the association between perceived stress and waist circumference and weight?

Approach: A simultaneous multiple linear regression was conducted to test the relationship between age, gender, ethnicity, duration of symptoms, number of attempted treatments, and perceived stress on waist circumference/weight after controlling for the independent variables.

Research Question Ten: Controlling for demographic variables (age, gender, ethnicity, duration of symptoms, and number of attempted treatments) after 8-week treatment with probiotics, digestive enzymes, and glutamine, what is the association between gastrointestinal quality of life and weight and waist circumference?

Approach: A simultaneous multiple linear regression was conducted to test the relationship between age, gender, ethnicity, duration of symptoms, number of attempted treatments, and gastrointestinal quality of life on waist circumference/weight after controlling for the independent variables.

Research Question Eleven: After 8-week treatment with probiotics, digestive enzymes, and glutamine, is there a statistically significant change in the gastrointestinal quality of life, weight, waist circumference, and perceived stress?

Approach: A paired samples t-test was used to evaluate whether there was significant changes in gastrointestinal quality of life, weight, waist circumference, and perceived stress after 8-weeks of probiotics, digestive enzymes, and glutamine.

CHAPTER IV

Results

The results of this prospective cohort study examine the effects of probiotics, digestive enzymes, and glutamine on restoring digestive health in participants suffering from Functional Gastrointestinal Disorders. Findings reported here include descriptive information concerning the participants, reliability of the instruments, and data addressing the research questions.

Data

Data screening was performed prior to conducting the statistical analysis. All data was verified using a double entry method where two separate databases were created and compared. Any discrepancies were reconciled with the participants' original data. Examination of all continuous variables was conducted to determine distribution using descriptive statistics for central tendency and Fisher's exact for skewness and kurtosis. The weekly surveys were examined and no participant missed more than three supplements per week.

The study's instruments were examined for missing data. When participant's had less than 20% of the scores missing on the perceived stress scale and gastrointestinal quality of life index, the sample means were substituted for those missing items (Shrive, Stuart, Quan, & Ghali, 2006). In this research study no participant missed greater than 20% of the data in the Perceived Stress Scale ($n = 0$) or Gastrointestinal Quality of Life Index ($n = 0$). In the pre-intervention survey, the following measures were missing age ($n = 1$), weight ($n = 1$), waist circumference ($n = 9$), and duration of symptoms ($n = 1$). Since these variables are not part of a total score, the missing variables were left missing.

Prior to answering the research questions, the variables were analyzed to see if they met the assumptions for an ANOVA and linear regression. Instead of including both weight and

waist circumference, only waist circumference was used to answer the clinical research questions and regressional analyses for a number of reasons: (1) waist circumference was normally distributed based on Fisher's exact skewness statistic (2.13) and kurtosis (.44) (Munro, 2005), (2) waist circumference is a better indicator of bloating, and (3) waist circumference was strongly correlated with weight ($r = 0.76$, $p < .001$).

Weight was not normally distributed based on Fisher's exact skewness statistic (3.71) and kurtosis (.44) (Munro, 2005; Tabachnick & Fidell, 2006). Analysis of the data indicated that no values were three standard deviations from the mean; therefore no outliers were removed (Kim & Mallory, 2014). A statistical correction using an inverse natural logarithm was performed on the variable as recommended by Tabachnick & Fidell (2006). After conducting the inverse natural logarithm weight was normally distributed based on Fisher's exact skewness statistic (2.28) and kurtosis (1.13). The resulting mean was 2.17 ($SD = 0.98$).

Duration of symptoms was initially divided into five different categories including: less than 1 year, 1-3 years, 4-6 years, 7-10 years, and greater than 10 years. In order to further analyze the data, the results were divided into two groups: those who have had symptoms less than 3 year and those that have had symptoms longer than 3 years. All analyzes were run using the data grouped as less than 3 years and longer than 3 years to meet the assumptions of the regression.

The number of attempted treatments was initially divided into four categories including: no treatment, 1-2 different treatments, 3-5 different treatments, and greater than 5 treatments. To further analyze the data, the results were divided into two groups: those who have attempted less than 3 different treatments and those that have attempted more than 3 different treatments. All

analyzes were run using the data grouped as less than 3 different treatments and more than 3 different treatments to meet the assumptions of the regression.

Ethnicities were divided into two categories including minorities and Caucasians. Hispanic (n = 5) and Native American (n = 2) participants were included in the minority group with African Americans due to the small number of participants.

The other variables including age, perceived stress, and gastrointestinal quality of life were normally distributed in this sample based on Fisher's exact. Each participant made his or her own independent appraisal of their symptoms, all participants were mutually exclusive, and the Levene tests were not significant indicating homogeneity of the variances of the participants on the dependent variables (Munro, 2005).

Pre-Intervention Sample Characteristics

The initial sample consisted of 98 adult participants suffering from Functional Gastrointestinal Disorders. The participants were recruited through Atlanta Center for Holistic and Integrative Medicine's social media including Facebook and blogs. Each participant voluntarily enrolled in the study and was screened based on the inclusion and exclusion criteria. Informed consent was obtained on each participant prior to initiating the study.

The initial study participants, as shown in Table 1, were 90.8% female (n = 89) and primarily Caucasian (n = 76). Prior to starting the study, the majority of participants had tried no more than five different treatment modalities to alleviate symptoms (78.6%). The participant's gastrointestinal symptoms were chronic in nature with the majority of the participants suffering from gastrointestinal symptoms for greater than 10 years (33.7%) and very few participants suffering from symptoms for less than 1 year (4.1%).

Table 1

Pre-Intervention Demographic Characteristics of Participants

Variables	*N*	*(%)*	Mean *(SD)*	Range
Age	97		43.9 (11.15)	18-65
Gender	98			
Female	89	(90.8)		
Male	9	(9.2)		
Ethnicity	98			
AfricanAmerican/Black/Caribbean	15	(15.3)		
Caucasian	76	(77.6)		
Hispanic	5	(5.1)		
Native American	2	(2)		
Asian	0	(0)		
Weight	97		153.3 (0.84)	98-253
Log10 Transformation			2.17 (0.098)	1.99-2.4
Waist Circumference	89		84.08 (13.4)	54-122
Attempted Treatments	98			
None	16	(16.3)		
1-2	28	(28.6)		
3-5	33	(33.7)		
> 5	21	(21.4)		
Duration of Symptoms	97			
< 1 year	4	(4.1)		
1-3 years	25	(25.5)		
4-6 years	22	(22.4)		
7-10 years	14	(14.3)		
> 10 years	32	(32.7)		

Note. Participant numbers may vary from 98 as not all participants answered all questions.

Description of Research Instruments (Pre-Intervention)

This section describes the study instruments, reliability in this sample, the mean scores, standard deviations and the percentage of study participants above the normal range (Table 2). Instruments used as a continuous variable were normally distributed except the original weight variable.

Table 2

D*escription of Research Instruments (Pre-Intervention)*

Variable	*M (SD)*	Observed Range	Possible Range	Cut-off or normative value	Cronbach Alpha (without means)
Weight Weight Log10	153.3 (36.71) 2.17 (0.098)	98-253 1.99-2.4	N/A N/A		
Waist Circumference	84.08 (13.44)	54-122	N/A		
Perceived Stress Scale (PSS-10)	16.6 (5.43)	2-29	0-40	Normative for female (13.7) and males (12.1) 68.3% scored above 13	0.876
Gastrointestinal Quality of Life Index (GQOLI) Total	95.4 (15.73)	57-131	0-144	Normative value 125.8 99% scored below 124	0.870
GQOLI Social	12.28 (5.47)	5-16	0-16		0.646
GQOLI Emotional	12.63 (3.68)	3-20	0-20		0.823
GQOLI Physical	14.43 (5.47)	1-26	0-28		0.793
GQOLI Symptoms	53.34 (7.10)	33-68	0-76		0.668

Waist Circumference. Waist circumference was measured in centimeters. Participants were advised to measure their waist circumference at the same time of day. Waist circumference was measured parallel to the floor and in line with the umbilicus. Participants were instructed to measure waist circumference flush against bare skin. Waist circumference measurements ranged from 54-122 centimeters.

Weight. Weight was measured in pounds with results ranging from 98-253 pounds. Participants were advised to measure on the same scale, at the same time of day, and in the same (or no) clothes to maintain internal consistency. Although only waist circumference was reported in the clinical research questions, the tests were run to examine weight and waist circumference to evaluate significance. Analyses were run using both the weight before transformation and after the log transformation to determine if there were any differences, none were noted.

Perceived Stress Scale. Participants suffering from Functional Gastrointestinal Disorders were evaluated for their perceived level of stress using the 10-item, Likert-type Perceived Stress Scale (Cohen & Williamson, 1988). Scores ranged from 2-29 with higher scores indicating higher levels of stress. The normative scores for females was 13.7 and for males was 12.1 (Cohen & Williamson, 1988). In this sample, 68.3% of the participants' scored above 13 on the Perceived Stress Scale. Out of the nine males in this sample, 5 scored above 12.5 on the Perceived Stress Scale (55.6%). Out of the eighty-five females in this sample, 64 scored above 14 on the Perceived Stress Scale (75.3%). Cronbach's alpha for the sample was an acceptable 0.88 (Di Lorio, 2005).

Gastrointestinal Quality of Life Index. Participants suffering from Functional Gastrointestinal Disorders were evaluated for their gastrointestinal quality of life based on the Gastrointestinal Quality of Life Index (Eypasch, 1995). Scores ranged from 57-131 with lower scores associated with lower quality of life. The normative value for the Gastrointestinal Quality of Life index is 125.8 (Eypasch, 1995). In this sample, at baseline, 99% of the participants scored below 124 with only one participant scoring 131. Several other studies evaluating participants with gastrointestinal dysfunction had similar results where the study participants had

significantly lower levels of gastrointestinal quality of life than the normative levels in the healthy population (Damon et al., 2008; Shi et al., 2011; Wierdsma et al., 2009).

The Gastrointestinal Quality of Life Index was divided into four subcategories including emotional, physical, social, and symptoms. Cronbach's alpha for each subcategory and total from the sample is as follows: emotional (0.82), physical (0.79), social (0.65), symptoms (0.67), and total (0.87). For the purpose of this study, subcategories were not tested separately due to low reliability based on their Cronbach's alpha scores (Di Lorio, 2005). The total Gastrointestinal Quality of Life Index score was normally distributed based on Fisher's exact skewness statistic (1.2) and kurtosis (0.85) (Munro, 2005). The total Gastrointestinal Quality of Life Index score had an acceptable Cronbach's alpha of 0.87 (Di Lorio, 2005).

Pre-Intervention Clinical Research Questions

The following research questions were conducted using the pre-intervention data findings.

Results for Research Question 1

Research Question 1: What demographic factors (age, gender, ethnicity, duration of symptoms, and number of attempted treatments) are associated with a lower level of gastrointestinal quality of life using the Gastrointestinal Quality of Life Index?

Age. Correlational analysis was used to evaluate whether age was associated with a lower level of gastrointestinal quality of life. Data indicated that there was no statistically significant association between age and gastrointestinal quality of life scores ($r = .022$, $p = .83$). For the purpose of this study, all of the independent variables were included in the Pearson correlation as seen in Table 3.

Gender. An independent samples t-test was used to evaluate whether gender was associated with a lower level of gastrointestinal quality of life. The covariate, gender, was dichotomously coded 0/1 for "male" or "female". The research found no statistically significant association between gastrointestinal quality of life scores between females (M = 94.64, SD = 15.76) and males (M = 102.85, SD = 14.15); t (96) = 1.5, p = .14).

Ethnicity. An independent samples t-test was used to test the association between ethnicity and gastrointestinal quality of life. The covariate, ethnicity, was dichotomously coded 0/1 for "Caucasian" or "Minority". There was statistically significant association between gastrointestinal quality of life and ethnicity. Minorities (M = 88.37, SD = 14.22) reported significantly lower gastrointestinal quality of life than Caucasians (M = 97.43, SD = 15.64); t (96) = -2.44, p = .02).

Duration of Symptoms. An independent samples t-test was conducted to examine the association between duration of symptoms and lower gastrointestinal quality of life. The covariate, duration of symptoms, was dichotomously coded 0/1 for "less than 3 years" or "greater than 3 years". There was no statistically significant association between less than 3 years of symptoms (M = 94.86, SD = 18.06) and greater than 3 years of symptoms (M = 95.34, SD = 14.7; t (95) = -.137, p = .89).

The analysis was verified with the initial data grouping for duration of symptoms (less than 1 year, 1-3 years, 4-6 years, 7-10 years, and greater than 10 years) with one-way ANOVA testing. No statistically significant differences were seen F (4, 92) = 2.06, p = .093.

Number of Attempted Treatments. An independent samples t-test was conducted to examine the association between the number of attempted treatments and lower gastrointestinal quality of life. The covariate, number of attempted treatments, was dichotomously coded 0/1 for

"less than 3 treatments" or "greater than 3 treatments". There was a statistically significant association between less than 3 attempted treatments (M = 100.33, SD = 15.57) and greater than 3 attempted treatments (M = 91.37, SD = 14.79; t (96) = -2.91, $p < .01$) on gastrointestinal quality of life. Therefore, the participants that had attempted more than 3 different treatments had significantly lower gastrointestinal quality of life.

