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Fatigue and Co-occurring Symptoms in Women with Irritable Bowel Syndrome

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## Abstract

Fatigue and Co-occurring Symptoms in Women with Irritable Bowel Syndrome

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Irritable bowel syndrome (IBS) is one of the most common bowel disorders. It is characterized by symptoms of abdominal discomfort or pain that are associated with changes in bowel habits such as diarrhea or constipation. However, fatigue is also common disabling symptom seen in patients with IBS. Fatigue frequently co-occurs with abdominal pain and psychological distress (i.e., depression and anxiety). Current management of fatigue for patients with IBS is difficult. It is a challenge to obtain clarity of separating fatigue from other co-occurring symptoms or the combinations of symptoms that come with fatigue. Because there are limited understanding of relationships among symptoms, and patient characteristics including underlying mechanisms of symptom cluster of fatigue and co-occurring symptoms.

The aims of this dissertation study were: [First part of the dissertation study] 1. To explore the relationships among fatigue and co-occurring symptoms (i.e., abdominal pain, depression and anxiety). (1-a) the relationships between abdominal pain and fatigue; and (1-b) whether psychological distress (i.e., depression and anxiety) mediates the effect of abdominal pain on fatigue, across-women and within-woman; and [Second part of the dissertation study] 2. To determine (2-a) if latent classes (i.e. subgroups) of women with IBS could be identified based

on the symptom cluster severity of fatigue, abdominal pain, depression and anxiety, (2-b) if these latent classes differed on patient characteristics, and (2-c) if genetic polymorphisms of tryptophan hydroxylase (TPH), serotonin reuptake transporter (SERT) and catecholamine methyl-O-transferase (COMT) are associated with fatigue, and (2-d) with latent class membership.

A secondary analysis of baseline data were conducted from two previous randomized controlled trials of a nurse-delivered symptom intervention. Study participants, Caucasian women with IBS, completed an initial interview, questionnaires, and kept a daily symptom diary for 28 days. For the first part of the dissertation, the relationships among daily diary fatigue, abdominal pain, and psychological distress were tested using a generalized estimating equation (GEE). For the second part of the dissertation, the latent class profile analysis (LCPA) was used to determine the latent classes, and analysis of variance/Chi-square test were used for testing group differences in patient characteristics and genetic polymorphisms. Buffy coat deoxyribonucleic-acid was analyzed by polymerase chain reaction for genetic analysis.

For the first part of the dissertation study, we found that fatigue, abdominal pain and psychological distress were positively related with each other as a symptom cluster. The positive and significant across-women relationships were observed between abdominal pain and fatigue. Abdominal pain predicted next-day fatigue within-woman, but not in the reverse. Psychological distress significantly mediated the effects of abdominal pain on fatigue across-women and within-woman. For the second part of the dissertation study, three latent classes were identified (Class-1, low severity; Class-2, medium severity; Class-3, high severity). Women in the high severity class had a lower social support, higher symptom burden (in particular poor sleep quality and high stress level), a poorer quality of life (QOL), and higher life interferences. The

TT genotype of TPH2 rs4570625 was positively associated with fatigue ($p < .05$). None of the genetic polymorphisms were associated with latent class membership.

By identifying the relationships among fatigue, abdominal pain and psychological distress, nurses would be able to utilize symptom management approaches aimed at decreasing abdominal pain and psychological distress in order to likely reduce fatigue. The utility of LCPA was to identify and to explain inter-individual variability of subgroups based on a symptom cluster of fatigue and co-occurring symptoms. In patients with IBS who reported high fatigue, there was decreased TPH2 transcriptional activity (prevalent TT genotype of TPH2 rs4570625) suggesting a possible role of serotonin dysregulation in fatigue. This study suggest the role of TPH2 in fatigue, and a comprehensive assessment for the IBS patients with fatigue and co-occurring symptoms.

Future studies are needed to 1) measure symptoms at different time points for better understanding of the relationships among symptoms; 2) further explore fatigue mechanisms; 3) develop fatigue management interventions, incorporating multiple factors such as social support, sleep quality, stress, QOL and genetic factors; and 4) replication findings in different populations and ethnic groups.

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## DEDICATION

I dedicate my dissertation work to my Lord and family members. Words fail to express my appreciation for my husband (Joon Sung), whose dedication and love stayed with me always. My deep gratitude goes to God for opening this opportunity to pursue a PhD in the United States and unfailingly guiding me throughout the journey.

# CHAPTER I.

# INTRODUCTION

## 1.1. Introduction and Content of the Dissertation

Irritable bowel syndrome (IBS) is a common condition characterized by abdominal pain/discomfort and changes in bowel patterns such as constipation and diarrhea (Thompson, Drossman, Talley, Walker, & Whitehead, 2006). To manage the symptoms of IBS, patients in the United States (U.S.) incur direct and indirect annual costs ranging from $742 to $7,547 (Hulisz, 2004). Multiple factors including genetics are part of the pathophysiology in IBS. Individuals with IBS have numerous gastrointestinal (GI) symptoms and often experience other equally distressing symptoms such as fatigue and depression (Lackner, Gudleski, DiMuro, Keefer, & Brenner, 2013).

IBS and its treatments are accompanied by a wide variety of symptoms that patients find challenging (Ford et al., 2014). Fatigue is one of the most frequent, stressful, and debilitating symptoms of IBS. Fatigue in patients with IBS frequently co-occurs with abdominal pain, depression, and anxiety (Lackner et al., 2013; Simren, Svedlund, Posserud, Bjornsson, & Abrahamsson, 2008). These symptoms result in reduced health-related quality of life (HRQOL) and higher health care costs for patients with IBS (Lackner et al., 2013). However, the underlying mechanisms of the symptom cluster with fatigue (i.e., fatigue, abdominal pain, depression, and anxiety) have not been explored extensively, and no clear understanding of the relationships among fatigue and its commonly co-occurring symptoms (i.e., abdominal pain, depression, and anxiety) has been reached. This gap in understanding prompted this dissertation study.

This dissertation is organized into four chapters. **Chapter I** is an introduction. It provides the background, statement of the problem, conceptual framework, and specific aims of the dissertation research. **Chapter II** (manuscript I: "Relationships between abdominal pain and fatigue with psychological distress as a mediator in women with irritable bowel syndrome") presents research findings reflecting Study Aims 1 and 2. **Chapter III** (manuscript II: "Comparison of subgroups of women with irritable bowel syndrome on fatigue and co-occurring symptoms: Patient characteristics and genetic polymorphisms") presents research findings reflecting Study Aims 3, 4, 5 and 6. **Chapter IV** concludes the dissertation with a summary of the research findings, study limitations, implications for future research and nursing practice, and recommendations for future studies.

## 1.2. Background

*Irritable Bowel Syndrome (IBS).* IBS is a GI disorder characterized by the presence of a cluster of symptoms that include abdominal pain, altered bowel habits, increased gas, bloating (distention), cramping, and food intolerance. While these symptoms can occur singly, they often co-occur as a cluster (Makhani, Yang, Mirocha, Low, & Pimentel, 2011). It is possible that IBS is not a disease but rather a complex subset of symptoms (Roisinblit, 2013). Current estimates of IBS prevalence range from 12% to 21% in Caucasian populations and from 7% to 17% in Asian populations; the annual societal burden is over 20 billion USD (Lovell & Ford, 2012; Taft, Riehl, Dowjotas, & Keefer, 2014). IBS is one of the most costly as well as most common functional bowel disorders, with significant impact on an individual's HRQOL (Lackner et al., 2013).

The Rome III diagnostic criterion for IBS is recurrent abdominal pain or discomfort at least 3 days per month in the last 3 months and associated with two or more of the following: improvement with defecation, onset associated with a change in frequency of stool, and onset

associated with a change in form (appearance) of stool. A diagnosis results when the criteria are fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis. According to the Rome III criteria, IBS is subcategorized as diarrhea predominant (IBS-D), constipation predominant (IBS-C), and mixture of diarrhea and constipation or mixed type (IBS-M) (Drossman & Dumitrascu, 2006).

*Fatigue in IBS.* Abdominal pain is the key symptom of IBS and is associated with a change in bowel habits. Other common symptoms of IBS include bloating, intestinal gas, and urgency and so on (Drossman & Dumitrascu, 2006). Non-GI symptoms such as depression, anxiety, and fatigue are co-occurring symptoms in IBS (Lackner et al., 2013). Of these, fatigue is a co-occurring symptom that many investigators have identified as one of the most frequent, stressful, and debilitating symptoms in IBS (Lackner et al., 2013). Fatigue is also one of the main components of HRQOL, independent of other symptoms, in patients with IBS (Anty et al., 2011; Piraino, Vollmer-Conna, & Lloyd, 2012; Reyes-Gibby et al., 2013; Witthoft, Hiller, Loch, & Jasper, 2013). One study showed fatigue to be a major disabling somatic complaint, reported by 61% of the patients with IBS (Lackner et al., 2013). In a large group of IBS patients, fatigue predicted both physical and mental aspects of HRQOL (Spiegel et al., 2004). Fatigue encompasses complex interactions among biological, psychological, and behavioral processes, and has been defined medically for IBS as “extreme weariness and a state of being very tired” (Hakanson, 2014, p. 221; Lackner, Gudleski, DiMuro, Keefer, & Brenner, 2013, p. 324).

*Symptom Cluster of Fatigue, Abdominal Pain, Depression, and Anxiety.* Fatigue is part of a symptom cluster that also includes abdominal pain, depression, and anxiety in patients with IBS (Han & Yang, 2016, Lackner et al., 2013; Simren et al., 2008). A number of researchers have reported that abdominal pain is associated with fatigue in IBS patients (Heitkemper et al.,

2011; Piche et al., 2007; Witthoft et al., 2013). Psychological distress variables, such as depression and anxiety, have also been positively associated with fatigue in IBS patients (Lackner et al., 2013; Simren et al., 2008; Witthoft et al., 2013). The National Institute of Nursing Research (NINR) reports that such symptoms are experienced simultaneously and are highly distressing in many patient groups (NINR, 2012). Research that addresses multiple symptoms that relate to each other and are co-occurring is called symptom cluster research (Barsevick, Whitmer, Nail, Beck, & Dudley, 2006). NINR (2012) has emphasized the importance of understanding the relationships among symptoms within a cluster. Since it is also probable that combinations of symptoms may be more etiologically relevant than single symptoms alone, NINR has supported symptom cluster research in chronic disease using biomarkers such as genes and omics with the aim of contributing to effective interventions for improving symptoms (NINR, 2012).