The analysis was verified with the initial data grouping for the number of attempted treatments (no treatment, 1-2 different treatments, 3-5 different treatments, and greater than 5 treatments) with one-way ANOVA testing. The overall F for the one-way ANOVA was statistically significant F (3, 94) = 2.82, p = .043. Post hoc testing was conducted using Tukey's HSD tests with no statistically significant difference between groups (p = .11).

Results for Research Question 2:

Research Question 2: What is the association between participants' perceived stress and gastrointestinal quality of life?

Since there were similarities between these two instruments, correlations between the questions on the instruments were evaluated. Although there were several significant correlations, there were only two items that were moderately correlated ($r < -.585$). Correlational analysis was used to evaluate the association between participants' perceived stress and gastrointestinal quality of life. Initial data screening indicated that both variables were normally distributed. There was a low negative correlation between the overall scores on the perceived stress and gastrointestinal quality of life scores (r = -.326, p = .001). Therefore, the more perceived stress participants reported the lower their gastrointestinal quality of life. Table 3 reports the Pearson correlations between all the main variables in this study.

Table 3

Pearson Correlations between the Major Variables (Pre-Intervention)

	1	2	3	4	5	6	7	8	9
1. Age	-								
2. Gender	.170	-							
3. Ethnicity	-.161	.086	-						
4. Duration of Symptoms	.086	.024	-.077	-					
5. Attempted Treatments	.141	.210*	-.006	.143	-				
6. Weight (Log)	.083	-.369**	.094	.003	-.111	-			
7. Waist Circumference	.218*	-.244	.078	.096	-.028	.761**	-		
8. Perceive Stress Scale	.035	.166	.097	.016	.163	.100	-.024	-	
9. Gastrointestinal Quality of Life	.022	-.152	.241*	.014	-.285**	-.164	-.212*	-.326**	-

Note: * $p < .05$, ** $p < .01$

Results for Research Question 3:

Research Question 3: Controlling for demographic variables (age, gender, ethnicity, duration of symptoms, and number of attempted treatments) what is the association of perceived stress on gastrointestinal quality of life?

Prior to beginning the analysis, the independent variables (age, gender, ethnicity, duration of symptoms, number of attempted treatments, and perceived stress) were examined for multicollinearity. There was only one statistically significant correlation between the independent variables including gender and number of attempted treatments ($r = .21$, $p = .04$). This was a weak correlation indicating multicollinearity was not a problem (Munro, 2005).

A simultaneous multiple linear regression was conducted to control for each variables effect on each other and to test the relationship between age, gender, ethnicity, duration of symptoms, number of attempted treatments, perceived stress, and gastrointestinal quality of life. Regression results indicated that the model accounted for 22.1% of the variance in the perceived stress and gastrointestinal quality of life (R^2= .221, R^2adj= .168, F (6, 89)= 4.206, p < .01). Table 4 summarizes the multiple regression analysis.

The results of this simultaneous regression report there are three statistically significant predictors of gastrointestinal quality of life including: ethnicity, perceived stress, and attempted treatments. Minorities, higher levels of perceived stress, and greater than 3 attempted treatments were associated with lower gastrointestinal quality of life after controlling for the other independent variables. Therefore, gastrointestinal quality of life is negatively correlated with perceived stress; as the participants reported higher levels of perceived stress their gastrointestinal quality of life decreased.

Table 4

Results of Simultaneous Regression of Predictors of Gastrointestinal Quality of Life Scores

Variable	*b weights*	*Std. β weights*	*t*	*p value*
Constant	119.97		*12.16*	*.00*
Age	.095	.066	.673	.503
Gender	-2.893	-0.54	-.545	.587
Ethnicity	-7.303	-.196	-2.03	.045*
Perceived Stress	-.845	-.288	-2.98	.004**
Attempted Treatments	-6.901	-.219	-2.23	.028*
Duration of Symptoms	1.267	.037	.391	.697

Note: * p < .05, ** p < .01

Results for Research Question 4:

Research Question 4: What demographic factors (age, gender, ethnicity, duration of symptoms and number of attempted treatments) are associated with an increased waist circumference?

Age and waist circumference was normally distributed and interval/ratio level data therefore the association between age and waist circumference was tested with Pearson's correlation coefficient. An independent samples t-test was conducted to test the association between gender, ethnicity, duration of symptoms, and number of attempted treatments on waist circumference. The only statistically significant association was between gender and waist circumference with males having a larger waist circumference than females. See table 5 for a summary of the independent samples t-test and Pearson correlation for the analysis.

Table 5

Examining Association of Age, Gender, Ethnicity, Duration of Symptoms, and Number of Attempted Treatments on Waist Circumference

Variable	*M (SD)*	*t*	*r*	*P value*
Age	43.90 (11.15)		*.22*	*.42*
Gender				
Male	93.82 (11.71)	2.35		.021*
Females	82.99 (13.24)			
Ethnicity				
Caucasians	83.50 (13.49)	.73		.468
Minorities	85.95 (13.43)			
Duration of Symptoms				
Less than 3 years	82.18 (13.18)	-.89		.380
Greater than 3 years	85.02 (13.59)			
Number of Attempted Treatments				
Less than 3	84.48 (14.6)	.26		.795
More than 3	83.73 (12.47)			

Note*: *p* < .05

Results for Research Question 5:

Research Question 5: Controlling for demographic variables (age, gender, ethnicity, duration of symptoms, and number of attempted treatments), what is the association between perceived stress and waist circumference and weight?

In this study, there was no statistically significant association between perceived stress and waist circumference (r = -.024, p = .822), therefore a simultaneous multiple linear regression controlling for the independent variables was not conducted.

Results for Research Question 6:

Research Question 6: Controlling for demographic variables (age, gender, ethnicity, duration of symptoms, and number of attempted treatments), is there an association between gastrointestinal quality of life and waist circumference?

Prior to beginning the analysis, the independent variables (age, gender, ethnicity, duration of symptoms, number of attempted treatments, and gastrointestinal quality of life) were examined for multicollinearity. Although there were three statistically significant correlations, the strengths of the correlations remained low ($r < -.285$, $p < .01$). This is a low relation indicating multicollinearity was not a problem (Munro, 2005).

A simultaneous multiple linear regression was conducted to test the relationship between age, gender, ethnicity, duration of symptoms, number of attempted treatments, and gastrointestinal quality of life on waist circumference. Regression results indicated that the model accounted for 21.2% of the variance in the participants' gastrointestinal quality of life and waist circumference ($R^2 = .212$, $R^2adj = .153$, F (6, 80)= 3.59, $p < .01$). There were three statistically significant predictors of waist circumference including age, gender, and gastrointestinal quality of life after controlling for independent variables. Waist circumference was positively correlated with age; as

age increased, waist circumference increased. There was a statistically significant association between the male participants in this sample and an increased waist circumference. Waist circumference was negatively correlated with gastrointestinal quality of life; the larger the participants' waist circumference the lower their gastrointestinal quality of life.

Table 6

Results of Simultaneous Regression of Predictors for Waist Circumference

Variable	*b weights*	*Std b weights*	*t*	*p value*
(Constant)	102.164		7.848	.000
Age	.349	.289	2.800	.006**
Gender	-14.421	-.328	-3.151	.002**
Ethnicity	2.850	.091	.876	.383
Gastrointestinal Quality of Life	-.234	-.274	-2.566	.012*
Attempted Treatments	-2.002	-.075	-.701	.485
Duration of Symptoms	2.771	.094	.927	.357

Note: * $p < .05$, ** $p < .01$

Post-Intervention Data

Sample Characteristics

Out of the 98 participants that enrolled in the study, 86 participants completed the entire 8-week study. Demographics of the 86 participants that completed the entire 8-week intervention can be found in Table 7.

Table 7

Post-Intervention Demographic Characteristics of Participants

Variables	*N*	*(%)*	Mean *(SD)*	Range
Age	85		44.34 (11.08)	18-65
Gender	86			
Female	77	(89.5)		
Male	9	(10.5)		
Ethnicity	86			
AfricanAmerican/Black/Carribbean	13	(12.1)		
Caucasian	67	(62.6)		
Hispanic	5	(4.7)		
Native American	1	(0.9)		
Asian	0	(0)		
Weight	86		148.97 (34.3)	98-250
Log10 Transformation	86		2.16 (0.093)	1.99-2.4
Waist Circumference	78		78 (12.74)	63-121
Attempted Treatments	86			
None	6	(7.0)		
1-2	24	(27.9)		
3-5	32	(37.2)		
> 5	24	(27.9)		
Duration of Symptoms	86			
< 1 year	4	(4.7)		
1-3 years	19	(22.1)		
4-6 years	24	(27.9)		
7-10 years	10	(11.6)		
> 10 years	29	(33.7)		

Note. Participant numbers may vary from 86 as not all participants answered all questions.

Two participants completed the pre-intervention survey, but withdrew prior to week one's survey. One of the participants was a 39-year-old Caucasian female with the initial

complaint of diarrhea, reflux, and abdominal pain with and without food; this participant withdrew due to family illness. The other participant was a 39-year-old Caucasian female with initial complaints of constipation, bloating, and flatulence. The researcher reached out to this participant numerous times without a response; therefore the reason for withdrawal remains unknown.

One participant withdrew by week 3. This participant was a 38-year-old Caucasian female with initial complaints of constipation, bloating, and flatulence. She withdrew due to unexpected travel out of the country without Internet excess.

Three participants withdrew by week 4 of the intervention: (1) 33-year-old Caucasian female with initial complaints of bloating, reflux, flatulence, and abdominal pain with food, (2) 38-year-old Caucasian female with initial complaints constipation, bloating, and belching, and (3) 59-year-old Caucasian female with initial complaints of constipation and bloating. The first participant withdrew due to increased bloating, the second withdrew due to increased constipation, and the third participant withdrew for unknown reasons.

One participant withdrew by week five. This participant was a 35-year-old African American female with initial complaints of constipation, bloating, and reflux. The researcher reached out to her numerous times without a response.

One participant withdrew by week six. This participant was a 42-year-old Caucasian female with complaints of constipation, bloating, reflux, and flatulence. This participant reported being too busy with her kids' schedules.

Two participants withdrew by week seven. One participant was a 55-year-old Caucasian female with initial complaints of constipation, bloating, and flatulence. The other participant was a 23-year-old Native American female with initial complaints of diarrhea, bloating, reflux,

flatulence, and abdominal pain with food. The researcher reached out to both of these participants numerous times without a response.

Lastly, two participants did not complete the post-intervention survey. One of the participants was a 57-year-old African American female with initial complaints of constipation, bloating, reflux, flatulence, and abdominal pain with food. The other participant was a 31-year-old Caucasian female with initial complaints of diarrhea, constipation, bloating, reflux, and abdominal pain with food. The researcher reached out to both of these participants without a response.

Self-Reported Gastrointestinal Symptoms

Each participant was asked to report his or her gastrointestinal symptoms at baseline, weekly, and after 8-weeks of probiotics, digestive enzymes, and glutamine. Each participant was asked to check which gastrointestinal symptom they experienced in the previous week. The covariate, gastrointestinal symptoms, was dichotomously coded 0/1 for “no” or “yes”. In order to do a more thorough comparison of symptoms, only those participants that completed the entire 8-week study were included (n = 86). A paired samples t-test was conducted to evaluate whether there was statistically significant improvement in self-reported gastrointestinal symptoms after the 8-week intervention. The researcher verified the results with McNemar's test and found the same results. The only significant reduction in symptoms was abdominal pain related to food. The pre and post intervention results are shown in Table 8.

Table 8

Self-Reported Gastrointestinal Symptoms of Sample Completing Entire 8-Week Study

	Pre-Intervention N=86		*Post-Intervention N= 86*			
Symptoms	*N*	*(%)*	*N*	*(%)*	*t*	*p value*
Diarrhea	28	(32.6)	26	(30.2)	.705	.483
Constipation	49	(57.0)	48	(55.8)	.332	.741
Bloating	77	(89.5)	74	(86.0)	1.000	.320
Reflux	27	(31.4)	30	(34.9)	-9.04	.369
Belching	22	(25.6)	18	(20.9)	1.070	.288
Excessive flatulence	53	(61.6)	45	(52.3)	1.583	.117
Abdominal pain related to food	46	(53.5)	34	(39.5)	2.787	.007**
Abdominal pain unrelated to food	16	(18.6)	15	(17.4)	.257	.798

Note: ** p < .01

Post-Intervention Description of Research Instruments

Prior to discussing the post-intervention research questions, table 9 provides a description of the research instruments and findings after eight weeks of probiotics digestive enzymes and glutamine.

Table 9

D*escription of Research Instruments (Post-Intervention)*

Variable	*M (SD)*	Observed Range	Possible Range	Cut-off or normative value	Cronbach Alpha (without means)
Weight	148.97 (34.33)	98-250	N/A		
Weight Log10	2.16 (0.093)	1.99-2.4	N/A		
Waist Circumference	84.43 (12.74)	63-121	N/A		
Perceived	15.78 (5.89)	3-28	0-40	Normative	0.889

Stress Scale (PSS-10)				for female (13.7) and males (12.1) 72.1% scored above 13	
Gastrointestinal Quality of Life Index (GQOLI) Total	105.63 (18.43)	59-138	0-144	Normative value 125.8 81.4% scored below 124	0.921
GQOLI Social	12.84 (2.80)	6-16	0-16		0.691
GQOLI Emotional	13.99 (3.88)	3-20	0-20		0.866
GQOLI Physical	17.13 (5.49)	4-28	0-28		0.800
GQOLI Symptoms	58.58 (8.73)	38-74	0-76		0.827

Perceived Stress Scale. The Perceived Stress Scale was normally distributed in the post intervention data based on Fisher's exact skewness statistic (.31) and kurtosis (.78) (Munro, 2005). The normative scores for females was 13.7 and for males was 12.1 (Cohen & Williamson, 1988). In this sample, 72.1% of the participants' scored above 13 on the Perceived Stress Scale. Out of the nine males in this sample, 3 scored above 12.5 on the Perceived Stress Scale (33.3%). Out of the seventy-three women that completed all of the necessary questions, 55 scored above 14 on the Perceived Stress Scale (75.3%). The Perceived Stress Scale had an acceptable Cronbach's alpha of .89 (Di Lorio, 2005).

Gastrointestinal Quality of Life Index. The Gastrointestinal Quality of Life Index was normally distributed in the post intervention data based on Fisher's exact skewness statistic (1.94) and kurtosis (.65) (Munro, 2005). The normative value for the Gastrointestinal Quality of Life index is 125.8 (Eypasch, 1995). In this sample (n = 86), 70 (81.4%) of the participants

scored 124 or lower on the total Gastrointestinal Quality of Life Index. The total Gastrointestinal Quality of Life Index had an acceptable Cronbach's alpha of .92 (Di Lorio, 2005).

Weight and Waist Circumference. Weight was not normally distributed in the post-intervention data based on Fisher's exact skewness statistic (4.04) and kurtosis (.86) (Munro, 2005; Tabachnick & Fidell, 2006). Analysis of the data indicated that there were no significant outliers. After completing a logarithm transformation, weight was normally distributed based on Fisher's exact skewness statistic (2.58) and (.78). The resulting mean was 2.16 (SD = 0.94).

Similarly to the pre-intervention data, there was a strong correlation between weight and waist circumference (r = .812, p < .01). Waist circumference was normally distributed in the post-intervention data based on Fisher's exact skewness (2.76) and kurtosis (.32) (Munro, 2005). Due to the strong correlation and normality of data, only the participants' waist circumference was reported when answering the clinical questions.

Post-Intervention Clinical Research Questions

The following research questions were conducted using the post-intervention data.

Results for Research Question 7:

Research Question 7: After 8-week treatment with probiotics, digestive enzymes, and glutamine, is there an association between perceived stress and gastrointestinal quality of life, weight, and waist circumference?

Correlational analysis was used to evaluate the association between participants' perceived stress, gastrointestinal quality of life, weight, and waist circumference after 8-week treatment with probiotics, digestive enzymes, and glutamine. Table 10 reports the Pearson correlations between all the main variables in this study after the 8-week intervention.

Table 10

Pearson Correlations between the Major Variables (Post-Intervention)

	1	2	3	4	5	6	7	8	9
1. Age	-								
2. Gender	-.110	-							
3. Ethnicity	.167	.090	-						
4. Duration of Symptoms	.025	.051	-.185	-					
5. Attempted Treatments	.041	.308**	.037	.274*	-				
6. Weight (Log)	.131	-.330**	.025	-.075	.021	-			
7. Waist Circumference	.080	-.280*	.043	-.141	.000	.812**	-		
8. Perceive Stress Scale	.040	.123	.076	-.021	.386**	.115	.057	-	
9. Gastrointestinal Quality of Life	-.030	-.208	-.166	.108	-.382**	-.012	-.050	-.526*	-

Note: * $p < .05$, ** $p < .01$

Perceived Stress Scale. The association between perceived stress and gastrointestinal quality of life, weight, and waist circumference was tested with Pearson's correlation coefficient. There was no statistically significant association between perceived stress and waist circumference ($r = .057$, $p = .619$). There was a statistically significant moderate correlation between perceived stress and gastrointestinal quality of life ($r = -.526$, $p < .01$). Participants with higher perceived stress reported the lower gastrointestinal quality of life.

Gastrointestinal Quality of Life. The association between gastrointestinal quality of life and perceived stress, weight, and waist circumference was tested with Pearson's correlation coefficient. There was no statistically significant association between gastrointestinal quality of

life and waist circumference (r = -.05, p = .664). As previously stated, there was a statistically significant moderate correlation between gastrointestinal quality of life and perceived stress (r = -.526, p < .01). Therefore the higher perceived stress reported the lower gastrointestinal quality of life.

Waist Circumference. The association between waist circumference, perceived stress, and gastrointestinal quality of life was tested with Pearson's correlation coefficient. There was no statistically significant association between waist circumference and gastrointestinal quality of life (r = -.05, p = .66) or perceived stress (r = .057, p = .62) in the post-intervention data.

Results for Research Question 8:

Research Question 8: Controlling for demographic variables (age, gender, ethnicity, duration of symptoms, and number of attempted treatments) after 8-week treatment with probiotics, digestive enzymes, and glutamine what is the association of perceived stress on gastrointestinal quality of life?

Prior to beginning the analysis, the independent variables (age, gender, ethnicity, duration of symptoms, number of attempted treatments, and perceived stress) were examined for multicollinearity. Although there were three statistically significant correlations, the strengths of the correlations remained low (r = 3.86, p < .01) indicating multicollinearity was not a problem (Munro, 2005).

A simultaneous multiple linear regression was conducted to test the relationship between age, gender, ethnicity, duration of symptoms, number of attempted treatments, and perceived stress on gastrointestinal quality of life. Regression results indicated that the model accounted for 35% of the variance in the participants' perceived stress and gastrointestinal quality of life (R^2= .350, R^2adj= .300, F (6, 78)= 7.005, p < .01). There were two statistically significant predictors of

gastrointestinal quality of life after controlling for independent variables included the number of attempted treatments and perceived stress. The higher level of perceived stress and the more treatments a participant had tried the lower the participants' gastrointestinal quality of life. Table 11 summarizes the multiple regression analysis.

Table 11

Results of Simultaneous Regression of Predictors of Gastrointestinal Quality of Life

Variable	*b weights*	*Std b weights*	*t*	*p value*
(Constant)	137.834		13.180	.000
Age	-.124	-.075	-.770	.443
Gender	-4.376	-.074	-.750	.456
Ethnicity	-4.214	-.096	-1.019	.311
Duration of Symptoms	7.184	.172	1.727	.088
Attempted Treatments	-9.144	-.238	-2.212	.030*
Perceived Stress	-1.221	-.383	-3.769	.000**

Note: * $p < .05$, ** $p < .01$

Results for Research Question 9:

Research Question 9: Controlling for demographic variables (age, gender, ethnicity, duration of symptoms, and number of attempted treatments) after 8-week treatment with probiotics, digestive enzymes, and glutamine, what is the association between perceived stress on waist circumference?

In this study, there was no statistically significant correlation between perceived stress and waist circumference; therefore, a simultaneous multiple linear regression controlling for independent variables was not conducted.

Results for Research Question 10

Controlling for demographic variables (age, gender, ethnicity, duration of symptoms, and number of attempted treatments) after 8-week treatment with probiotics, digestive enzymes, and

glutamine, what is the association between gastrointestinal quality of life on waist circumference?

In the study, there was no statistically significant correlation between gastrointestinal quality of life and waist circumference; therefore, a simultaneous multiple linear regression controlling for variables was not conducted.

Results for Research Question 11

Research Question 11: After 8-week treatment with probiotics, digestive enzymes, and glutamine, is there a statistically significant change in the gastrointestinal quality of life, weight, waist circumference, and perceived stress?

Paired samples t-test was used to evaluate whether there was statistically significant change in gastrointestinal quality of life, weight, waist circumference, and perceived stress after 8 weeks of probiotics, digestive enzymes, and glutamine. A summary of the findings can be found in Table 12.

Table 12

Paired Samples T-Test after 8-Week Intervention

	Pre-Intervention	*Post-intervention*		
Variable	*N= 86* *M (SD)*	*N= 86* *M (SD)*	*t*	*p value*
Gastrointestinal Quality of Life	95.95 (15.94)	105.63 (18.43)	-6.55	.000**
Weight Log	2.17 (.097)	2.16 (.094)	2.55	.012*
Waist Circumference	84.21 (13.11)	84.18 (12.8)	.039	.969
Perceived Stress	16.37 (5.38)	15.78 (5.89)	1.302	.196

Note: * $p < .05$, ** $p < .01$

Gastrointestinal Quality of Life. There was a significant difference in the gastrointestinal quality of life scores from the pre-intervention scores (M = 95.95, SD = 15.94) to post-intervention scores (M = 105.63, SD = 18.43); t (85)= -6.56, $p < .01$. Therefore, participants had statistically significant improvements in their gastrointestinal quality of life after 8 weeks of probiotics, digestive enzymes, and glutamine.

Weight. There was a significant difference in the participants' weight from pre-intervention (M = 2.17, SD = .097) to post-intervention (M = 2.16, SD = .094); t (84) = 2.55, p = .012. Initially weight was not normally distributed; therefore the original weight data was examined with a Wilcoxon signed-rank test to verify the significance. A Wilcoxon signed-rank test showed that after 8 weeks of probiotics, digestive enzymes, and glutamine there was a statistically significant weight lost in participants (Z = -4.71, $p < .01$). The pre-intervention weight mean was 152.18 pounds and the post-intervention weight was 149.07. As evident, with both the paired samples t-test and Wilcoxon signed-rank test, participants lost a statistically significant amount of weight over the 8-week intervention.

Waist Circumference. There was no significant difference in waist circumference prior to the study (M = 84.21, SD = 13.11) and after the 8-week study (M = 84.18, SD = 12.8); t (70) = .39, p = .969.

Perceived Stress. There was no significant change in perceived stress from baseline (M = 16.37, SD = 5.38) to after the 8-week study (M =15.78, SD = 5.89); t (85) = 1.302, p = .196.

Conclusion

This chapter presented the results of the research study. A total of 98 adults suffering from Functional Gastrointestinal Disorders were recruited from an Integrative Medicine office in Atlanta, Georgia. A total of 86 participants completed the entire 8-week intervention of

probiotics, digestive enzymes, and glutamine. Results indicated that there was a statistically significant association between minorities, higher levels of stress, and greater than 3 attempted treatments with lower gastrointestinal quality of life based on the Gastrointestinal Quality of Life Index.

There was no statistically significant association between age, gender, or duration of symptoms and gastrointestinal quality of life. Men and increasing age were associated with larger waist circumferences. Results indicated that even though all of the self-reported gastrointestinal symptoms improved over the 8-week intervention (except for reflux), the only statistically significant improvement was seen in abdominal pain related to food.

After the 8-week intervention, there was significant weight loss and increased gastrointestinal quality of life scores based on the Gastrointestinal Quality of Life Index. In conclusion, the results of this study support the use of probiotics, digestive enzymes, and glutamine to improve weight loss and gastrointestinal quality of life in individuals suffering from Functional Gastrointestinal Disorders.

CHAPTER V

Discussion

The purpose of this 8-week prospective cohort study was to determine whether probiotics, digestive enzymes, and glutamine are an effective regimen for improving gastrointestinal symptoms. Chapter V presents a discussion of the study's results and concludes with the study's strengths, limitations, implications for practice, and future research. This study is unique as it is the first to examine the combined benefits of probiotics, digestive enzymes, and glutamine for the management of Functional Gastrointestinal Disorder symptoms.

This gastrointestinal protocol was designed to be an alternative method for restoring digestive health rather than managing symptoms in individuals suffering from Functional Gastrointestinal Disorders. The findings of this study examine the demographics associated with Functional Gastrointestinal Disorders and explore the hypothesis that there is a brain-gut connection. This study examined the brain-gut connection through the evaluation of the participants' perceived stress based on the Perceived Stress Scale and gastrointestinal quality of life based on the Gastrointestinal Quality of Life Index.

Demographics

Age

When examining the impact of age on Functional Gastrointestinal Disorders it does not appear to be an important demographic variable. In this study, there was no significant correlation between age and perceived stress or gastrointestinal quality of life. The only significant finding related to the participants' age was that as their age increased, their waist circumference increased as well. Previous studies have found similar results. A longitudinal study conducted over 15 years in Australia found age to be the most important factor associated

with change in both weight and waist circumference (Arabshahi, Lahmann, Williams & van der Pols, 2014). Participants in this study continued to gain weight and waist circumference until age 55 and 65 years old, respectively (Arabshahi et al., 2014).

The age most affected by Functional Gastrointestinal Disorders remains inconclusive. This research study limited its sample to participants between the ages of 18-65 years old. The findings in this study resulted in a wide range of ages from 18-65 years old with a mean age of 43.9 years old. The results of this study are congruent with other study findings. One study found that individuals younger than 50 years old were affected by irritable bowel syndrome more frequently (Scalera & Loguercio, 2012). Another large cohort study of 4,224 patients with Functional Gastrointestinal Disorders found the mean age to be 47.6 years old with an age range from 16-93 years old (Ford et al., 2014). This is similar to a large case-control study of 23,471 diagnosed with Functional Gastrointestinal Disorders that reported a mean of 51.4 years old (Ford, Talley, et al., 2014). In Europe, a study was conducted that examined 199 patients with Functional Gastrointestinal Disorders and found the mean age to be 50 years old, with the ages ranging from 21-85 years old (Lahner et al., 2013).