*Methodological Issues in Symptom Cluster Research.* Several attempts have been made to understand symptom clusters in IBS based on a variety of different parameters, such as visceral hypersensitivity and intestinal transit (Guthrie et al., 2003). However, research to understand comprehensive characteristics of symptom clusters and inter-individual variability is still limited in IBS (Makhani et al., 2011). In recent years, latent class profile analysis (LCPA) has been recommended to explore the inter-individual variability of patient sub-classifications based on the severity of a symptom cluster, and several non-IBS studies used an LCPA method to understand symptom clusters (Dziak, Lanza, & Tan, 2014; Guthrie et al., 2003; Langford et al., 2016; Williams & Kibowski, 2016). Previous statistical methods used for symptom clusters (e.g., factor analysis, principal component analysis, cluster analysis, correlations) failed to translate findings to individuals (Aktas, Walsh, & Rybicki, 2010), possibly because the previously used

statistical approaches utilize methods oriented to variables, not individuals (Bergman & Magnusson, 1997). LCPA postulates that there are unobservable (i.e., latent) subgroups (i.e., classes) within a population. An LCPA uses a probability-based classification, not an ad hoc approach, to classify patients, and it does not require normal distributions with unknown variances (Muthén & Muthén, 2010). The literature supports the notion that identifying subgroups of IBS patients based on the severity of a symptom cluster can enhance comprehensive understanding of the symptom cluster. It may also influence better personalized management of patients with IBS and complex symptoms.

*Underlying Mechanisms of Fatigue.* Recent reviews suggest that individual variability in symptom experiences in IBS may result from individuals' genetic vulnerability to physical and psychological stressors through changes in serotonin and catecholamine (Dinan, Cryan, Shanahan, Keeling, & Quigley, 2010; Ford et al., 2014; Fukudo & Kanazawa, 2011). There is some knowledge of the mechanisms through which genetic polymorphisms of tryptophan hydroxylase 1 and 2 (TPH1 and TPH2) (Jun, Kohen, Cain, Jarrett, & Heitkemper, 2011), serotonin transporter (SERT) (Jarrett et al., 2007), and catechol-O-methyl transferase (COMT) (Hall et al., 2012) contribute to inter-individual variability in various symptoms of IBS. These TPH, SERT and COMT genetic polymorphisms are also associated with fatigue in non-IBS chronic diseases such as cancer, fibromyalgia, and chronic fatigue syndrome (Landmark-Høyvik et al., 2010; Swain, 2000). However, a unifying shared etiology of fatigue in chronic diseases and fatigue in IBS has yet to emerge; and there are no published studies on the associations of the genetic polymorphisms of TPH, SERT, and COMT with fatigue and/or the symptom cluster with fatigue in IBS.

### 1.3. Statement of the Problem

Fatigue management in IBS is challenging for both patients and health care providers (Lackner et al., 2013; Simren et al., 2008). Much of the IBS research to date has focused on symptoms such as abdominal pain and depression. The relationship among symptoms, including fatigue, has not been fully studied. This has resulted in a lack of effective fatigue management for patients with IBS. There do not appear to be any interventions for IBS patients that directly treat fatigue. A challenge for researchers is separating fatigue from its co-occurring symptoms—abdominal pain, depression, and anxiety—versus treating them together as a symptom cluster. Clarity is difficult to obtain due to a lack of understanding of the relationships among the symptoms and limited knowledge of the underlying biological mechanisms (Guthrie et al., 2003). Research into fatigue in IBS continues to be challenging due to its frequent overlap and clustering with other symptoms (Lackner et al., 2013). Although many previous IBS studies (Heitkemper et al., 2012; Jun, Kohen, Cain, Jarrett, & Heitkemper, 2011; Quigley, 2015; Rubio et al., 2014) have found characteristics of both GI symptoms and psychological distress, fatigue is often not addressed. Few studies have provided comprehensive understandings of fatigue or suggested effective management for fatigue in IBS (Cohen et al., 2014). The explanation of fatigue in IBS patients remains unclear (Hausteiner-Wiehle & Henningsen, 2014; Van Oudenhove, Vandenberghe, Vos, Holvoet, & Tack, 2011). Therefore, increased knowledge of the relationships among fatigue and co-occurring symptoms, as well as of specific mechanisms leading to symptom cluster with fatigue, is necessary.

### 1.4. Study Aims

This dissertation study is a secondary analysis that aims to expand a comprehensive understanding of fatigue and co-occurring symptoms—abdominal pain, depression, and anxiety—as a symptom cluster in women with IBS. The following were the specific aims:

***Manuscript I.*** *Relationships between fatigue, abdominal pain and psychological distress.*

1. To explore the relationships between abdominal pain and fatigue both across-women and within-woman.
2. To examine whether psychological distress (i.e., depression and anxiety) mediates the effect of abdominal pain on fatigue across-women and within-woman.

***Manuscript II.*** *Comparisons among subgroups of women with IBS on fatigue and co-occurring symptoms using an LCPA.*

3. To determine if latent classes (i.e., subgroups) of women with IBS can be identified based on the severity of the symptom cluster with fatigue, abdominal pain, depression, and anxiety.
4. To determine if the identified latent classes differ on individual characteristics.
5. To determine if genetic polymorphisms of TPH, SERT, and COMT are associated with fatigue.
6. To determine if genetic polymorphisms of TPH, SERT, and COMT are associated with identified latent class membership.

## 1.5. Conceptual Framework

The research for this dissertation is based on the Symptom Science Model (SSM) developed by the NINR (Cashion & Grady, 2015) to address current NINR research priorities (NINR, 2012). The SSM conceptual framework (Figure 1-1) begins by identifying a complex symptom, which is then characterized into a phenotype with biological and clinical data. Genomic and other discovery methodologies are then applied to illuminate targets for therapeutic and clinical interventions. The SSM supports research on symptom clusters and biological mechanisms (e.g., genetics), such as this dissertation study that aims to contribute to effective individualized interventions for improving HRQOL for patients with IBS. Among the concepts in the SSM, the concept of a "complex symptom" guides manuscript I, the concepts of "phenotype characterization" and "biomarker discovery" guide manuscript II, and the concept of "clinical application" is planned to guide a future study.

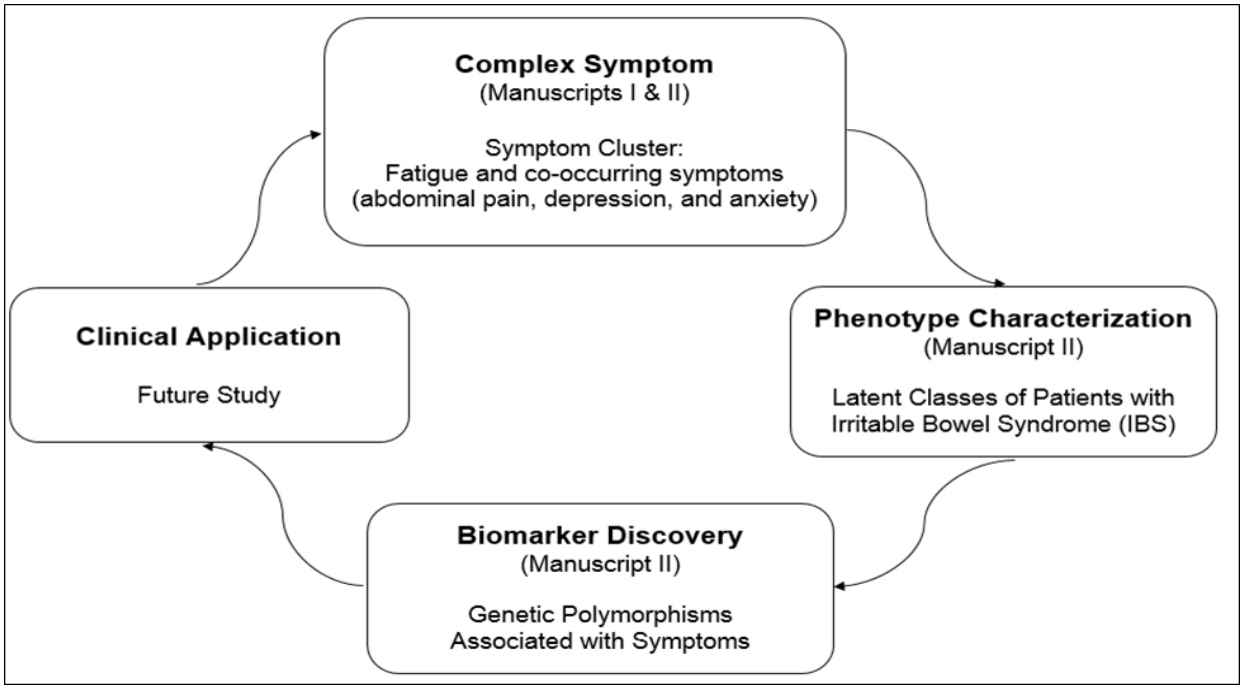


Figure 1-1. Conceptual Framework for Study of Fatigue in Irritable Bowel Syndrome. Adapted from "The National Institutes of Health/National Institutes of Nursing Research Intramural Research Program and the Development of the National Institutes of Health Symptom Science Model." by 2015 Cashion and Grady (2015), Nursing Outlook, 63, p. 485.