Although this study's mean age results were similar to those found in other larger studies, it is important to remember that Functional Gastrointestinal Disorders do not discriminate based on age. Individuals can suffer from functional gastrointestinal symptoms from birth until death. This study limited the inclusion criteria to adult participants; however Functional Gastrointestinal Disorders affect children as well. Roughly 38% of school aged children complain of abdominal pain from functional origin on a weekly basis (Saps, Seshadri, Sztainberg, Schaffer, Marshall, & Lorenzo, 2009). It is estimated that anywhere from 25-66% of children with Functional Gastrointestinal Disorders continue to experience gastrointestinal

symptoms as adults (Campo et al., 2001). Therefore, patient outcomes can improve the earlier healthcare providers initiate a plan of care focusing on restoring digestive health.

Gender

Atlanta Center for Holistic and Integrative Medicine has more female than male patients. Since participants were recruited through the Center, it is not a surprise that the majority of the participants in this study were female (90.8%). Due to the majority of the participants being female, the analysis was run using females only to evaluate whether there were any differences in their self-reported gastrointestinal symptoms pre- and post- intervention, none were noted. However, literature worldwide has found that females suffer from Functional Gastrointestinal Disorders more frequently than males (Markert et al., 2014; Scalera & Loguercio, 2012; Myer et al., 2013; Sagawa et al., 2013; Ford et al., 2014; Porter et al., 2011; Lahner et al., 2013). In Western countries, it is estimated that females suffer from irritable bowel syndrome three times more frequently than males (Scalera & Loguercio, 2012). In Japan, a large Internet survey found a higher prevalence of functional dyspepsia and irritable bowel syndrome in females than males (Miwa, 2012). Porter et al (2011) found a seven-fold higher rate of functional constipation among females compared to males.

In contrast, there was an epidemiological study conducted in Mexico that found all Functional Gastrointestinal Disorders to be equally prevalent across both genders except for irritable bowel syndrome and functional constipation, which was found to be more prevalent in women (López-Colombo et al., 2012). The exact etiology behind female predominance remains unclear. Further research is needed to explore the etiology behind this finding. Some possible theories include hormonal changes (especially in menstruating women) and differences in perceived stress since this study found a significant correlation between perceived stress and

gastrointestinal quality of life. However, since there were so few males in this study further research would need to be conducted to explore the impact gender has on Functional Gastrointestinal Disorders.

Ethnicity

Research examining the association between ethnicities and Functional Gastrointestinal Disorders remains limited. In this study sample, the majority of the participants were Caucasian (77.9%). This finding is even more diverse than other research studies conducted in the past. One study examined participants suffering from irritable bowel syndrome, diarrhea dominant (n = 380) and functional diarrhea (n = 95) (Ford et al., 2013). The study reported a sample that was 94.2% Caucasian in the irritable bowel syndrome group and 90.5% Caucasian in the functional diarrhea group (Ford et al., 2013). Another study conducted by Ford et al. (2014) found the majority of irritable bowel syndrome (87.4%) and chronic idiopathic constipation (88.9%) patients to be Caucasian. In contrast, Myer et al. (2013) found no statistically significant differences in ambulatory visits related to gastrointestinal symptoms between Caucasians and African Americans (Myer et al., 2013).

Due to the majority of the participants being Caucasian, minorities were examined alone for improvements in self-reported gastrointestinal symptoms pre- and post-intervention. There were no statistically significant improvements in minorities' self-reported gastrointestinal symptoms pre- and post-intervention; however, there was a statistically significant improvement in minorities gastrointestinal quality of life based on the gastrointestinal quality of life index. While both Caucasians and minorities had statistically significant improvements in their gastrointestinal quality of life, minorities had a larger change in their gastrointestinal quality of

mean scores. Figure 2 presents the pre- and post- Gastrointestinal Quality of Life scores in Caucasians versus minorities.

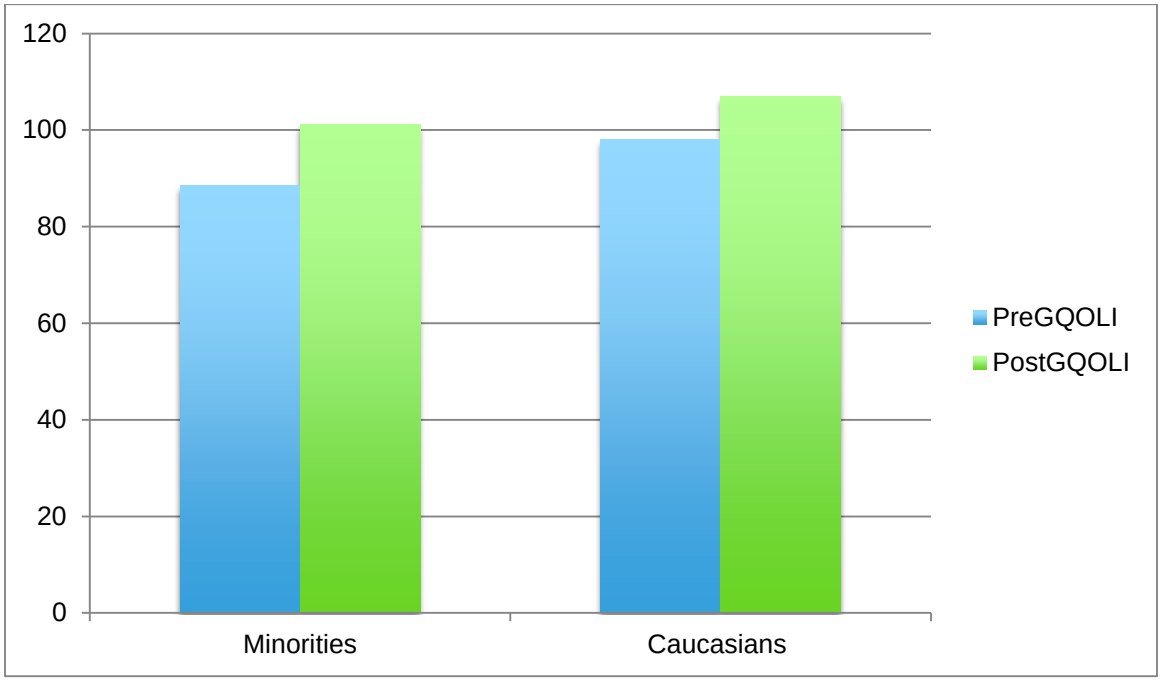

Figure 2. Gastrointestinal Quality of Life Scores Pre- and Post- Intervention Based on Ethnicity

Even with the low minority representation, the results found in this study were statistically significant. In this study, there was a significant association between minorities and lower gastrointestinal quality of life based on the Gastrointestinal Quality of Life Index. Even though there was an association between stress and gastrointestinal quality of life, the results of this study found no significant association between minorities and higher levels of perceived stress. Therefore, further research is needed to determine the reason why minorities have lower gastrointestinal quality of life and the role ethnicity plays on Functional Gastrointestinal Disorders.

Duration of Symptoms

The symptoms associated with Functional Gastrointestinal Disorders are typically chronic in nature. The diagnosis of Functional Gastrointestinal Disorders is given after an

individual has suffered from symptoms in the upper or lower gastrointestinal tract at least one time per week for 6 months without an organic cause (Lahner et al., 2013).

In this study sample, the majority of the participants have suffered from functional gastrointestinal symptoms for longer than 10 years (32.7%). This validates the notion that those suffering from Functional Gastrointestinal Disorders have little to no improvement in their symptoms, leading to physical, mental, and emotional distress. There were no statistically significant differences found in the self-reported gastrointestinal symptoms pre- and post-intervention between participants that had symptoms for less than three years and those that had symptoms greater than three years. The purpose of this intervention is to offer an alternative method to shorten the length of time individuals with Functional Gastrointestinal Disorders have to suffer from the corresponding symptoms.

Number of Attempted Treatments

Due to the chronic nature of Functional Gastrointestinal Disorders, most individuals have attempted a number of therapies to improve their symptoms without success. Individuals suffering from functional gastrointestinal symptoms are desperate for relief. In this study, the majority of participants had tried 3-5 different treatments (33.7%) to alleviate their symptoms. In addition, the results of this study found a negative correlation between the number of attempted treatments and gastrointestinal quality of life scores. In other words, the more treatments a participant has tried the lower their gastrointestinal quality of life. There were no statistically significant differences found in self-reported gastrointestinal symptoms pre- and post-intervention between participants that had tried less than three different treatments and those that had tried more than three different treatments.

Conventional or standard treatment for functional gastrointestinal disorders focuses primarily on symptom management with the use of laxatives, antidiarrheal, antispasmodics, or antidepressants. This symptom management approach has not been effective for managing Functional Gastrointestinal Disorders (Lahner et al., 2013). It is estimated that less than 50% of patients with irritable bowel syndrome are satisfied with their treatment plan (Aucoin, 2014). This is causing 21-51% of irritable bowel syndrome patients to seek complementary and alternative modalities (Aucoin, 2014). This gastrointestinal protocol of probiotics, digestive enzymes, and glutamine has the ability to restore digestive health and alleviate their symptoms.

Self-Reported Gastrointestinal Symptoms

Although the gastrointestinal symptoms improved (except for reflux) after the 8-week intervention, the only statistically significant improvement was abdominal pain related to food. There are several theories to support the improvement in abdominal pain related to food. For instance, individuals that have a compromised digestive tract are more prone to having food allergies and food sensitivities. Each of the three components in this gastrointestinal protocol (probiotics, digestive enzymes, and glutamine) plays a unique role in enhancing digestion and minimizing the negative effects of food allergies and sensitivities.

First of all, probiotics have been shown to function as a protective barrier, enhance immune response, and clear pathogens in the gastrointestinal tract (Ritchie & Romanuk, 2012). Marrs et al. (2013) conducted a systematic review to determine whether the human gut microbiota plays a role in food allergies. Out of five studies evaluating the gut microbiota, three of the publications reported significant findings to support the hypothesis that altered microbial exposure modulates risk of food allergies (Marrs et al., 2013).

Secondly, the amino acid glutamine is required for the normal production of immunoglobulin A in the intestines (Resnick, 2010). Improving immunoglobulin A in the mucosal lining can enhance the immune system and reduce the negative effects of food allergies and sensitivities. Glutamine also has been shown to have anti-inflammatory benefits in the intestinal tract (Ren et al., 2013). Therefore, glutamine can decrease the unpleasant side effects associated with gut inflammation after being exposed to food allergies or food sensitivities.

Lastly, digestive enzymes have the ability to increase gastric digestion, which plays a role on food allergies (Untersmayr, 2015). The specific digestive enzyme used in this research study, Similase GFCF, contains enzymes that support the digestion of gluten and casein. These two proteins have been shown to cause a number of side effects. Gluten has been shown to have negative effects on individuals' overall health including depression (Peters et al., 2014), foggy mind, bloating, and abdominal pain (Di Sabatino, 2015). Haq et al. (2014) found casein to cause a Th- mediated inflammatory response in the digestive tract of mice.

In conclusion, although this study did not examine the participants' diet, the implementation of this protocol can improve the way individuals respond to certain foods. Further research would be needed to examine the impact of various diets on Functional Gastrointestinal symptoms.

Additional Comments

Each week participants had the opportunity to leave additional comments. There were several positive comments, as well as some negative feedback. It was interesting that some of the participants reported symptoms returning after missing just one day of supplements. Table 13 presents some of the pertinent quotes found on the weekly survey.

Table 13

Additional Comments Found on Weekly Survey

Week	Pros	Cons
Week 1	"Constipation not quite as bad"	"Feeling less bloaty. Still having some days where I have excessive gross gas...And dont feel fully ""regular"" yet..."
	"My bloating has started to decrease some and less nausea after my largest meal"	"Extreme amount of gas"
	"Happy to say that my bowel movements are very regular and good. Better than normal. Also...been on vacation and eating a lot. Desserts! So not expecting to lose weight"	"Not noticing any changes yet. But hopeful"
	"Symptoms less intense and frequent"	"Feel extra gassy"
	"My nausea does not seem to be as bad after eating. Think the powder is part of it."	"I have more gas than usual. I feel like I am having more normal stools. I have begun an exercise program."
	"I have noticed a difference with the probiotic as I have less bloating and gas than the previous week."	"I was very bloated and constipated for the first four days. It is better now but not great."
	"I will say that I have been going to the bathroom more frequently and my stool is softer, which I like."	"I have experienced occasional nausea while on the supplements."
	"My bowel movements have become more frequent."	"Increased gas and stomach gurgling!"
	"I do feel like my constipation is a lot better"	
	"I feel I am having much less bloating, no diarrhea, more steady consistent BM's"	
Week 2	"My digestive system seems to have adjusted to the supplements!"	"The excess gas is on a daily basis"
	"Gas seems to be less and diarrhea was only once"	"Still experiencing slower transit of bowels each day"
	"Excited! The first time in 30 years I have gone a week without taking laxatives of	"I believe my constipation has gotten worse since I started these supplements"

	some kind. I am 44 years old and had constipation all my life. I am going regular every morning!! That is a blessing!!"	"I did not feel as good this weak. But I have had a lot of excess stress."
	"Noticed I feel a burning in my adam Apple area and stomach when I missed the enzymes. I can see how how enzymes are important." "less bloating!"	"Experiencing extreme bloating when coffee is consumed, which was not present prior to this study. Significant decrease in bowel movements as well."
	"lol. It is my birthday week and I ate alot but my waist is shrinking."	
Week 3	"Feeling good!"	"Had a really bad flare up Sat through Tues....very very gassy, bloated, stomach pain, culminating in a lot of diarrhea Monday night. Kept me up all night."
	"Can see big difference in regularity. Less run to restroom/ diarrhea"	
	"Feeling better mentally. Much less bloating and cravings!"	"Hormonal changes seems to change how digestive system works!"
	"Bowel movements are more regular"	
	"Reflux only 3 days last week. Getting better."	"These supplements make me so constipated I am nauseous. I have to stop taking them this week. I believe it is the Glutamine, as I suspected I had similar problems when I tried it in the past."
		"Still no significant changes in bowels, gas, belching...still hopeful though!" "I have not had bad stomach pains until this week. I ate some ice cream and it killed my stomach."
		"Excessive gas this week. Constipation is little better from last week"
Week 4	"Bloating still present, but feels reduced."	"I've occasionally felt nauseated after taking the digestive enzymes."
	"Starting to notice that my bowel movements are more complete, and I don't still feel constipated afterwards."	
	"I have felt really good this week. I have had zero gluten or dairy."	
Week 5	"This program has consistently improved constipation symptoms."	"Really lots of gas"

	"The constipation was only for two days this week and no discomfort. Much better than prior weeks. I do see improvement"	"I've noticed bloating and gurgling for a couple hours after the enzymes are taken."
Week 6	"Bloating discomfort is less!"	"By week 6 I discovered that the supplements were making more uncomfortable than comfortable. My constipation did not subside but I also become more crampy and bloated when taking the supplements."
	"Overall, my stomach has felt really good doing this study. I still have a little constipation."	
	"Feeling better, but still occasionally a lot of gas"	"Enjoying the process, yet still no significant changes in belching and constipation. Thank you for doing this research though."
	"See improvement in consistent bowel movements--even eating red meat and some dairy. No problems. I'm in week 2 of a workout regimen so expect to see weight and inches lost due to this"	"I am extremely constipated."
	"While doing this study I have only had one really bad stomach pains. Usually I would have had several."	
	"Really want to purchase these items after the test is over if possible. Thanks"	
Week 7	"Gas symptoms are consistent but the supplements aid in digestion (constipation has improved dramatically). This is a more comfortable remedy than laxatives."	"I'm surprised that I've struggled with constipation throughout this study."
	"Bloating sensation is not as uncomfortable"	"These past 2 weeks I have been extremely constipated, gassy and belching. I haven't felt good at all."
	"I think the results would be more effective if I took the supplements for a longer period of time. I can feel the benefits, but I don't think 8 weeks is enough time."	
	"I experienced the above symptoms only on the 1 day that I missed my supplements for the day. Otherwise, I have been 95% symptom free, and have recommended the supplements to many people with similar	

symptoms."

"Feeling more joyful & energetic, Praise the Lord!!"

"Noticed a difference when I missed the glutamine."

"Bloating was better this week"

"My stomach feels great! Still some constipation but overall I feel good."

"Bloating was significantly less this week - not sure why"

"the day I skipped I had the issues"

"Thanks for the trial made a big difference in my life."

"This is the first week I've not had diarrhea - so happy!"

Instruments

Weight and Waist Circumference

The results of this study reported a mean waist circumference of 84 cm. The mean waist circumference in this study (84 cm) is below the criteria for the diagnosis of overweight or obesity (> 88 cm) based on the National Institute of Health (n.d) criteria. Due to the fact that participants did not report height, the researcher was unable to calculate participants body mass index to classify whether the participants were overweight or obese. However, based on waist circumference alone, the results of this study vary from the majority of the studies found in literature examining the relationship between Functional Gastrointestinal Disorders and weight and waist circumference.

Several studies found that individuals suffering from Functional Gastrointestinal Disorders were more likely to be overweight or obese (Lee et al., 2015, Yilmaz, 2013; Lahner et al., 2013). Lee et al (2005) reported an increased waist circumference associated with an increased risk of irritable bowel syndrome. Yilmaz (2013) conducted a descriptive study in Turkey to evaluate effects of obesity on gastrointestinal quality of life. The results of this study found that obese patients suffered from gastrointestinal symptoms more frequently and had a decreased quality of life based on the Gastrointestinal Quality of Life Index (Yilmaz, 2013). Another study conducted on 199 European adults diagnosed with Functional Gastrointestinal Disorders found the average body mass index to be 39.2, which is considered class II obesity (Lahner et al., 2013). The findings in this study may differ from other studies due to the fact that the participants were recruited from a fee-for-service Integrative Medicine office in Atlanta where the majority of the patients are financially invested in their health and wellbeing.

Although it is no surprise, this study found a significant association between weight and waist circumference. There was a positive correlation between weight and waist circumference; as participants' weight increased, their waist circumference increased as well. Also, as suspected, the men in this study weighed more and had a larger waist circumference than females. These two statistically significant findings were anticipated.

The researcher was specifically exploring the association between weight and waist circumference on gastrointestinal quality of life and perceived stress. The results of this study found no statistically significant correlation between waist circumference and gastrointestinal quality of life or perceived stress. However, over the 8-week course of probiotics, digestive enzymes, and glutamine there was a significant amount of weight loss. Surprisingly, based on

this study's research findings, waist circumference was not a good indicator for the impact of Functional Gastrointestinal Disorders.

Perceived Stress

The results of this study validate the association between perceived stress and gastrointestinal quality of life. This study reported a negative correlation between perceived stress and gastrointestinal quality of life; as perceived stress increased, participants reported a lower level of gastrointestinal quality of life. These findings are similar to other research studies. Markert et al. (2014) conducted a study on 1857 participants, of that 62.78% met the criteria for at least one Functional Gastrointestinal Disorder. The results of this study found that those with higher levels of self-reported stress had worse gastrointestinal symptoms (Markert et al., 2014).

Another study was conducted on participants with irritable bowel syndrome ($n = 105$) to examine the association between social support and the severity of irritable bowel syndrome (Lackner et al., 2010). The Perceived Stress Scale was used to measure how the participants appraised their stress. The study found that perceived stress was a statistically significant predictor of pain severity ($p < 0.05$) (Lackner et al., 2010). Overall, this study validates that there is a brain-gut connection. However, further research is needed to explore whether stress or gastrointestinal symptoms is the initiating factor. In other words, is the association more brain-gut or gut-brain?

Gastrointestinal Quality of Life

Although this study did not have a control (healthy) group, the total gastrointestinal quality of life scores were significantly lower than the normative results found in other studies;

confirming individuals suffering from Functional Gastrointestinal Disorders have lower gastrointestinal quality of life. Several other studies have confirmed the results found in this study, that Functional Gastrointestinal Disorders are associated with lower gastrointestinal quality of life (Sagawa et al., 2013; Miwa, 2012, Aro et al., 2011; Singh et al., 2012; Vu et al., 2014).

However after the 8-week intervention of probiotics, digestive enzymes, and glutamine there was a significant improvement in the participants' self-reported gastrointestinal quality of life. In the post-intervention survey, the participants' gastrointestinal quality of life scores were closer to the normative values seen in a healthy population, indicating significant improvements in their symptoms with the intervention (Eypasch, 1995). Therefore, this gastrointestinal protocol has the ability to improve individuals suffering from Functional Gastrointestinal Disorders overall gastrointestinal quality of life.

Strengths of the Study

The researcher of this study has experience working with patients suffering from Functional Gastrointestinal Disorders. In practice, this protocol has been shown to improve patients' gastrointestinal symptoms. However, this is the first research study to examine and validate the combined benefits of probiotics, digestive enzymes, and glutamine on Functional Gastrointestinal Disorders. The procedures involved in this study were safe to take with additional medications or supplements. The primary purpose was to examine how the protocol would work in the average patient as they conducted their normal life. One of the strengths of this study was the large sample size (n = 98). The attrition rate was low (12.2%) with 86 completing the entire 8-week intervention. Another strength of the study was that all of the instruments had strong internal consistency based on Cronbach's alpha of greater than 0.7.

Limitations of the Study

There were several limitations in this study. One of the largest limitations was that there was not a control group to compare findings. Also, participants self-reported their own weight and waist circumference increasing risk of human error. Since participants used their own scales at home, there was no standardized calibration of the scales to ensure accuracy. All results were self-reported and not validated through medical examination. However, the way a participant perceives their gastrointestinal symptoms is essential to how they perceive their overall health. The fewer symptoms patients experience the fewer medical office visits they will require; which will ultimately decrease the costs associated with Functional gastrointestinal Disorders.

The participants did not complete the full Rome III Criteria survey to diagnosis participants with specific Functional Gastrointestinal Disorders, such as irritable bowel syndrome, functional constipation, functional dyspepsia, etc. Further research would be needed to examine whether specific Functional Gastrointestinal Disorders respond better to the intervention of probiotics, digestive enzymes, and glutamine.

Another limitation to the study was that the population examined was not diverse with the majority of the participants being Caucasian and female; this is partly due to the fact that participants were recruited from Atlanta Center for Holistic and Integrative Medicine where the primary demographic is Caucasian and female. This study did not control for a number of variables including dietary changes, alcohol intake, or prescribed medications that may alter the findings. A prospective cohort study is a good way to measure outcomes over time, however with this study design causality cannot be inferred.

Implications for Practice

Several implications for healthcare practice can be derived from the findings of this study. One of the significant findings, that is relevant to practice, is the higher level of perceived stress participants report the lower their gastrointestinal quality of life. It is essential to implement measures that encourage healthcare providers to address the whole patient including their perceived level of stress.

Secondly, this intervention of probiotics, digestive enzymes, and glutamine resulted in improvements in participants' quality of life. Being that this protocol has been shown to be safe and effective, implementing this protocol into practice has the ability to improve Functional Gastrointestinal Disorder patients' quality of life and decrease the costs associated with frequent medical office visits related to gastrointestinal symptoms.

If feasible, healthcare providers should explore potential food allergies and sensitivities that may be playing a key role in individuals' abdominal pain related to food. As evident in this research study, the gastrointestinal protocol significantly improved the participants' abdominal pain related to food. However, it would be beneficial to have an understanding of which foods may be aggravating their symptoms.

Being that these three supplements are naturally derived from food and do not go through the CYP450 system, there are less adverse effects and drug-drug interactions. Conventionally, proton pump inhibitors are one of the most widely used drugs for reflux. These medications can have detrimental effects on individuals overall health including malabsorption of B12, iron, magnesium and decreased bone density (Ito & Jensen, 2010). Implementing the more natural alternative of probiotics, digestive enzymes, and glutamine has been shown to be a safe and effective treatment for managing Functional Gastrointestinal Disorder symptoms.

Implications for Theory Building

Betty Neuman's Healthcare System model was the foundation for this research study. This model stresses the fact that each client's system is unique with no two patients identical. On a daily basis, the human body is exposed to known and unknown stressors that can disrupt the body's stability (Neuman, 1989). Based on the findings in this study, Betty Neuman's Healthcare System model could be expanded to specifically relate to individuals suffering from Functional Gastrointestinal Disorders. It is clear that the gastrointestinal tract could be affected by a number of stressors including food sensitivities, food allergies, emotional stress, or bacteria. The digestive tract would remain the core with three surrounding lines of defense. Each line of defense would represent a component of the gastrointestinal protocol including probiotics, digestive enzymes, and glutamine. The primary purpose of the lines of defense is to strengthen the digestive tract to prevent dysfunction from both internal and external stressors.

Future Research

Based on the results of this study, there are several areas that need additional research. The participants in this study were not diverse. Further research is needed to evaluate the role gender and ethnicity play on Functional Gastrointestinal Disorders. Possible theories for the female predominance include hormonal variations and perceived stress; however, the exact etiology behind the increased female prevalence remains vague and inconclusive.

Although minorities were shown to have lower gastrointestinal quality of life, the cause for this correlation remains unknown. Initially, it was thought that perceived stress might be contributing to lower gastrointestinal quality of life in minorities. However, the statistical analysis did not support this hypothesis. Therefore, future research is needed to explain the correlation between minorities and lower gastrointestinal quality of life.

Also, this study examined the combined benefit of probiotics, digestive enzymes, and glutamine; further research would be needed to determine which of the three of these supplements makes the largest impact on gastrointestinal symptoms. Lastly, further research is needed to determine whether these supplements actually restore digestive health or whether they just temporarily improve the symptoms. Therefore, future follow up with the participants is necessary to determine whether the symptoms returned after completing the 8-week intervention.