### 1.6. Significance of This Study

The findings of this dissertation research add to prior research findings related to fatigue in patients with IBS, by investigating the relationships among fatigue and the co-occurring symptoms of abdominal pain, depression, and anxiety. This study used a latent class perspective that adds to current knowledge of inter-individual variability among patients with IBS. The advanced model fit indices used in the LCPA provide objective and precise information for identifying latent classes based on symptom clusters. In addition, this study investigated possible predictors and outcomes of severity of the symptom cluster with fatigue. Finally, this study provided evidence that there may be a different molecular basis for subgroups of patients with distinct symptom phenotypes and suggested a possible genetic marker (i.e., TPH2) for high fatigue and/or high symptom severity groups among women experiencing both IBS and fatigue. Genetic biomarkers could help match patients with IBS who experience fatigue to interventions they are most likely to benefit from.

### 1.7. Human Subjects

This dissertation employed a secondary analysis of the baseline data was conducted from two randomized controlled trials of a nurse-delivered symptom intervention for patients with IBS (Jarrett et al., 2016; Jarrett et al., 2009). This dissertation project used the existing de-identified data, in which subjects cannot be identified. This secondary data analysis was approved by the Human Subjects Division of University of Washington, Seattle and was determined to be exempt under Research Risk Code of Federal Regulations 45 CFR 46.102 (f) (November, 2015) and does not require review by the Institutional Review Board (IRB).

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# CHAPTER II.

## MANUSCRIPT I

Relationships between abdominal pain and fatigue with psychological distress as a mediator in women with irritable bowel syndrome

## Abstract

**Background:** Women with irritable bowel syndrome (IBS) often report fatigue, along with abdominal pain and psychological distress (i.e., depression and anxiety). But there is a dearth of information about the relationships between fatigue and the other co-occurring symptoms. **Objective:** The purpose of this study was to test (1) the relationships between abdominal pain and fatigue; and (2) whether psychological distress (i.e., depression and anxiety) mediates the effect of abdominal pain on fatigue across-women and within-woman. **Methods:** Baseline data from two randomized controlled trials were used in this secondary analysis. Women with IBS in Study-1 ($n$ = 255) and in Study-2 ($n$ = 101) completed an initial interview and questionnaires and kept a daily symptom diary for 28 days. The diary data was used to test the relationships among abdominal pain, fatigue, and psychological distress using a generalized estimating equation (GEE). To test mediation effects in GEE models, a bootstrapped test with 1,000 resamples was performed. The relationships among symptoms were examined in three models (same-day, prior-day abdominal pain predicts next-day fatigue, and prior-day fatigue predicts next-day abdominal pain). **Results:** Positive and significant across-women relationships between abdominal pain and fatigue were observed in each model. Abdominal pain predicted next-day fatigue within-woman, but the reverse was not found. Psychological distress mediated the effects of abdominal pain on fatigue both across-women and within-woman. **Conclusions:** Symptom management that incorporates strategies to decrease abdominal pain and psychological distress are likely to also reduce fatigue. A longitudinal study to measure symptoms at different time points is needed to confirm these findings, which also suggest that a better understanding of the underlying mechanisms of these symptoms is warranted.


**Key words:** irritable bowel syndrome, fatigue, abdominal pain, psychological distress

## 2.1. Introduction

Irritable bowel syndrome (IBS) is the most common functional gastrointestinal (GI) disorder seen by health care providers (Thompson, Heaton, Smyth, & Smyth, 2000). It affects about 22 million people in the United States (U.S.), representing 14% of the U.S. population (Hungin, Chang, Locke, Dennis, & Barghout, 2005). The worldwide prevalence of IBS in adults is between 9% and 24% (Hungin et al., 2005; IFFGD, 2013; Lovell & Ford, 2012). IBS predominantly affects females, with 2 to 3 women affected for every 1 man affected in the U.S. (Canavan, West, & Card, 2014; IFFGD, 2013). The diagnosis of IBS is currently based on the Rome III criteria. To meet the criteria, a person has to have recurrent abdominal pain/discomfort that occurs at least 3 days/month for the last 3 months, and that is associated with 2 or more of the following: (a) improvement with a bowel movement, (b) a change in stool frequency, and (c) a change in stool form. In addition, the symptoms need to be present for at least 6 months prior to the IBS diagnosis (Drossman & Dumitrascu, 2006). Common subtypes of IBS are based on predominant bowel patterns: constipation (IBS-C), diarrhea (IBS-D), and mixed (IBS-M). Individuals with IBS often experience multiple symptoms, including GI and non-GI symptoms together (Drossman & Dumitrascu, 2006). Common GI symptoms include bloating, intestinal gas, distension, flatulence, incomplete evacuation, and urgency (Yao et al., 2012). Non-GI symptoms include depression, anxiety, fatigue, and sleep disturbance (Lackner, Gudleski, DiMuro, Keefer, & Brenner, 2013; Makhani, Yang, Mirocha, Low, & Pimentel, 2011).

To provide effective symptom management, multiple symptoms need to be accounted for (Guthrie et al., 2003). Direct health care costs for symptom management of IBS in the U.S. ranges from $742 to $7,547 per patient annually (Canavan et al., 2014). Indirect costs such as over-the-counter medications, lost productivity, and time spent seeking health care providers add

to patients' expenses (Hulisz, 2004). This economic burden, along with the symptom burden and poorer health-related quality of life (HRQOL) experienced by individuals, makes IBS a significant public health issue.

Fatigue is a frequent co-occurring symptom in IBS. The most frequently used terms to describe fatigue in IBS are "extreme weariness and a state of being very tired" (Hakanson, 2014, p. 221; Lackner, Gudleski, DiMuro, Keefer, & Brenner, 2013, p. 324). Fatigue is important because it interferes with work productivity, cost of care, usual activity in daily life, and HRQOL. In a recent U.S. study by Lackner et al. (2013), researchers found that 61% of adults with moderate to severe IBS ($n$ =176) experienced fatigue at least some of the time. Piche et al. (2007) surveyed 51 IBS patients and found that 63% experienced moderate fatigue, defined as more than 4 on a 10-point visual analog scale. In a study by Simrén et al. (2008), 80 participants with IBS had more severe fatigue than the 399 controls ($p < .05$). Anty et al. (2011) found that among 42 patients with IBS, 55% verbally expressed fatigue. Twenty percent considered fatigue the worst symptom of their disease, whereas 45% stated that it was as disabling as their abdominal pain. The fatigue score was significantly higher in IBS patients (mean, standard deviation [SD]: 68 [32]) than in controls (16 [11]) (Anty et al., 2011).

A number of researchers have reported that abdominal pain was associated with fatigue in IBS patients (Heitkemper et al., 2011; Lackner et al., 2013; Piche et al., 2007; Witthoft, Hiller, Loch, & Jasper, 2013). In a recent systematic review of fatigue in IBS, abdominal pain was the most common related symptom (Han & Yang, 2016). Psychological distress such as depression and anxiety has also been positively associated with fatigue in IBS patients (Lackner et al., 2013; Simren, Svedlund, Posserud, Bjornsson, & Abrahamsson, 2008; Witthoft et al., 2013). Longstreth and colleague (2005) also found that the depression and anxiety were positively and

strongly associated with fatigue measured by IBS Impact Scale ($r$ = 0.78, $p$ <.001), and with vital exhaustion measured by Short From-36 ($r$ = 0.58, $p$ <.001).

Previous intervention studies (e.g., comprehensive self-management) for patients with IBS showed the effects of interventions at reducing GI and psychological symptoms than usual care, but fatigue was not addressed in prior studies (Heitkemper et al., 2004; Jarrett et al., 2016; Jarrett et al., 2009). In addition, much of the IBS research to date has focused on symptoms such as abdominal pain and depression; the relationships among these symptoms, including fatigue, has not been fully studied. This has resulted in a lack of effective fatigue management for patients with IBS: there do not appear to be any interventions that directly treat fatigue. The challenge is separating fatigue from the other co-occurring symptoms (i.e., abdominal pain and psychological distress), given the limited knowledge and understanding of relationships among the symptoms in IBS (Guthrie et al., 2003). For example, due to the frequent overlap of fatigue with abdominal pain, it is not clear if abdominal pain directly causes fatigue, or fatigue causes abdominal pain. Another unknown is whether psychological distress mediates the relationship between abdominal pain and fatigue.

When examining IBS symptoms over time (weeks or months), mean values across persons reflect an association between two variables across the entire sample without regard to within-person fluctuations over time (Buchanan et al., 2014). For example, do people who rate abdominal pain high overall tend to also rate fatigue high overall? Examining co-variation of variables *within* individuals can also be useful by helping to identify symptom triggers and temporality of the relationships between variables such as abdominal pain and fatigue (e.g., If abdominal pain increases for 1 or 2 days, does an increase in fatigue follow?). In other words, the within-person effect can address the question of whether an individual's next-day fatigue is

worse than average after periods when that person's abdominal pain is worse than average. In a cross-sectional study (Lackner et al., 2013), abdominal pain and psychological distress were both found to be predictors of fatigue in IBS. A clearer understanding of the processes through which abdominal pain might lead to fatigue, or the reverse, as well as of the mediation effects of psychological distress, can lead to more specific targets for effective interventions for IBS patients with fatigue.

The primary aim of this study was to test the relationships between abdominal pain and fatigue both across-women and within-woman. A secondary aim was to examine the relationships between abdominal pain and fatigue while controlling for psychological distress to see whether it mediated the relationship. We tested these aims in three models (same-day Model-A: relationship of abdominal pain with fatigue on the same day; day-to-day Model-B: prior-day abdominal pain predicts next-day fatigue; and reverse-direction Model-C: prior-day fatigue predicts next-day abdominal pain).

The hypotheses of this study were based on prior IBS studies (Lackner et al., 2013; Piche et al., 2007; Simren et al., 2008). For the primary aim, the hypotheses were that in Model-A, abdominal pain and fatigue across-women would be significantly and positively associated. For the within-woman analyses, we hypothesized that abdominal pain would predict next-day fatigue in Model-B, but not the reverse in Model-C. For the secondary aim, we hypothesized that the relationships between abdominal pain and fatigue, shown in the primary aim, would be weakened when controlling for psychological distress; and that a statistically significant indirect path exists between abdominal pain and fatigue through psychological distress, meaning that psychological distress mediates the effect of abdominal pain on fatigue.

## 2.2. Methods

### Design, Setting, and Sample

This study is a secondary analysis of baseline data from two previous randomized controlled trials that used similar baseline assessments and research design (Nursing Management of IBS: Improving Outcomes). Study-1 was conducted from 2002 to 2007 (Jarrett et al., 2009) and Study-2 from 2008 to 2013 (Jarrett et al., 2016); both studies included men and women. The participants in these studies were recruited through community advertisement. To be included, participants had to have a medical diagnosis of IBS, be between 18 and 70 years of age, and meet the Rome-II (Study-1) or Rome-III (Study-2) criteria for IBS (Drossman & Dumitrascu, 2006). Potential participants were excluded for co-existing GI pathology (e.g., inflammatory bowel disease), abdominal surgery, renal or reproductive pathology (e.g., endometriosis), or select medications (e.g., anticholinergics, cholestyramine, narcotics, colchicines, iron supplements, or laxatives). Gender-related differences in abdominal pain, fatigue, and psychological symptoms are apparent in patients with IBS, but women experienced these symptoms more severely and frequently than men (Cain et al., 2009; Kroenke & Spitzer, 1998). Thus men were excluded in this study. Sample size for the secondary analyses was 356 women with IBS: 255 from Study-1 and 101 from Study-2.

### Procedures

Study-1 and Study-2 were approved by the Institutional Review Board of the University of Washington, with approval renewed annually until each study was closed (Jarrett et al., 2016; Jarrett et al., 2009). Participants were initially screened over the phone for eligibility and baseline symptom assessment. If they met the criteria for inclusion, they were mailed a consent form and questionnaires. Eligible participants then came to the research office, where they gave

written consent, returned their completed questionnaires, and were oriented to the study. At home, they completed a daily diary each evening for 28 days. A gastroenterologist reviewed each participant's health assessment and IBS-specific GI symptoms.

**Measures**

**Demographics.** All participants completed a demographic data sheet that included age, race and ethnicity, marital status, education, occupation, and personal/family annual income levels.

**Symptom characteristics.** The questionnaires assessed both IBS-specific health history (e.g., IBS symptoms, diagnosis process, management strategies, family history of GI diseases) and general health history (e.g., general health, medication, lifestyle, surgery). General history of past and current symptoms and diseases (e.g., respiratory, cardiac, skin) were reviewed by a gastroenterologist. Criteria for functional GI disorders (e.g., IBS) as well as GI symptom-related items (e.g., bowel pattern subtypes) were assessed in Study-1 with the Rome II diagnostic questionnaire for functional GI disorders (Drossman, Talley, Whitehead, Thompson, & Corazziari, 1999) and in Study-2 with the Rome III questionnaire (Thompson, Drossman, Talley, Walker, & Whitehead, 2006). For a retrospective measure of psychological distress, participants completed the Brief Symptom Inventory (BSI), a 53-item questionnaire that evaluates psychological distress (including subscales for somatization, anxiety, obsessive-compulsive, phobic anxiety, depression, interpersonal sensitivity, hostility, paranoia, and psychoticism; (Derogatis, 1993). We calculated the Global Severity Index (GSI) as a sum-score of psychological distress subscales (Derogatis, 1993). The internal consistency of the GSI was $\alpha$ = 0.87 in this study.

**Daily diary symptoms.** Participants completed a daily symptom diary each evening for 28 days to assess the severity of abdominal pain, fatigue, and psychological distress experienced over the past 24 hours. Participants rated each symptom on a Likert scale of 0 (*not present*), 1 (*mild*), 2 (*moderate*), 3 (*severe*), to 4 (*very severe*). In our secondary analysis, depression and anxiety were used as a narrow definition of psychological distress, which as a concept differentiates between strain, stress, distress, somatization, and psychological distress as "the unique discomforting, emotional state including depression and anxiety" (Ridner, 2004, p. 539).

**Data Analyses**

We first explored the relationship between abdominal pain and fatigue in women with IBS who participated in Study-1. We then looked at women with IBS from Study-2 to see if these results would be consistent; finally we merged the data from Study-1 and Study-2 participants. Descriptive statistics (percentages, mean, SD) were used to summarize demographic and symptom characteristics and the symptoms reported in the 28-day daily diary. Independent *t*-test (continuous variables)/Chi-square test (categorical variables) were conducted to compare variables between Study-1 and Study-2. Since fatigue scores were correlated with age, age was controlled as a covariate in the across-women analyses. To test the mediation models, we checked that the symptom variables were positively and significantly correlated with each other using a Pearson correlation ($0.485 \leq r \leq 0.681$).

Details of fitted statistical models were described for each aim (Table 2-1, Figure 2-1). For the primary aim, to test the relationships between abdominal pain and fatigue, a generalized estimating equation (GEE) model was applied to each pair of variables (e.g., abdominal pain as predictor and fatigue as the outcome variable, or the reverse). The GEE model was run for both across-women and within-woman effects of the predictor variable, as

well as to estimate the correlations between the pair of variables (Buchanan et al., 2014; Jarrett, Heitkemper, Cain, Burr, & Hertig, 2000; Reding, Cain, Jarrett, Eugenio, & Heitkemper, 2013).

Table 2-1 shows the technical details of the GEE model analysis. The across-women term was calculated as the within-woman mean value of the predictor (e.g., $Xm_i$). The within-woman term was calculated as the deviation of the daily value of the predictor from the within-woman mean (e.g., $X_{it} – Xm_i$). Therefore, the coefficient of $Xm_i$ would be interpreted as an estimate of the across-women effect ($\beta_1$), and the coefficient of $X_{it} – Xm_i$ would be interpreted as an estimate of the within-woman effect ($\beta_2$) (Buchanan et al., 2014). The GEE model was set up with independent correlations and robust standard errors. GEE modeling allows for a time-series correlation of observations within each subject, which means one can model both the across-persons and within-person relationships simultaneously in one model (Buchanan et al., 2014; Jarrett et al., 2000; Reding et al., 2013).

The secondary aim was to test the mediation effects of psychological distress. To conclude that psychological distress (Z) mediates the relationship between abdominal pain (X) and fatigue (Y), the following a priori criteria had to be met - Step 1: X is significantly associated with Y; Step 2: X is significantly associated with the psychological distress variables (Z); Step 3: after controlling for X, Z is significantly associated with Y; and Step 4: the relationship between X and Y becomes weakened. Then, if the relationship between X and Y in Step 4 is significant, it is considered to be a partially mediated model, and the relationship between X and Y in Step 4 becomes non-significant, it is considered a fully mediated model (Hayes, 2009; Ross et al., 2015). GEE models with a bootstrapped test of mediation effects ($r_1$ - $r_2$ in Figure 2-1) were conducted with 1,000 resamples using R-3.2.2 software to confirm

statistical significance of the mediation effect. In all analyses mentioned above, a *p* value of less than .05 was considered statistically significant, and all tests were two-tailed. GEE model testing was conducted with IBM SPSS Statistics for Windows, version 22.0 (SPSS, Inc., Armonk, NY: IBM Corp, USA).

## 2.3. Results

### Demographics and Baseline Symptom Characteristics

In both Study-1 and Study-2, the majority of the women participating identified themselves as Caucasian (Study-1, 91%; Study-2, 82%), married (Study-1, 55%; Study-2, 51%), and with a college or graduate degree (Study-1, 74%; Study-2, 75%). Participants reported having had symptoms of IBS for 10 years on average (SD 0.7) in Study-1 and 11 years (SD 0.7) in Study-2. They were diagnosed by a health care provider an average of 8 years ago in both Study-1 (SD 0.6) and Study-2 (SD 0.7). Participants' reported bowel pattern subtypes were IBS-D (Study-1, 45%; Study-2, 47%), IBS-C (Study-1, 28%; Study-2, 32%), and IBS-M (Study-1, 23%; Study-2, 20%). No statistically significant differences in demographics or baseline symptom characteristics were found between the two studies (data not shown). In both studies, the mean severity levels for abdominal pain and fatigue were higher than those for depression and anxiety (Table 2-2).

### Study-1: Across-Women and Within-Woman Relationships

In Study-1, across-women relationships between daily abdominal pain and fatigue were positive and significant in all three models (Table 2-3): Model-A (same-day relationship), Model-B (abdominal pain to next-day fatigue), and Model-C (fatigue to next-day abdominal pain). These relationships were weaker after controlling for depression and anxiety. The

mediation effects of depression and anxiety were statistically significant in Model-A (33%) and in Model-B (32%), but not in Model-C.

The within-woman relationships between abdominal pain and fatigue were positive and significant in Model-A and Model-B (Table 2-3). Abdominal pain predicted next-day fatigue in Model-B, but fatigue did not predict next-day abdominal pain in the reverse in Model-C. When controlling for depression and anxiety, Model-A and Model-B showed significant mediation effects, but Model-C did not.

**Study-2: Across-Women and Within-Woman Relationships**

In Study-2, the across-women relationships between abdominal pain and fatigue were positive and significant in all three models (Table 2-4). The mediation effects of depression and anxiety were significant in Model-A and Model-B, but not in Model-C.

For the within-woman analyses, a positive and significant relationship occurred only in Model-A. The mediation effect of psychological distress on the relationship between symptoms was 20% (Table 2-4). No significant within-woman relationships were found when abdominal pain was used to predict next-day fatigue (Model-B, $p = .145$) or when fatigue was used to predict next-day abdominal pain (Model-C, $p = .430$).

**Merged Data: Across-Women and Within-Woman Relationships**

In the merged daily dairy data from the two studies, with a larger sample, the across-women and within-woman relationships were found to be comparable to the results of individual studies. i.e., Study-1 and Study-2. (Table 2-5). Abdominal pain predicted next-day fatigue in Model-B, but fatigue did not predict next-day abdominal pain in Model-C. Depression and anxiety were not found to mediate the effect of fatigue upon abdominal pain to a statistically significant level either across-women or within-woman in Model-C.