Dissemination

The research findings were disseminated through a podium presentation at Georgia Nursing Leadership Coalition's Doctoral Symposium in November 2015. The findings of this study will be shared with each of the three supplement companies including Metagenics, Orthomolecular, and Integrative Therapeutics. The author plans to apply for publication with the Functional Medicine Journal, the American Journal of Gastroenterology, the Journal for Nurse Practitioners, or Journal of Family Medicine and Primary Care.

Conclusion

This study adds to the body of literature that explores effective therapies for addressing Functional Gastrointestinal Disorders. This population often has little to no improvement in their symptoms with conventional therapies focusing on symptom management. Functional Gastrointestinal Disorders have a negative effect on patients overall health. The intervention of probiotics, digestive enzymes, and glutamine has been shown to be safe, natural, and effective for reducing gastrointestinal symptoms. While this study is the first to collectively examine the benefits of probiotics, digestive enzymes, and glutamine, the science behind each component is evident. After the 8-week intervention, there were significant improvements in weight loss and gastrointestinal quality of life. Therefore, this protocol has the power to transform patient's

quality of life and reduce the overall healthcare cost associated with Functional Gastrointestinal Disorders.

References

Andreou, E., Alexopoulos, E. C., Lionis, C., Varvogli, L., Gnardellis, C., Chrousos, G. P., & Darviri, C. (2011). Perceived Stress Scale: reliability and validity study in Greece. *International Journal Of Environmental Research And Public Health, 8*(8), 3287-3298. doi: 10.3390/ijerph8083287

Arabshahi, S., Lahmann, P. H., Williams, G. M., & van der Pols, J. C. (2014). Predictors of change in weight and waist circumference: 15-year longitudinal study in Australian adults. *European Journal Of Clinical Nutrition, 68*(3), 309-315. doi:10.1038/ejcn.2013.260

Aro, P., Talley, N. J., Agréus, L., Johansson, S. E., Bolling-Sternevald, E., Storskrubb, T., & Ronkainen, J. (2011). Functional dyspepsia impairs quality of life in the adult population. *Alimentary Pharmacology & Therapeutics, 33*(11), 1215-1224. doi: 10.1111/j.1365-2036.2011.04640.x

Aucoin, M.-P. M.-J. K. (2014). Mindfulness-Based Therapies in the Treatment of Functional Gastrointestinal Disorders: A Meta-Analysis. *Evidence-based Complementary & Alternative Medicine (eCAM)*, 1-11. doi: 10.1155/2014/140724

Ayala, A., Nijpels, G., & Lakerveld, J. (2014). Validity of self-measured waist circumference in adults at risk of type 2 diabetes and cardiovascular disease. *BMC Medicine, 12*(1), 1-12. doi: 10.1186/s12916-014-0170-x

Barbosa-Leiker, C., Kostick, M., Lei, M., McPherson, S., Roper, V., Hoekstra, T., & Wright, B. (2013). Measurement invariance of the perceived stress scale and latent mean differences across gender and time. *Stress & Health: Journal of the International Society for the Investigation of Stress, 29*(3), 253-260.

Benjamin, J., Makharia, G., Ahuja, V., Anand Rajan, K., Kalaivani, M., Gupta, S., & Joshi, Y. (2012). Glutamine and Whey Protein Improve Intestinal Permeability and Morphology in Patients with Crohn's Disease: A Randomized Controlled Trial. *Digestive Diseases & Sciences, 57*(4), 1000-1012. doi: 10.1007/s10620-011-1947-9

Borgaonkar, M. R., & Irvine, E. J. (2000). Quality of life measurement in gastrointestinal and liver disorders. *Gut, 47*(3), 444-454.

Camilleri, M., Madsen, K., Spiller, R., Van Meerveld, B. G., & Verne, G. N. (2012). Intestinal barrier function in health and gastrointestinal disease. *Neurogastroenterology & Motility, 24*(6), 503-512. doi: 10.1111/j.1365-2982.2012.01921.x

Campo, J., Lorenzo, C., Chiappetta, L., Bridge, J., Colborn, D., Jr, J., . . . Brent, D. (2001). Adult Outcomes of Pediatric Recurrent Abdominal Pain: Do They Just Grow Out of It? Pediatrics.

Cary, V. A., & Boullata, J. (2010). What is the evidence for the use of probiotics in the treatment of inflammatory bowel disease? *Journal of Clinical Nursing, 19*(7-8), 904-916. doi: 10.1111/j.1365-2702.2009.03123.x

Castellazzi, A. M., Valsecchi, C., Caimmi, S., Licari, A., Marseglia, A., Leoni, M. C., . . . Marseglia, G. L. (2013). Probiotics and food allergy. *Italian Journal of Pediatrics, 39*(1), 1-10. doi: 10.1186/1824-7288-39-47

Chen, L., Tao, S.-f., Xu, Y., Fang, F., & Peng, S.-y. (2005). Patients' quality of life after laparoscopic or open cholecystectomy. *Journal Of Zhejiang University. Science. B, 6*(7), 678-681.

Choung, R. S., Locke, G. R., Schleck, C. D., Zinsmeister, A. R., & Talley, N. J. (2013). Associations between medication use and functional gastrointestinal disorders: a

population-based study. *Neurogastroenterology & Motility, 25*(5), 413-e298. doi: 10.1111/nmo.12082

Cohen, S., Kamarck, T., & Mermelstein, R. (1983). A global measure of perceived stress, 385.

Cohen, S., & Williamson, G. (1988). Perceived Stress Scale [Instrument]. Published instrument. Retrieved from http://www.psy.cmu.edu/~scohen/

Damon, H., Schott, A. M., Barth, X., Faucheron, J. L., Abramowitz, L., Siproudhis, L., & ... Mion, F. (2008). Clinical characteristics and quality of life in a cohort of 621 patients with faecal incontinence. *International Journal Of Colorectal Disease*, *23*(9), 845-851. doi:10.1007/s00384-008-0489-x

De-Souza, D. A., & Greene, L. J. (2005). Intestinal permeability and systemic infections in critically ill patients: effect of glutamine. *Critical Care Medicine, 33*(5), 1125-1135.

Dekkers, J. C., van Wier, M. F., Hendriksen, I. J. M., Twisk, J. W. R., & van Mechelen, W. (2008). Accuracy of self-reported body weight, height and waist circumference in a Dutch overweight working population. *BMC Medical Research Methodology, 8*, 69-69. doi: 10.1186/1471-2288-8-69

Di Lorio, C. K. (2005). Measurement in health behavior: Methods for research and evaluation. San Francisco, CA: John Wiley & Sons.

Dimidi, E., Christodoulides, S., Fragkos, K. C., Scott, S. M., & Whelan, K. (2014). The effect of probiotics on functional constipation in adults: a systematic review and meta-analysis of randomized controlled trials. *American Journal of Clinical Nutrition, 100*(4), 1075-1084. doi: 10.3945/ajcn.114.089151

Di Sabatino, A., Volta, U., Salvatore, C., Biancheri, P., Caio, G., De Giorgio, R., & ... Corazza, G. R. (2015). Original article: Small Amounts of Gluten in Subjects With Suspected

Nonceliac Gluten Sensitivity: A Randomized, Double-Blind, Placebo-Controlled, Cross-Over Trial. *Clinical Gastroenterology And Hepatology*, *13*1604-1612.e3. doi:10.1016/j.cgh.2015.01.029

Eypasch, E., Williams, J. I., Wood-Dauphinee, S., Ure, B. M., Schmülling, C., Neugebauer, E., & Troidl, H. (1995). Gastrointestinal quality of life index: development, validation and application of a new instrument. *The British Journal Of Surgery, 82*(2), 216-222.

Ezzati, A. (2013). Validation of the Perceived Stress Scale in a community sample of older adults. *International Journal of Geriatric Psychiatry, 28*(12), 645-652. doi: 10.1002/gps.4049

Ford, A. C., Bercik, P., Morgan, D. G., Bolino, C., Pintos-Sanchez, M. I., & Moayyedi, P. (2014a). Characteristics of functional bowel disorder patients: a cross-sectional survey using the Rome III criteria. *Alimentary Pharmacology & Therapeutics, 39*(3), 312-321. doi: 10.1111/apt.12573

Ford, A. C., Quigley, E. M., Lacy, B. E., Lembo, A. J., Saito, Y. A., Schiller, L. R., & ... Moayyedi, P. (2014b). Efficacy of prebiotics, probiotics, and synbiotics in irritable bowel syndrome and chronic idiopathic constipation: systematic review and meta-analysis. *The American Journal Of Gastroenterology*, *109*(10), 1547. doi:10.1038/ajg.2014.202

Ford, A. C., Talley, N. J., Walker, M. M., & Jones, M. P. (2014c). Increased prevalence of autoimmune diseases in functional gastrointestinal disorders: case-control study of 23 471 primary care patients. *Alimentary Pharmacology & Therapeutics, 40*(7), 827-834. doi: 10.1111/apt.12903

Gaylord, S. A., Palsson, O. S., Garland, E. L., Faurot, K. R., Coble, R. S., Mann, J. D., . . . Whitehead, W. E. (2011). Mindfulness training reduces the severity of irritable bowel

syndrome in women: results of a randomized controlled trial. *The American Journal Of Gastroenterology*, *106*(9), 1678-1688. doi: 10.1038/ajg.2011.184

Hickson, M. (2013). Examining the evidence for the use of probiotics in clinical practice. *Nursing Standard*, *27*(29), 35-41.

Hungin, A. P. S., Mulligan, C., Pot, B., Whorwell, P., Agréus, L., Fracasso, P., . . . Wit, N. (2013). Systematic review: probiotics in the management of lower gastrointestinal symptoms in clinical practice - an evidence-based international guide. *Alimentary Pharmacology & Therapeutics*, *38*(8), 864-886. doi: 10.1111/apt.12460

International Foundation for Functional Gastrointestinal Disorders (2015). Dyspepsia. Retrieved from http://www.iffgd.org/site/gi-disorders/functional-gi-disorders/dyspepsia

International Foundation for Functional Gastrointestinal Disorders (2015). Functional Gastrointestinal Disorders. Retrieved from http://www.iffgd.org/site/gi-disorders/functional-gi-disorders/

International Foundation for Functional Gastrointestinal Disorders (2009). Reporter's Guide to Functional Gastrointestinal Disorders. Retrieved from http://www.iffgd.org/pdfs/reporters-guide-fgid.pdf

Ito, T., & Jensen, R. T. (2010). Association of long-term proton pump inhibitor therapy with bone fractures and effects on absorption of calcium, vitamin B12, iron, and magnesium. *Current Gastroenterology Reports*, *12*(6), 448-457. doi:10.1007/s11894-010-0141-0

Jafari, E., Vahedi, H., Merat, S., Momtahen, S., & Riahi, A. (2014). Therapeutic effects, tolerability and safety of a multi-strain probiotic in Iranian adults with irritable bowel syndrome and bloating. *Archives of Iranian Medicine (AIM)*, *17*(7), 466-470.

Jerome, G. J., Dalcin, A., Coughlin, J. W., Fitzpatrick, S., Wang, N.-Y., Durkin, N., . . . Appel, L. J. (2014). Longitudinal accuracy of web-based self-reported weights: results from the Hopkins POWER Trial. *Journal Of Medical Internet Research, 16*(7), e173-e173. doi: 10.2196/jmir.3332

Karam, F., Bérard, A., Sheehy, O., Huneau, M. C., Briggs, G., Chambers, C., . . . Wolfe, L. (2012). Reliability and validity of the 4- item Perceived Stress Scale among pregnant women: Results from the OTIS antidepressants study. *Research in Nursing & Health, 35*(4), 363-375. doi: 10.1002/nur.21482

Kaur, R., & Sekhon, B. S. (2012). Enzymes as drugs: an overview. *Journal of Pharmaceutical Education & Research, 3*(2), 29-41.

Kearney, D. J., McDermott, K., Martinez, M., & Simpson, T. L. (2011). Association of participation in a mindfulness programme with bowel symptoms, gastrointestinal symptom-specific anxiety and quality of life. *Alimentary Pharmacology & Therapeutics, 34*(3), 363-373. doi: 10.1111/j.1365-2036.2011.04731.x

Kim, M., & Mallory, C. (2014). *Statistics for evidence-based practice in nursing*. Burlington, MA: Jones & Bartlett Learning.