## 2.4. Discussion

Patients with IBS experienced not only GI and psychological symptoms but also fatigue. The relationships between fatigue and the other co-occurring symptoms have not been clearly understood, which has resulted in a lack of effective fatigue management for IBS patients. This study is the first to examine both across-women and within-woman relationships between abdominal pain and fatigue, as well as the first to show that psychological distress (e.g., depression and anxiety) partially mediates the effects of abdominal pain upon fatigue.

The study analyzed data from large samples of women with IBS in two previous studies; and this secondary analysis used a GEE and a bootstrapping method. Overall, consistent results were found in the two studies as well as in the merged data. Prior researchers reported that abdominal pain and fatigue often co-occur, and a positive and significant bivariate correlation between the two symptoms (Lackner et al., 2013; Piche et al., 2007; Witthoft et al., 2013). We found that a positive and significant across-women relationship between abdominal pain and fatigue. Within-woman relationships between day-to-day variations in abdominal pain and fatigue were also found: abdominal pain was found to predict next-day fatigue, while the reverse (fatigue predicting next-day abdominal pain) was not found. Abdominal pain is a primary symptom of distress in IBS, one that could affect other symptoms, including fatigue as well as quality of life (Cain et al., 2006). The clinical significance of these findings is that relieving abdominal pain is an important strategy for reducing fatigue.

The results of the mediation analysis indicate that abdominal pain directly influenced fatigue and indirectly influenced fatigue mediated by psychological distress. These effects were found both across-women and within-woman. However, the mediation effects found in Model-C (in which fatigue predicts next-day abdominal pain) were not statistically significant in any

combination of the data (Study-1, Study-2, or merged). In other words, the reason that IBS patients experience abdominal pain and fatigue concurrently is explained in part by the mediation effect of psychological distress, which, in turn, leads to fatigue. Our findings are supported by previous studies that have found abdominal pain and psychological distress to predict fatigue in IBS (Lackner et al., 2013), pain to predict psychological distress in many chronic diseases including IBS (Trivedi, 2004), and psychological factors to exacerbate the overall symptoms of IBS (van Tilburg, Palsson, & Whitehead, 2013).

Depression and anxiety have similar features and commonly co-occur (Wehrenberg, 2014). We used depression and anxiety as a combined symptom of psychological distress, although it is a narrow definition (Masse, 2000; Ridner, 2004, p 539). We used this narrow definition of psychological distress to focus on how it mediated abdominal pain and fatigue. As a post-hoc analysis, we controlled the sum-scores of other possible psychological symptoms (i.e., depression, anxiety, stress, and sleep disturbance) using a diary. The overall results were similar to or unchanged from our original analyses using the narrow definition (data not shown). These results might indicate that depression and anxiety are major mediators of abdominal pain to fatigue. This is a meaningful result with clinical implications for patients with IBS: depression and anxiety are amenable to change by cognitive behavioral and/or psychological intervention, such as comprehensive self-management in IBS (Jarrett et al., 2016; Jarrett et al., 2009). Interventions that target not only abdominal pain, but also depression and anxiety, may lessen fatigue in IBS patients.

This study's strengths include the large sample of participants with a homogeneous-phenotype of IBS included for analysis. Another strength is the repeated and similar patterns of results found in two similar studies (Study-1 and Study-2) and in the combined data. In addition,

we attempted to use prospective diary data for our analyses to explore the directionality of the relationships among abdominal pain, fatigue, and psychological distress. Lastly, a GEE model with a bootstrapping analysis is preferred to the more commonly used Sobel test, path analysis, or structure equation modeling (SEM) for testing rigorous statistical significance of mediation effects and for quantifying indirect effects to overcome the assumption of normality with bias-corrected confidence intervals (Preacher & Hayes, 2008).

Several study limitations need to be acknowledged. First, we cannot make definitive conclusions about exact causal relationships, even when changes in fatigue were preceded by changes in psychological distress and abdominal pain, within this short time frame (day-to-day). Because it would still be unclear whether, in a single day, the abdominal pain existed before the onset of psychological distress. Thus the results from this study should be interpreted with caution. In addition, we focused on the mediation effects of psychological distress in this study, but it is also plausible that psychological distress could be a confounder, and there may be other confounders and mediators, apart from psychological distress. Furthermore, environmental factors not measured in this study may play a role. The mean severity of symptoms in this study was mild to moderate, which limits information for patients with severe symptoms such as those most likely seen in clinical practice. Lastly, our sample was limited to Caucasian women and limits the more global generalizability of the results.

Fatigue is likely to be recognized by clinical providers when a patient's primary complaints are related to abdominal pain or psychological distress (Lackner et al., 2013). We suggest that health professionals in clinical practice assess abdominal pain and psychological distress when meeting patients with IBS complaining of fatigue. Our research implies that current nurse-delivered self-management (Heitkemper et al., 2004; Jarrett et al., 2016; Jarrett et

al., 2009) and cognitive-behavioral therapy (Li, Xiong, Zhang, Yu, & Chen, 2014) can be applied for patients with IBS at high risk for the symptoms of abdominal pain, fatigue, and psychological distress.

### 2.5. Conclusions

Abdominal pain was positively and significantly related with fatigue both across-women and within-woman. Although only weak within-woman relationships were observed between day-to-day variations in abdominal pain and day-to-day variations in fatigue, we found that abdominal pain predicted next-day fatigue within-woman. Psychological distress mediated the effects of abdominal pain on fatigue. These results shed light on strategies for fatigue management in IBS, which can be enhanced not only by self-management for abdominal pain, but also by psychological interventions that target depression and anxiety. To better characterize the relationships and understand directionality among abdominal pain, fatigue, and psychological distress, longitudinal follow-up of IBS patients with measurement of each symptom at different time points (i.e., time series analysis) is needed to confirm our findings and future studies exploring underlying mechanisms of these symptoms are also recommended.

Table 2-1. Technical Details of Generalized Estimating Equation (GEE) Model Analysis.

| | Symptom severity in woman *(i) on* day *(t)* | $m_i$ = Mean symptom severity during the past 4 weeks in woman *(i)* |
|---|---|---|
| Abdominal pain (X) | $X_{it}$ | $Xm_i$ |
| Fatigue (Y) | $Y_{it}$ | $Ym_i$ |
| Psychological distress (Z) | $Z^D_{it}$, $Z^A_{it}$ | $Z^Dm_i$, $Z^Am_i$ |

Models = A: Relationship between X and Y on the same day.

B: X predicts next-day Y. C: Y predicts next-day X.

| | |
|---|---|
| A | $Y_{it} = \beta_0 + \beta_1 Xm_i + \beta_2 (X_{it} - Xm_i) + \beta_3 AGE + \varepsilon_{it}$ |
| B | $Y_{i(t+1)} = \beta_0 + \beta_1 Xm_i + \beta_2 (X_{it} - Xm_i) + \beta_3 AGE + \varepsilon_{it}$ |
| C | $X_{i(t+1)} = \beta_0 + \beta_1 Ym_i + \beta_2 (Y_{it} - Ym_i) + \beta_3 AGE + \varepsilon_{it}$ |

Models' = Models with controlling for psychological distress (i.e., depression and anxiety)

| | |
|---|---|
| A' | $Y_{it} = \beta_0 + \beta_1 Xm_i + \beta_2 (X_{it} - Xm_i) + \beta_3 Z^Dm_i + \beta_4 (Z^D_{it} - Z^Dm_i) + \beta_5 Z^Am_i + \beta_6 (Z^A_{it} - Z^Am_i) + \beta_7 AGE + \varepsilon_{it}$ |
| B' | $Y_{i(t+1)} = \beta_0 + \beta_1 Xm_i + \beta_2 (X_{it} - Xm_i) + \beta_3 Z^Dm_i + \beta_4 (Z^D_{it} - Z^Dm_i) + \beta_5 Z^Am_i + \beta_6 (Z^A_{it} - Z^Am_i) + \beta_7 AGE + \varepsilon_{it}$ |
| C' | $X_{i(t+1)} = \beta_0 + \beta_1 Ym_i + \beta_2 (Y_{it} - Ym_i) + \beta_3 Z^Dm_i + \beta_4 (Z^D_{it} - Z^Dm_i) + \beta_5 Z^Am_i + \beta_6 (Z^A_{it} - Z^Am_i) + \beta_7 AGE + \varepsilon_{it}$ |

Note. *i* = $i^{th}$ woman. *t* = on day t. $\varepsilon$ = independently distributed normal errors. $\beta_1$: across-women effects. $\beta_2$: within-woman effects. $Z^D$ = depression, $Z^A$ = anxiety. AGE = covariate for $i^{th}$ subject.

Table 2-2. Symptom Severity in Women with Irritable Bowel Syndrome

| | Study-1 | Study-2 | Merged | $p^a$ |
|---|---|---|---|---|
| Retrospective psychological distress (mean symptom severity) | | | | |
| Depression[b] | 0.4 (0.6) | 0.7 (0.6) | 0.6 (0.6) | .988 |
| Anxiety[b] | 0.6 (0.6) | 0.5 (0.5) | 0.5 (0.5) | .985 |
| Global Severity Index (GSI)[b] | 0.5 (0.5) | 0.5 (0.5) | 0.5 (0.5) | .983 |
| Daily diary (mean symptom severity) | | | | |
| Abdominal pain | 1.4 (0.6) | 1.4 (0.6) | 1.4 (0.3) | .999 |
| Fatigue | 1.2 (0.6) | 1.2 (0.7) | 1.2 (0.3) | .954 |
| Depression | 0.4 (0.5) | 0.4 (0.5) | 0.4 (0.3) | .891 |
| Anxiety | 0.7 (0.6) | 0.8 (0.7) | 0.7 (0.4) | .995 |
| Daily diary (percent of days with moderate to very severe symptoms) | | | | |
| Abdominal pain | 36.9 (26.1) | 38.2 (26.5) | 37.8 (26.2) | .895 |
| Fatigue | 34.9 (27.7) | 36.2 (27.5) | 35.6 (27.6) | .821 |
| Depression | 9.9 (16.9) | 9.6 (17.8) | 9.8 (17.2) | .901 |
| Anxiety | 18.7 (22.2) | 19.5 (23.9) | 19.1 (23.0) | .934 |

Note.
Data were presented with mean and standard deviation.
Sample size (Study-1 N =255, Study-2 N =101, and Merged N = 356).
[a] two-group comparison between Study-1 and Study-2. [b] using a Brief Symptom Inventory (rating scale: 0-4).

Table 2-3. Study-1: Relationships of Abdominal Pain with Fatigue in Women with Irritable Bowel Syndrome

| | Main models | | | Models controlling for depression and anxiety (day = t) | | | Bootstrap results for significances of mediation effect[b] | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | β[a] | SE | *p* | β[a] | SE | *p* | β[a] | SE | 95% CI | Z | *p* | Mediation (%)[c] |
| Same-Day Model-A: Relationships of Abdominal Pain (day = t) with Fatigue (day = t) | | | | | | | | | | | | |
| Across | .534 | .075 | <.001 | .360 | .074 | <.001 | .174 | .058 | .063 to .290 | 3.03 | <.001 | 33% |
| Within | .219 | .019 | <.001 | .181 | .018 | .001 | .038 | .007 | .023 to .051 | 5.14 | <.001 | 17% |
| Day-to-Day Model-B: Abdominal Pain (day = t) predicts Next-day Fatigue (day = t+1) | | | | | | | | | | | | |
| Across | .528 | .076 | <.001 | .357 | .104 | <.001 | .171 | .017 | .062 to .290 | 3.02 | <.001 | 32% |
| Within | .071 | .017 | <.001 | .054 | .016 | <.001 | .017 | .004 | .008 to .026 | 3.74 | <.001 | 24% |
| Reverse Model-C: Fatigue (day = t) predicts Next-day Abdominal Pain (day = t+1) | | | | | | | | | | | | |
| Across | .489 | .068 | <.001 | .410 | .073 | <.001 | .079 | .043 | -.006 to .164 | 1.82 | .069 | NS |
| Within | .073 | .017 | .132 | .066 | .017 | .259 | .007 | .004 | -.002 to .016 | 1.92 | .064 | NS |

Note.
CI = confidence interval. NS = non-significant. SE = standard error. Sample size (Study-1 N =255).
[a] unstandardized β-coefficient, controlling for age. [b] resamples n = 1,000. [c]mediation (%): $\frac{\text{main model } \beta - \text{ adjustiment } \beta}{\text{main model } \beta}$ x 100.

Table 2-4. Study-2: Relationships of Abdominal Pain with Fatigue in Women with Irritable Bowel Syndrome

| | Main models | | | Models controlling for depression and anxiety (day = t) | | | Bootstrap results for significances of mediation effect[b] | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | β[a] | SE | *p* | β[a] | SE | *p* | β[a] | SE | 95% CI | Z | *p* | Mediation (%)[c] |
| Same-day Model-A: Relationships of Abdominal Pain (day = t) with Fatigue (day = t) | | | | | | | | | | | | |
| Across | .514 | .103 | <.001 | .350 | .102 | <.001 | .164 | .062 | .053 to .274 | 2.89 | <.001 | 32% |
| Within | .140 | .034 | <.001 | .112 | .032 | <.001 | .028 | .007 | .014 to .042 | 3.92 | <.001 | 20% |
| Day-to-Day Model-B: Abdominal Pain (day = t) predicts Next-day Fatigue (day = t+1) | | | | | | | | | | | | |
| Across | .518 | .102 | <.001 | .360 | .101 | <.001 | .158 | .053 | .055 to .263 | 3.00 | <.001 | 31% |
| Within | .035 | .024 | .145 | .023 | .024 | .337 | .012 | .004 | -.001 to .019 | 1.40 | .132 | NS |
| Reverse Model-C: Fatigue (day = t) predicts Next-day Abdominal Pain (day = t+1) | | | | | | | | | | | | |
| Across | .481 | .087 | <.001 | .307 | .100 | 002 | .174 | .052 | -.046 to .277 | 1.46 | .144 | NS |
| Within | .019 | .024 | .430 | .011 | .025 | .658 | .008 | .005 | -.002 to .018 | 1.52 | .128 | NS |

Note.
CI = confidence interval. NS = non-significant. SE = standard error. Sample size (Study-2 N =101).
[a]unstandardized β-coefficient, controlling for age. [b] resamples n = 1,000. [c]mediation (%): $\frac{\text{main model } \beta - \text{ adjustiment } \beta}{\text{main model } \beta}$ x 100.

Table 2-5. Merged data from Study-1 and Study-2: Relationships of Abdominal Pain with Fatigue in Women with Irritable Bowel Syndrome

| | Main models | | | Models controlling for depression and anxiety (day = t) | | | Bootstrap results for significances of mediation effect[b] | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | β[a] | SE | *p* | β[a] | SE | *p* | β[a] | SE | 95% CI | Z | *p* | Mediation (%)[c] |
| Same-day Model-A: Relationships of Abdominal Pain (day = t) with Fatigue (day = t) | | | | | | | | | | | | |
| Across | .529 | .061 | <.001 | .363 | .060 | <.001 | .166 | .042 | .085 to .252 | 3.94 | <.001 | 31% |
| Within | .194 | .017 | <.001 | .159 | .016 | <.001 | .035 | .006 | .023 to .046 | 6.04 | <.001 | 18% |
| Day-to-Day Model-B: Abdominal Pain (day = t) predicts Next-day Fatigue (day = t+1) | | | | | | | | | | | | |
| Across | .527 | .062 | <.001 | .363 | .061 | <.001 | .164 | .043 | .083 to .254 | 3.88 | <.001 | 31% |
| Within | .060 | .014 | <.001 | .044 | .014 | .001 | .016 | .003 | .009 to .021 | 4.90 | <.001 | 27% |
| Reverse Model-C: Fatigue (day = t) predicts Next-day Abdominal Pain (day = t+1) | | | | | | | | | | | | |
| Across | .453 | .055 | <.001 | .375 | .059 | <.001 | .077 | .040 | -.003 to .152 | 2.32 | .059 | NS |
| Within | .056 | .014 | .188 | .049 | .014 | .109 | .007 | .005 | -.002 to .017 | 2.42 | .072 | NS |

Note.
SE = standard error. NS = non-significant. CI = confidence interval. Sample size (Study-1 N =255, Study-2 N =101, and Merged N = 356). [a] unstandardized β-coefficient, controlling for age and study design (Study-1 and Study-2).
[b] resamples n = 1,000. [c]mediation (%): $\frac{\text{main model } \beta - \text{ adjustiment } \beta}{\text{main model } \beta}$ x 100.

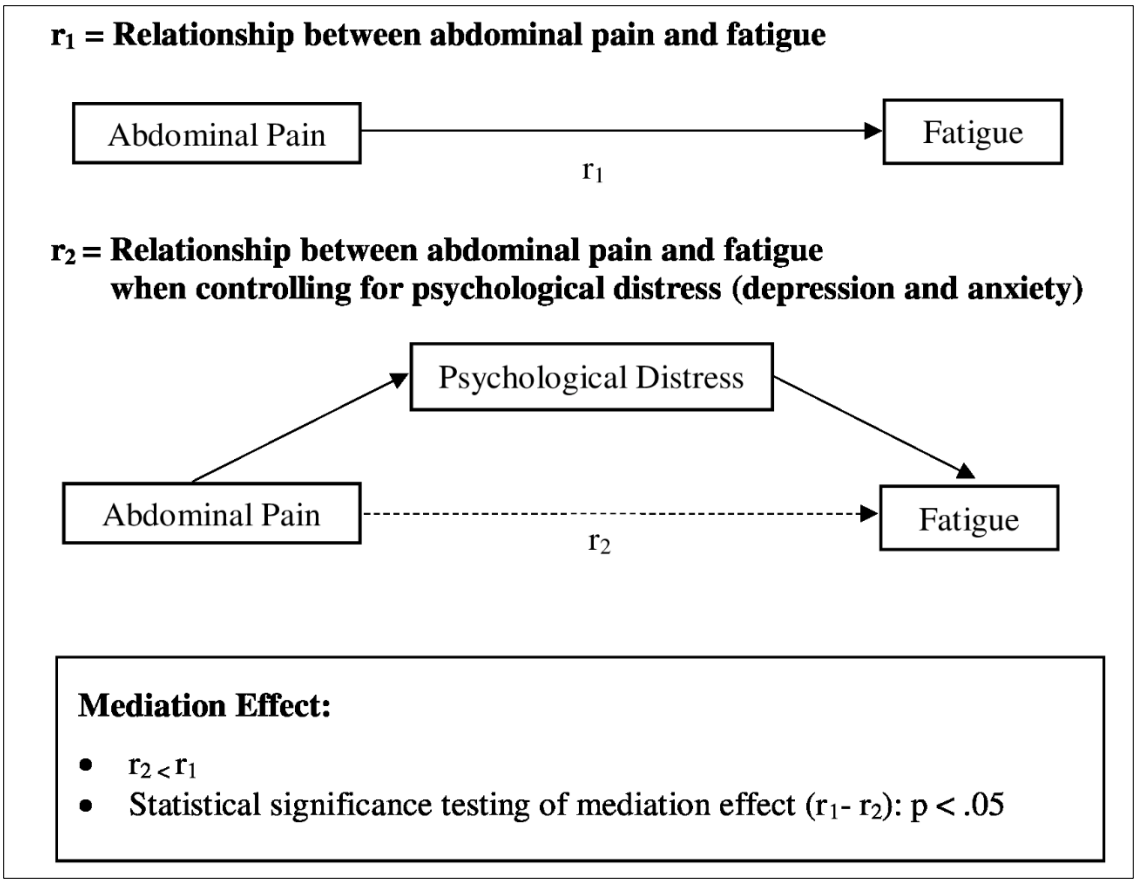


Figure 2-1. Conceptual Mediation Model. When $r_1$, and ($r_1$- $r_2$) are significant ($p < .05$), the mediation effect by psychological distress between abdominal pain and fatigue exists (If $r_2$ become non-significant, it means a full mediation effect, and if $r_2$ is still significant, it means a partial mediation effect).