Kushnir, V. M., Cassell, B., Gyawali, C. P., Newberry, R. D., Kibe, P., Nix, B. D., . . . Sayuk, G. S. (2013). Genetic variation in the beta-2 adrenergic receptor (ADRB2) predicts functional gastrointestinal diagnoses and poorer health-related quality of life. *Alimentary Pharmacology & Therapeutics, 38*(3), 313-323. doi: 10.1111/apt.12378

Lackner, J. M., Brasel, A. M., Quigley, B. M., Keefer, L., Krasner, S. S., Powell, C., . . . Sitrin, M. D. (2010). The ties that bind: perceived social support, stress, and IBS in severely affected patients. *Neurogastroenterology And Motility: The Official Journal Of The*

European Gastrointestinal Motility Society, *22*(8), 893-900. doi: 10.1111/j.1365-2982.2010.01516.x

Lackner, J. M., Gudleski, G. D., Dewanwala, A., Ma, C.-X., & Naliboff, B. (2014). Fear of GI Symptoms has an Important Impact on Quality of Life in Patients With Moderate-to-Severe IBS. *American Journal of Gastroenterology*, *109*(11), 1815-1823. doi: 10.1038/ajg.2014.241

Lahner, E., Bellentani, S., Bastiani, R. D., Tosetti, C., Cicala, M., Esposito, G., . . . Annibale, B. (2013). A survey of pharmacological and nonpharmacological treatment of functional gastrointestinal disorders. *United European Gastroenterology Journal*, *1*(5), 385-393. doi: 10.1177/2050640613499567

Le Pluart, D., Sabaté, J. M., Bouchoucha, M., Hercberg, S., Benamouzig, R., & Julia, C. (2015). Functional gastrointestinal disorders in 35 447 adults and their association with body mass index. *Alimentary Pharmacology & Therapeutics*. doi: 10.1111/apt.13143

Lee, C. G., Lee, J. K., Kang, Y.-S., Shin, S., Kim, J. H., Lim, Y. J., . . . Kang, H. W. (2015). Visceral Abdominal Obesity Is Associated With an Increased Risk of Irritable Bowel Syndrome. *American Journal of Gastroenterology*, *110*(2), 310-319. doi: 10.1038/ajg.2014.422

Leite, R. D., Lima, N. L., Leite, C. A. C., Farhat, C. K., Guerrant, R. L., & Lima, A. A. M. (2013). Improvement of intestinal permeability with alanyl-glutamine in HIV patients: a randomized, double blinded, placebo-controlled clinical trial. *Arquivos De Gastroenterologia, 50*(1), 56-63.

Lim, L. L. Y., Seubsman, S.-a., Sleigh, A., & Bain, C. (2012). Validity of self-reported abdominal obesity in Thai adults: A comparison of waist circumference, waist-to-hip

ratio and waist-to-stature ratio. *Nutrition, Metabolism and Cardiovascular Diseases, 22,* 42-49. doi: 10.1016/j.numecd.2010.04.003

López-Colombo, A., Morgan, D., Bravo-González, D., Montiel-Jarquín, A., Méndez-Martínez, S., & Schmulson, M. (2012). The Epidemiology of Functional Gastrointestinal Disorders in Mexico: A Population-Based Study. *Gastroenterology Research & Practice,* 1-8. doi: 10.1155/2012/606174

Machnicki, G., Pefaur, J., Gaite, L., Linchenco, A. M., Raimondi, C., Schiavelli, R., . . . Margolis, M. K. (2008). Gastrointestinal (GI)-Specific patient reported outcomes instruments differentiate between renal transplant patients with or without GI symptoms: results from a South American cohort. *Health & Quality of Life Outcomes, 6,* 1-10. doi: 10.1186/1477-7525-6-53

Markert, C., Suarez-Hitz, K., Ehlert, U., & Nater, U. M. (2014). Distress criterion influences prevalence rates of functional gastrointestinal disorders. *BMC Gastroenterology*, *14*(1), 206-220. doi: 10.1186/s12876-014-0215-9

Maxwell, D., Thompson, S., Richmond, B., McCagg, J., & Ubert, A. (2012). Quality of life after laparoscopic cholecystectomy for biliary dyskinesia in the pediatric population: a pilot study. *The American Surgeon, 78*(1), 111-118.

McCormick, J. B., Hammer, R. R., Farrell, R. M., Geller, G., James, K. M., Loftus, E. V., Jr., . . . Sharp, R. R. (2012). Experiences of patients with chronic gastrointestinal conditions: in their own words. *Health And Quality Of Life Outcomes, 10,* 25-25. doi: 10.1186/1477-7525-10-25

McFarland, L. V. (2008). Antibiotic-associated diarrhea: epidemiology, trends and treatment. *Future Microbiology, 3*(5), 563-578. doi: 10.2217/17460913.3.5.563

Miwa, H. (2012). Life style in persons with functional gastrointestinal disorders--large-scale internet survey of lifestyle in Japan. *Neurogastroenterology And Motility: The Official Journal Of The European Gastrointestinal Motility Society, 24*(5), 464. doi: 10.1111/j.1365-2982.2011.01872.x

Mochiki, E., Ohno, T., Yanai, M., Toyomasu, Y., Andoh, H., & Kuwano, H. (2011). Effects of glutamine on gastrointestinal motor activity in patients following gastric surgery. *World Journal Of Surgery, 35*(4), 805-810. doi: 10.1007/s00268-011-0962-5

Morgan, E. S., Umberson, K., & Hertzog, C. (2014). Construct validation of self-reported stress scales. *Psychological Assessment, 26*(1), 90-99. doi: 10.1037/a0034714

Munro, B. H. (2005). Statistical Methods for Health Care Research (5th ed.). Philadelphia, PA: Lippincott Williams & Wilkins.

Myer, P. A., Mannalithara, A., Singh, G., Singh, G., Pasricha, P. J., & Ladabaum, U. (2013). Clinical and economic burden of emergency department visits due to gastrointestinal diseases in the United States. *The American Journal Of Gastroenterology, 108*(9), 1496-1507. doi: 10.1038/ajg.2013.199

Naliboff, B. D., Kim, S. E., Bolus, R., Bernstein, C. N., Mayer, E. A., & Chang, L. (2012). Gastrointestinal and psychological mediators of health-related quality of life in IBS and IBD: a structural equation modeling analysis. *The American Journal Of Gastroenterology, 107*(3), 451-459. doi: 10.1038/ajg.2011.377

Neuman, B. M. (1989). *The Neuman systems model / by Betty Neuman*: Norwalk, Conn. : Appleton & Lange, c1989. 2nd ed.

Nordin, M. S. (2013). Psychometric evaluation and normative data of the Swedish version of the 10-item perceived stress scale. *Scandinavian Journal of Psychology, 54*(6), 502-507. doi: 10.1111/sjop.12071

Owen, C., Marks, D. J. B., & Banks, M. (2014). The dangers of proton pump inhibitor therapy. *British Journal Of Hospital Medicine (London, England: 2005), 75*(7), C108-C112.

Marrs, T., Bruce, K. D., Logan, K., Rivett, D. W., Perkin, M. R., Lack, G., & Flohr, C. (2013). Is there an association between microbial exposure and food allergy? A systematic review. *Pediatric Allergy & Immunology, 24*(4), 311-320.e8. doi:10.1111/pai.12064

Paez, K. A., Griffey, S. J., Thompson, J., & Gillman, M. W. (2014). Validation of self-reported weights and heights in the avoiding diabetes after pregnancy trial (ADAPT). *BMC Medical Research Methodology, 14*(1), 1-16. doi: 10.1186/1471-2288-14-65

Paschal, A. M., Rush, S. E., & Sadler, T. (2014). Factors associated with medication adherence in patients with epilepsy and recommendations for improvement. *Epilepsy & Behavior, 31*, 346-350. doi: 10.1016/j.yebeh.2013.10.002

Peters, S. L., Biesiekierski, J. R., Yelland, G. W., Muir, J. G., & Gibson, P. R. (2014). Randomised clinical trial: gluten may cause depression in subjects with non-coeliac gluten sensitivity - an exploratory clinical study. *Alimentary Pharmacology & Therapeutics, 39*(10), 1104-1112. doi:10.1111/apt.12730

Phatak, U. P., & Pashankar, D. S. (2014). Prevalence of functional gastrointestinal disorders in obese and overweight children. *International Journal of Obesity, 38*(10), 1324. doi: 10.1038/ijo.2014.67

Porter, C. K., Gormley, R., Tribble, D. R., Cash, B. D., & Riddle, M. S. (2011). The Incidence and gastrointestinal infectious risk of functional gastrointestinal disorders in a healthy US

adult population. *The American Journal Of Gastroenterology*, *106*(1), 130-138. doi: 10.1038/ajg.2010.371

Rao, R. K., & Samak, G. (2013). Protection and Restitution of Gut Barrier by Probiotics: Nutritional and Clinical Implications. *Current Nutrition And Food Science*, *9*(2), 99-107.

Ren, W. K., Yin, J., X-P, Z. H. U., Liu, G., Li, N. Z., Y-Y, P., & Y-L, Y. I. N. (2013). Glutamine on intestinal inflammation: a mechanistic perspective *European Journal of Inflammation, 11*(2), 315-326.

Ringel, Y., & Ringel-Kulka, T. (2011). The rationale and clinical effectiveness of probiotics in irritable bowel syndrome. *Journal Of Clinical Gastroenterology, 45 Suppl*, S145-S148. doi: 10.1097/MCG.0b013e31822d32d3

Ritchie, M. L., & Romanuk, T. N. (2012). A meta-analysis of probiotic efficacy for gastrointestinal diseases. *PLoS ONE*, *7*(4), 1-11. doi: 10.1371/journal.pone.0034938

Rogha, M., Esfahani, M. Z., & Zargarzadeh, A. H. (2014). The efficacy of a synbiotic containing Bacillus Coagulans in treatment of irritable bowel syndrome: a randomized placebo-controlled trial. *Gastroenterology & Hepatology from Bed to Bench, 7*(3), 156-163.

Sagawa, T., Okamura, S., Kakizaki, S., Zhang, Y., Morita, K., & Mori, M. (2013). Functional gastrointestinal disorders in adolescents and quality of school life. *Journal Of Gastroenterology And Hepatology, 28*(2), 285-290. doi: 10.1111/j.1440-1746.2012.07257.x

Sandblom, G., Videhult, P., Karlson, B.-M., Wollert, S., Ljungdahl, M., Darkahi, B., . . . Rasmussen, I. C. (2009). Validation of gastrointestinal quality of life index in Swedish for assessing the impact of gallstones on health-related quality of life. *Value in Health, 12*, 181-184. doi: 10.1111/j.1524-4733.2008.00396.x

Saps, M., Seshadri, R., Sztainberg, M., Schaffer, G., Marshall, B., & Lorenzo, C. (n.d.). A Prospective School-based Study of Abdominal Pain and Other Common Somatic Complaints in Children. The Journal of Pediatrics, 322-326.

Scalera, A., & Loguercio, C. (2012). Focus on irritable bowel syndrome. *European Review For Medical And Pharmacological Sciences, 16*(9), 1155-1171.

Sevastiadou, S., Malamitsi-Puchner, A., Costalos, C., Skouroliakou, M., Briana, D. D., Antsaklis, A., & Roma-Giannikou, E. (2011). The impact of oral glutamine supplementation on the intestinal permeability and incidence of necrotizing enterocolitis/septicemia in premature neonates. *The Journal Of Maternal-Fetal & Neonatal Medicine: The Official Journal Of The European Association Of Perinatal Medicine, The Federation Of Asia And Oceania Perinatal Societies, The International Society Of Perinatal Obstetricians, 24*(10), 1294-1300. doi: 10.3109/14767058.2011.564240

Shi, H., Lee, K., Lee, H., Uen, Y., & Chiu, C. (2011). Response shift effect on gastrointestinal quality of life index after laparoscopic cholecystectomy. *Quality Of Life Research, 20*(3), 335-341 7p. doi:10.1007/s11136-010-9760-z

Shrive, F. M., Stuart, H., Quan, H., & Ghali, W. A. (2006). Dealing with missing data in a multi-question depression scale: A comparison of imputation methods. BioMed Central, 6:57. doi: 10.1186/1471-2288-6-57

Simrén, M., Barbara, G., Flint, H. J., Spiegel, B. M. R., Spiller, R. C., Vanner, S., . . . Zoetendal, E. G. (2013). Intestinal microbiota in functional bowel disorders: a Rome foundation report. *Gut, 62*(1), 159-176. doi: 10.1136/gutjnl-2012-302167

Singh, P., Agnihotri, A., Pathak, M. K., Shirazi, A., Tiwari, R. P., Sreenivas, V., . . . Makharia, G. K. (2012). Psychiatric, somatic and other functional gastrointestinal disorders in patients with irritable bowel syndrome at a tertiary care center. *Journal Of Neurogastroenterology And Motility, 18*(3), 324-331. doi: 10.5056/jnm.2012.18.3.324

Spiegel, B. M. R., Khanna, D., Bolus, R., Agarwal, N., Khanna, P., & Lin, C. (2011). Understanding gastrointestinal distress: a framework for clinical practice. *American Journal of Gastroenterology, 106*(3), 380-385. doi: 10.1038/ajg.2010.383

Stake-Nilsson, K., Hultcrantz, R., Unge, P., & Wengström, Y. (2012). Complementary and alternative medicine used by persons with functional gastrointestinal disorders to alleviate symptom distress. *Journal of Clinical Nursing, 21*(5/6), 800-808. doi: 10.1111/j.1365-2702.2011.03985.x

Stout, J. (2013). Are you obtaining the proper enzymes? *Life Extension, 19*(1), 1-8.

Suardi, E., Crippa, F., & Monforte, A. d. A. (2013). PROBIOTICS IN THE PREVENTION OF ANTIBIOTIC-ASSOCIATED DIARRHEA IN ADULTS. *International Journal of Probiotics & Prebiotics, 8*(1), 41-44.

Taylor, J. M. (2014). Psychometric analysis of the ten-Item Perceived Stress Scale. *Psychological Assessment*. doi: 10.1037/a0038100

Tielemans, M. M., Jaspers Focks, J., van Rossum, L. G. M., Eikendal, T., Jansen, J. B. M. J., Laheij, R. J. F., & van Oijen, M. G. H. (2013). Gastrointestinal symptoms are still prevalent and negatively impact health-related quality of life: a large cross-sectional population based study in the netherlands. *PLoS ONE, 8*(7), 1-7. doi: 10.1371/journal.pone.0069876

Tillisch, K., & Labus, J. S. (2011). Imaging and Advanced Technology: Advances in Imaging the Brain–Gut Axis: Functional Gastrointestinal Disorders. *Gastroenterology, 140*, 407-411.e401. doi: 10.1053/j.gastro.2010.12.014

Toledo, A. H., Hendrix, L., Buchholz, V., Fisher, E., Newton, K., Smith, C., & Gerber, D. A. (2012). Improvement of gastrointestinal symptoms after conversion from mycophenolate mofetil to enteric-coated mycophenolate sodium in liver transplant patients. *Clinical Transplantation, 26*(1), 156-163. doi: 10.1111/j.1399-0012.2011.01444.x

Untersmayr, E. (2015). The influence of gastric digestion on the development of food allergy. *Revue Francaise D'allergologie*, *55*(7), 444. doi:10.1016/j.reval.2015.09.004

van Dijkum, E. J. M. N., Terwee, C. B., Oosterveld, P., van der Meulen, J. H. P., Gouma, D. J., & de Haes, J. C. J. m. (2000). Validation of the gastrointestinal quality of life index for patients with potentially operable periampullary carcinoma. *British Journal of Surgery*, *87*(1), 110-115. doi: 10.1046/j.1365-2168.2000.01307.x

Vu, J., Kushnir, V., Cassell, B., Gyawali, C. P., & Sayuk, G. S. (2014). The impact of psychiatric and extraintestinal comorbidity on quality of life and bowel symptom burden in functional GI disorders. *Neurogastroenterology And Motility: The Official Journal Of The European Gastrointestinal Motility Society*, *26*(9), 1323-1332. doi:10.1111/nmo.12396

Waller, P. A., Gopal, P. K., Leyer, G. J., Ouwehand, A. C., Reifer, C., Stewart, M. E., & Miller, L. E. (2011). Dose-response effect of Bifidobacterium lactis HN019 on whole gut transit time and functional gastrointestinal symptoms in adults. *Scandinavian Journal of Gastroenterology*, *46*(9), 1057. doi: 10.3109/00365521.2011.584895

Walter, S. A., Jones, M. P., Talley, N. J., Kjellström, L., Nyhlin, H., Andreasson, A. N., & Agréus, L. (2013). Abdominal pain is associated with anxiety and depression scores in a sample of the general adult population with no signs of organic gastrointestinal disease. *Neurogastroenterology And Motility: The Official Journal Of The European Gastrointestinal Motility Society, 25*(9), 741-e576. doi: 10.1111/nmo.12155

Wang, B., Wu, G., Zhou, Z., Dai, Z., Sun, Y., Ji, Y., . . . Wu, Z. (2014). Glutamine and intestinal barrier function. *Amino Acids*.

Wang, Y. M., Chang, Y., Chang, Y. Y., Cheng, J., Li, J., Wang, T., . . . Wang, B. M. (2012). Serotonin transporter gene promoter region polymorphisms and serotonin transporter expression in the colonic mucosa of irritable bowel syndrome patients. *Neurogastroenterology And Motility: The Official Journal Of The European Gastrointestinal Motility Society, 24*(6), 560. doi: 10.1111/j.1365-2982.2012.01902.x

Wierdsma, N. J., van Bodegraven, A. A., Uitdehaag, B. J., Arjaans, W., Savelkoul, P. M., Kruizenga, H. M., & van Bokhorst-de van der Schueren, M. E. (2009). Fructo-oligosaccharides and fibre in enteral nutrition has a beneficial influence on microbiota and gastrointestinal quality of life. *Scandinavian Journal Of Gastroenterology*, *44*(7), 804. doi:10.1080/00365520902839675

Whitcomb, D. C., & Lowe, M. E. (2007). Human pancreatic digestive enzymes. *Digestive Diseases And Sciences, 52*(1), 1-17.

Yilmaz, T. U. (2013). Obesity and gastrointestinal quality of life: A hospital-based survey. *Saudi Journal of Obesity, 1*(2), 57.

Ziegler, F., Seddiki, L., Marion-Letellier, R., Lavoinne, A., & Déchelotte, P. (2011). Original article: effects of l-glutamine supplementation alone or with antioxidants on hydrogen

peroxide-induced injury in human intestinal epithelial cells. *e-SPEN, the European e-Journal of Clinical Nutrition and Metabolism, 6*, e211-e216. doi: 10.1016/j.eclnm.2011.07.001

Appendix A

Flow Diagram

Appendix B

Recruiting Flyer

Suffering with Digestive Issues?

Do you have *bloating*, *constipation*, *diarrhea*, *flatulence*, *reflux*, or *abdominal pain*?
We may have the solution for you!

Atlanta Center for Holistic and Integrative Medicine is starting a research study to help restore your digestive health THIS summer and we NEED you!

This research study will be conducted over 8 weeks. As a participant of the study, you will receive all supplements FREE OF CHARGE. Over the 8 weeks, you will be responsible for taking a pre and post survey, responding to a brief weekly email, and taking the daily supplements as recommended.

Please see the inclusion and exclusion criteria below to see if you may qualify. If you are interested please email kristin.corbin@bobcats.gcsu.edu for more information.

Inclusion Criteria:

- Male or female aged 18-65 years old
- Current digestive symptoms
- Physical exam within the past 12 months
- Proficient in English
- Have internet access for weekly emails
- Own a scale and measuring tape in centimeter
- Be willing to sign an informed consent

Exclusion Criteria:

- Younger than 18 years old or older than 65 years old
- Pregnant or nursing
- Diagnosed with an organic disease, such as Crohn's disease, ulcerative colitis, or gastrointestinal tumors
- You will be excluded from this study if you respond "yes" to any of the following questions:
    - In the past 3 months, have you noticed blood in your stools?
    - In the past 3 months, have you noticed black stools, unrelated to iron supplements?
    - In the past 3 months, how often have you vomited blood?
    - Have you been told by your doctor that you are anemic (if female, not due to your menstrual cycle)?
    - In the past 3 months, have you lost 10 lbs of weight unintentionally?

- If over the age of 50, have you had a recent major change in bowel movements?
- In the past 3 months, have you had persistent or worsening hoarseness of the voice?
- In the past 3 months, have you had persistent or worsening neck or throat pain?
- In the past 3 months, have you had chest pain on exertion, or chest pain related to heart problems?
- In the past 3 months, have you had difficulty swallowing?

Appendix C

Informed Consent

Informed Consent Form

Restoring Digestive Health
With Probiotics, Digestive Enzymes, and Glutamine

PURPOSE OF RESEARCH

You are invited to participate in a research study on restoring digestive health. The primary goal of this research study is to determine whether a well-established protocol used at Atlanta Center for Holistic and Integrative Medicine is effective at restoring digestive health. This protocol utilizes probiotics, digestive enzymes, and glutamine.

You were selected as a possible participant in this study because you are currently suffering from gastrointestinal symptoms. This research study is looking for 100 participants with functional gastrointestinal disorders including reflux, constipation, diarrhea, nausea, abdominal pain, bloating, and irritable bowel syndrome.

VOLUNTARY PARTICIPATION

Your participation in this study is entirely voluntary. You are free to terminate your participation in this study at any point without reason. If you decide to terminate your participation, please notify Kristin Corbin at kristin.corbin@bobcats.gcsu.edu.

INCLUSION AND EXCLUSION CRITERIA

By signing this informed consent you are agreeing to the sample criteria. Please read through the inclusion and exclusion criteria entirely.

Inclusion Criteria:

- Male or female aged 18-65 years old
- Current digestive symptoms
- Physical exam within the past 12 months
- Proficient in English
- Have internet access for weekly emails
- Own a scale and measuring tape in centimeter
- Be willing to sign an informed consent

Exclusion Criteria:

- Younger than 18 years old or older than 65 years old
- Pregnant or nursing

- Diagnosed with an organic disease, such as Crohn's disease, ulcerative colitis, or gastrointestinal tumors
- Please read and answer the questions below thoroughly:
    - In the past 3 months, have you noticed blood in your stools?
      _____ Yes _____ No
    - In the past 3 months, have you noticed black stools, unrelated to iron supplements?
      _____ Yes _____ No
    - In the past 3 months, how often have you vomited blood?
      _____ Yes _____ No
    - Have you been told by your doctor that you are anemic (if female, not due to your menstrual cycle)?
      _____ Yes _____ No
    - In the past 3 months, have you lost 10 lbs of weight unintentionally?
      _____ Yes _____ No
    - If over the age of 50, have you had a recent major change in bowel movements?
      _____ Yes _____ No
    - In the past 3 months, have you had persistent or worsening hoarseness of the voice?
      _____ Yes _____ No
    - In the past 3 months, have you had persistent or worsening neck or throat pain?
      _____ Yes _____ No
    - In the past 3 months, have you had chest pain on exertion, or chest pain related to heart problems?
      _____ Yes _____ No
    - In the past 3 months, have you had difficulty swallowing?
      _____ Yes _____ No

DURATION OF STUDY INVOLVEMENT

This research study is expected to take 8 weeks. The study is estimated to start June 29, 2015.

PROCEDURES

If you choose to participate, you will be asked to complete a pre and post intervention questionnaire and measurements including weight and waist circumference. The initial and post questionnaire is estimated to take 20-30 minutes to complete. Over the course of the 8 weeks, you will receive a brief weekly email with four questions to answer including (1) how many supplements were missed in the previous week, (2) what is your current weight, (3) what is your current waist circumference, and (4) any additional comments you would like to share. The weekly email is estimated to take 5-10 minutes to complete.

The intervention for this study consists of probiotics, digestive enzymes, and glutamine. It is important that these supplements are taken daily. The probiotics and glutamine are taken by mouth in the morning and the digestive enzymes can be taken with your largest meal of the day.

The brands most commonly used at Atlanta Center for Holistic and Integrative Medicine will be used for the study. You will receive the probiotics, digestive enzymes, and glutamine for free. Orthomolecular, Integrative Therapeutics, and Metagenics donated the supplements for the purpose of this study. Kristin Corbin does not have any financial benefits from using these products, nor is she invested in the companies in anyway.

Risks:
The risks associated with each of these supplements are minimal. The only associated side effects found is mild cramping, abdominal pain, or bloating.

IF YOU FEEL DISCOMFORT AT ANY TIME, NOTIFY KRISTIN CORBIN AT KRISTIN.CORBIN@BOBCATS .GCSU.EDU AND DISCONTINUE THE SUPPLEMENTS.

The results of the study will remain anonymous and will not be linked with your name. The results are to be used for research purposes only.

PARTICIPANT RESPONSIBILITIES

As a participant, your responsibilities include:

- Follow the instructions outlined in the introduction video
- Complete the pre and post questionnaire
- Complete the weekly email questionnaire
- Take the study supplements as instructed
- Tell the researcher about any side effects you may experience
- Tell the researcher if you believe you might be pregnant
- Keep the study supplement in a safe and cool place- out of the direct sun
- Ask questions as needed
- Tell the researcher if you would like to terminate your participation

WITHDRAWAL FROM STUDY

If you first agree to participate and then change your mind, you are free to withdraw your consent and discontinue your participation at any time. If you decide to withdraw your consent to participate in this study, you should notify Kristin Corbin at Kristin.corbin@bobcats.gcsu.edu

POTENTIAL BENEFITS

The researcher cannot guarantee or promise that you will receive any benefits from this study. However, this well-established protocol has been found beneficial at Atlanta Center for Holistic and Integrative Medicine.

PARTICIPANT'S RIGHTS

You should not feel obligated to agree to participate. Your questions should be answered clearly and to your satisfaction. If you decide not to participate, tell the researcher, Kristin Corbin.

FINANCIAL CONSIDERATIONS

There are no costs associated with this research study. All necessary supplements will be given to you at no cost.

CONFIDENTIALITY

The purpose of this research study is to obtain data or information on the safety and effectiveness of probiotics, digestive enzymes, and glutamine; the results may be disseminated in medical journals, healthcare conferences, and poster presentations. Your identity and/or your personal health information will not be disclosed**.** Prior to beginning the study you will receive a unique identification number that you will be prompted to input on each questionnaire rather than your name.

_____ _____

Signature of Adult Participant Date

Appendix D

Participants Study Checklist

Items to Complete	**Estimated Date**	**Completed Date**
Sign Informed Consent	June 15, 2015	
Pick Up Supplements	By June 20, 2015	
Watch the Introduction Video	By June 25, 2015	
Watch the “How to Measure Weight and Waist Circumference” Video	By June 25, 2015	
Complete the pre-intervention questionnaires	By June 28, 2015	
Start the supplements	July 1, 2015	
Week 1 Email	July 8, 2015	
Week 2 Email	July 15, 2015	
Week 3 Email	July 22, 2015	
Week 4 Email	July 29, 2015	
Week 5 Email	August 5, 2015	
Week 6 Email	August 12, 2015	
Week 7 Email	August 19, 2015	
Week 8: Post-intervention questionnaire	August 26, 2015	