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# CHAPTER III.

## MANUSCRIPT II

Comparison of subgroups of women with irritable bowel syndrome

on fatigue and co-occurring symptoms: Patient characteristics and genetic polymorphisms

## Abstract

**Background:** Fatigue is part of a symptom cluster that also includes abdominal pain, depression, and anxiety in irritable bowel syndrome (IBS). Fatigue management in IBS is challenging due to limited knowledge such as patient characteristics, and bio-mechanisms (i.e., genetics) about fatigue and these co-occurring symptoms. **Objective:** The purposes of this study were to determine (1) if subgroups of women with IBS could be identified based on the severity of symptom cluster of fatigue, abdominal pain, depression, and anxiety; (2) if these subgroups differed on patient characteristics; and if genetic polymorphisms of tryptophan hydroxylase (TPH), serotonin reuptake transporter (SERT) and catecholamine methyl-O-transferase (COMT) were associated with (3) fatigue or (4) latent class membership. **Methods:** A secondary analysis of baseline data from previous studies was conducted. A daily 4-week symptom diary was completed by 249 Caucasian women with IBS. Assessment of deoxyribonucleic acid (DNA) for presence of polymorphisms was analyzed by polymerase chain reaction. Latent class profile analysis (LCPA) was used to determine patient subgroups; and analysis of variance and Chi-square tests were used to test group differences. **Results:** Three latent classes were identified (Class 1, n = 158, low severity; Class 2, n = 70, medium severity; and Class 3, n = 21, high severity). Women in Class 3 had lower social support, higher symptom burden, poorer quality of life, and higher life interferences. The TPH2 polymorphism rs4570625 was associated with fatigue. **Conclusions:** LCPA was capable of identifying and explaining inter-individual variability of subgroups based on a symptom cluster of fatigue and co-occurring symptoms. This study contributes to the ability to identify IBS patients at risk of high symptom burden and guide interventions tailored to individuals' symptom profiles.


**Keywords:** fatigue, symptom cluster, genetic polymorphism, irritable bowel syndrome

### 3.1. Introduction

Irritable bowel syndrome (IBS) is a common functional gastrointestinal (GI) disorder that is characterized by abdominal pain or discomfort and changes in bowel movement. The prevalence of IBS in adults worldwide is 9% to 23% (IFFGD, 2013); the prevalence in the United States (U.S.) is 14% (Hungin, Chang, Locke, Dennis, & Barghout, 2005). Diagnosis of IBS is currently based upon (Drossman & Dumitrascu, 2006). Predominant bowel pattern subgroups are constipation (IBS-C), diarrhea (IBS-D), and a mix of constipation and diarrhea (IBS-M). Other common co-occurring GI symptoms include bloating, intestinal gas, nausea, and flatulence (Yao et al., 2012). Individuals with IBS also experience other equally disturbing symptoms, such as fatigue, depression, and anxiety (Lackner, Gudleski, DiMuro, Keefer, & Brenner, 2013). To manage symptoms of IBS, U.S. patients incur annual costs (direct and indirect) ranging from $742 to $7,547 (Hulisz, 2004). To date, the etiology of IBS is poorly understood. Multiple factors including genetics have been implicated in pain sensitivity, motility alterations, and symptom perceptions, all of which may be part of the pathophysiology of IBS (Saito, 2011).

Fatigue is one of the most common symptoms reported by patients with IBS. Fatigue in patients with IBS is also related to reduce health-related quality of life (HRQOL) and higher health care costs (Lackner, Gudleski, DiMuro, Keefer, & Brenner, 2013). In patients with IBS, fatigue frequently co-occurs with abdominal pain, depression, and anxiety (Han & Yang, 2016; Lackner et al., 2013). Strategies for patients with IBS that specifically focus on fatigue management are lacking. The challenge is separating fatigue from the other co-occurring symptoms (i.e., abdominal pain, depression, and anxiety). It has been suggested that fatigue is part of a symptom cluster in individuals with IBS—a cluster that also includes abdominal pain

and psychological distress (Lackner et al., 2013; Simren, Svedlund, Posserud, Bjornsson, & Abrahamsson, 2008). It is also possible that this symptom cluster (fatigue, abdominal pain, depression, and anxiety) is more etiologically relevant than fatigue alone (Hausteiner-Wiehle & Henningsen, 2014; Witthoft, Hiller, Loch, & Jasper, 2013). There could be common underlying pathophysiological mechanisms that account for fatigue and these co-occurring symptoms. One potential etiologic factor that could explain the clustering of symptoms is genetic polymorphisms makeup of the individual (Dinan, Cryan, Shanahan, Keeling, & Quigley, 2010; Saito, 2011).

**Genetics in Symptoms of IBS.** Previous researchers have demonstrated an association between specific genes that influence the function of proteins involved in neurotransmission (i.e., serotonin and catecholamine pathways) with GI and psychological symptoms in IBS (Dinan et al., 2010; Fukudo & Kanazawa, 2011). Serotonin is known to affect mood and visceral sensitivity in the GI tract in patients with IBS (O'Mahony, Clarke, Borre, Dinan, & Cryan, 2015). In the serotonin pathways (Figure 3-1), tryptophan hydroxylase (TPH) is the rate-limiting enzyme in serotonin biosynthesis. The gene that regulates it has two isoforms, TPH1 and TPH2. TPH1 is expressed in tissues in the periphery (e.g., skin, gut, pineal gland) and is mostly expressed in enterochromaffin cells in the gut. In contrast, TPH2 is the predominant isoform in the central nervous system (Allegri, Costa, Ragazzi, Steinhart, & Laresio, 2012). The genetic polymorphisms of TPH have been associated with abdominal pain in Japanese men and women with IBS (Brown et al., 2011) and with mental health QOL in Caucasian women with IBS (Jun, Kohen, Cain, Jarrett, & Heitkemper, 2014).

Serotonin transporter is a protein that is responsible for the reuptake of serotonin into the presynapse. A common polymorphism in serotonin pathways is a polymorphism of the serotonin

transporter gene (SERT). The SERT promoter insertion/deletion polymorphisms are “short” (14 repeat) or “long” (16 repeat) alleles; and short allele (s) is associated with reduced transcription and functional capacity of serotonin transporter relative to long allele (l) (Canli & Lesch, 2007). Although one meta-analysis with eight IBS study (van Kerkhoven, Laheij, & Jansen, 2007) reported that SERT polymorphism was not associated with IBS and its symptom phenotype in different populations (e.g., Asians and Caucasian), a few IBS studies found the associations between SERT polymorphisms and IBS. In studies with IBS participants, the short allele of SERT was associated with abdominal pain in Caucasian men and women (Colucci et al., 2013) and Indian men and women (Kumar, Ranjan, Mittal, & Ghoshal, 2012); and it was associated with psychological distress in Caucasian women (Jarrett et al., 2007).

In the catecholamine pathways (Figure 3-1), the catechol-O-methyltransferase (COMT) is one of several enzymes that degrade catecholamines (Bisogni, Pengo, Maiolino, & Rossi, 2015). The methionine (Met) allele results in a 3-fold to 4-fold decrease in the activity of the COMT enzyme, compared to the valine (Val) allele (Bisogni et al., 2015). The relationship between COMT polymorphism and IBS was explored in previous studies. Karling et al (2011) found that Val/Val genotype was associated with IBS-D in Swedish population. In contrast, Wang et al (2014) reported that Met/Met genotype was associated with IBS-D in Chinese population. The Met/Met genotype has been positively associated with abdominal pain (Hall et al., 2012); and Saito (2011) suggested that COMT gene as a candidate gene of GI and psychological symptoms in patients with IBS.

**Genetics in Fatigue**. Although the mechanisms of fatigue remain largely unknown, previous researchers have suggested that biochemical substances such as serotonin and catecholamine may be important biomarkers (Hickok, Morrow, McDonald, & Bellg, 1996;

Landmark-Høyvik et al., 2010; Parker, Wessely, & Cleare, 2001). Studies of fatigue as a major symptom of patients with other chronic illnesses, such as chronic fatigue syndrome or cancer, have shown associations between fatigue and TPH, SERT, and COMT genetic polymorphisms (Landmark-Høyvik et al., 2010; Swain, 2000). As such, these polymorphisms may be candidates for further exploration with respect to understanding the genetic influences associated with fatigue and its co-occurring symptoms (i.e., the symptom cluster of fatigue, abdominal pain, depression, and anxiety) in IBS patients.

For effective management of fatigue in IBS, a better understanding of its characteristics including biological mechanisms, together with its symptom clusters, is important. To the best of our knowledge, no other studies have conducted this line of research to date. Further, the majority of the research on symptoms in IBS has focused on the characteristics of single symptoms, such as abdominal pain, constipation, diarrhea, or depression.

Therefore, the aims of this hypothesis-generating study were to determine (1) if distinct latent classes of IBS patients could be identified based on categories of severity of the symptom cluster of fatigue, abdominal pain, depression, and anxiety; (2) if these latent classes differed on patient characteristics (e.g., sociodemographics, clinical characteristics, symptoms, life impact variables); (3) if genetic polymorphisms of TPH, SERT and COMT were associated with single symptoms (i.e., fatigue - exploratory, abdominal pain, depression and anxiety - confirmatory); and (4) if these genetic polymorphisms were associated with the latent class membership.

The hypotheses were:

1. Distinct latent classes of IBS patients could be identified based on severity of the symptom cluster of fatigue, abdominal pain, depression, and anxiety.

2. The identified latent classes would differ on sociodemographics, clinical characteristics, symptoms, and life impact variables.
3. Genetic polymorphisms of TPH, SERT and COMT would be associated with each of the four single symptoms (fatigue, abdominal pain, depression, and anxiety).
4. Genetic polymorphisms of TPH, SERT and COMT would be associated with the identified latent class membership.

**Theoretical/Conceptual Framework**

The conceptual framework that guides this study is influenced by the biopsychosocial model (Tanaka, Kanazawa, Fukudo, & Drossman, 2011, p. 133) and was modified for this study (Figure 3-2) with permission of Drossman. Figure 3-2 shows the conceptual framework, which illustrates the relationships among personal/biological variables; psychosocial, physiological, and IBS symptom variables; and life impact variables. This conceptual framework includes each sub-concept: genetic variations of TPH, SERT, and COMT genes together with gender and age as personal/biological variables; diagnosis of mental history (lifetime mental disorders), retrospective psychological distress, and sociodemographic factors as psychosocial variables; fatigue, abdominal pain, depression, and anxiety as IBS symptom variables; and cognitive beliefs about the seriousness of IBS symptoms, life interference such as missed days of work, and HRQOL as life impact variables (outcomes).

## 3.2. Methods

**Design, Participants, and Settings**

This study is a secondary analysis of a baseline symptom data collected over 28 days from two previous randomized controlled trials (Study-1 and Study-2) (Jarrett et al., 2016; Jarrett et al., 2009). Study-1 was conducted from 2002 to 2007, and Study-2 from 2008 to 2013. The

participants in these studies were recruited through community advertisement. Participants had to have a diagnosis of IBS, be between 18 and 70 years of age, and met the Rome-II (Study-1) and Rome-III (Study-2) criteria for IBS. Rome II criteria included - at least 12 weeks, which need not be consecutive, in the preceding 12 months of abdominal discomfort or pain that has two or more of the following: improvement with defecation, onset associated with a change in frequency of stool, onset associated with a change in form of stool; while Rome III criteria included - recurrent abdominal pain or discomfort at least 3 days/month in last 3 months associated with two or more of the symptoms aforementioned above (Drossman & Dumitrascu, 2006). Participants were excluded for co-existing GI pathology (e.g., inflammatory bowel disease) or surgery; renal or reproductive pathology (e.g., endometriosis); or select medications (e.g., antibiotics, anticholinergics, narcotics, iron supplements). After participants were recruited, orientation to questionnaires was given at the first study visit, and each participant underwent a screening for eligibility. After obtaining informed consents including genetic data collections from participants, eligible participants came to the research office and they were oriented to the study, and completed baseline questionnaires. Participants had blood drawn for genomic analyses. At home they completed the daily diary each evening for 28 days.

Since both randomized controlled trials (Jarrett et al., 2016; Jarrett et al., 2009) had similar protocols, recruitment approaches, and sample characteristics conducted by the same research team and in the same research settings, we combined data from both studies. Gender-related differences in abdominal pain, fatigue, and psychological symptoms are apparent in patients with IBS, but women experienced these symptoms more severely and frequently than men (Cain et al., 2009; Kroenke & Spitzer, 1998). Thus men were excluded in this study. In addition, to minimize racial/ethnic bias, only Caucasian women, which were the majority of

participants, were included. A total of 249 eligible Caucasian women with IBS were included for this proposed sample.

**Measures**

**Demographics and symptom characteristic questionnaires.** Participants were asked for information regarding their age, race and ethnicity, marital status, education, occupation, annual personal income levels using a demographic questionnaire. General history of past and current symptoms and diseases were assessed (respiratory, cardiac, skin, etc.) by a study gastroenterologist. In addition, IBS specific information was ascertained on IBS symptoms, diagnosis procedures, management strategies (psychological medications, oral contraceptives, etc.), and family history of GI diseases using a health history questionnaire. Adult Rome II (Study-1) and Rome III (Study-2) diagnostic questionnaires were used to assess IBS bowel pattern subtypes (IBS-C, IBS-D, and IBS-M) and to identify GI symptom frequency and presence consistent with the criteria for IBS subgroups. Average Cronbach's α coefficient of the overall items in both questionnaires were 0.95~ 0.98 (Drossman, Talley, Whitehead, Thompson, & Corazziari, 1999; Thompson, Drossman, Talley, Walker, & Whitehead, 2006).

**Daily fatigue, abdominal pain, depression, and anxiety.** Daily fatigue, abdominal pain, depression and anxiety were measured using a daily diary over 28 consecutive days during the baseline assessment. The diary was used to assess symptom severity experienced over the past 24 hours. Participants rated each symptom on a Likert scale of 0 (*not presen*t), 1 (*mild*), 2 (*moderate*), 3 (*severe*) to 4 (*very severe*). Reliability of diary data was good ($\alpha = 0.72$). For the data analysis in this study, the daily symptoms were collapsed into the percent of days with either '*not present to mild*' symptoms or '*moderate to very severe'* symptoms (Jarrett et al., 2007; Jun et al., 2011).

**History of mental disorders.** The history of mental disorders was measured using the world health organization Composite International Diagnostic Interview (CIDI). This instrument is a fully structured diagnostic interview administered via a computer to derive diagnoses of diagnostic and statistical manual of mental disorders (DSM)-IV and International Classification of Disease (ICD)-10 mental disorders. CIDI included mood-disorders module, anxiety-disorders module, and suicidal ideation module (Rubio-Stipec, Bravo, & Canino, 1991). Reliability was good (α: 0.95-0.98). Only any types of single and recurrent episode of major depression disorder and global anxiety disorder were included for this study.

**Retrospective psychological distress.** For retrospective measure of psychological distress, the Brief Symptom Inventory (BSI) was completed. The BSI is a 53-item questionnaire that evaluates recalled psychological distress over 7 days (subscales: somatization, anxiety, obsessive-compulsive, phobic anxiety, depression, interpersonal sensitivity, hostility, paranoia, psychoticism) (Derogatis, 1993). In our study, we also calculated the general severity index (GSI) as a sum-score of psychological distress subscales. The internal consistency of the GSI was $\alpha = 0.91$ in this study.

**IBS-related cognitive beliefs.** The Cognitive Scale for Functional Bowel Disorders (CSFBD) consists of 31 items to assess cognitive beliefs related to functional bowel disorder, using a 7-point Likert scale ranging from 1 *(strongly disagree*) to 7 (*strongly agree*) (Toner et al., 1998). An example item is "*I often worry that there might not be a bathroom available when I need it."* A mean of all items was computed with the higher scores indicating more negative IBS-related cognitive beliefs. Overall internal consistency for the items was $\alpha = 0.89$ (Toner et al., 1998).

**Life interference.** The work productivity and activity impairment questionnaire (WPAI) includes nine questions related to the impact of IBS on work and other regular activities. The test–retest ranged from $r$ = 0.71 to 0.95 for the items (Reilly, Zbrozek, & Dukes, 1993). For this analysis two items were used, the overall work productivity loss (missed work and work impairment due to IBS) and the daily activity impairment items (impairment while working due to IBS).

**HRQOL.** IBS Quality of Life (IBSQOL) developed by Hahn, Kirchdoerfer, Fullerton, and Mayer (1997), was used to assess HRQOL. This questionnaire has 42 items in nine domains: emotional, mental health, sleep, energy, physical functioning, diet, social role, physical role, and sexual relations. Scores were recorded on a 5–6-point Likert scale and transformed to a 100-point score, where a higher score represented a better QOL. A total score was calculated by averaging all, items except for those regarding diet and sexual relations (Jarrett et al., 2009). The diet item was omitted because participants in the intervention groups were encouraged to avoid foods that cause problems for them. The sexual relations item was omitted because of the large fraction of women not sexually active (Jarrett et al., 2009). The questions were asked in a recall period over the previous 4 weeks. Sample items include: "*How often did your IBS make you feel fed up or frustrated?"* and rated as 1 *(always)* to *5 (never).* Cronbach's was from 0.73 to 0.93 (Hahn et al., 1997).

**Genotyping**

Deoxyribonucleic acid (DNA) was isolated from whole blood using buffy coat preparations and Puregene DNA purification kits (Gentra Systems, Inc., Minneapolis, MN for TPH and SERT genes, and Qiagen Sciences LLC, Louisville KY for COMT Val158Met gene) according to the manufacturer's instructions. After DNA extraction, the samples were analyzed

for the genetic polymorphism. TaqMan protocol with a polymerase chain reaction (PCR) was used for single nucleotide polymorphism (SNP) genotyping. In the parent studies (Jarrett et al., 2016; Jarrett et al., 2009), tagging SNPs were required to be common (defined as having a minor allele frequency ≥ 0.05) in public databases (e.g., HapMap). The quality control filterings of all SNPs were performed. SNPs with call rates of < 95% or Hardy-Weinberg p-values of < .001 were excluded. Measures of linkage disequilibrium (LD) were computed from the participants' genotypes with Haploview 4.2.

There is no published study to examine the genetic associations with fatigue and with latent classes of IBS patients based on the symptom cluster of fatigue, abdominal pain, depression and anxiety. Thus, based on the previous literature, genes and SNPs of serotonin and catecholamine were selected from the pre-selected candidate genes and SNPs from the existing dataset collected from the parent studies (Jarrett et al., 2016; Jarrett et al., 2009). As a result, TPH1 and TPH 2, SERT (short/long allele), and COMT Val158Met genes were selected. SNPs from existing dataset were rs4537731, rs684302, rs211105, and rs1800532 of TPH1; rs4570625 of TPH2; rs25531 of SERT; and rs4680 of COMT.

**Statistical Analyses**

Descriptive statistics were used to calculate the mean and standard deviation, and the total number and percentage of outcome variables. The *z* scores were used for all analyses. Given the complete data in this study, missing data analyses were not considered for this study. Data analysis was conducted with Mplus Version 7.4 for latent class profile analysis (LCPA) and overall data analysis with IBM SPSS Statistics for Windows, version 19.0 (SPSS, Inc., Armonk, NY: IBM Corp, USA). A $p$ value ≤ .05 was considered statistically significant. All tests were two-tailed.

Aim 1) LCPA was used to identify latent classes of IBS patients based on symptom severity of fatigue, abdominal pain, depression and anxiety using Mplus Version 7.4. LCPA identifies a set of latent classes (i.e., subgroups) characterized by similar patterns of responses to symptom items (Muthén & Muthén, 2010). LCPA is a person-centered, model-based cluster procedure, which is a type of latent variable mixture modeling used with continuous variables. LCPA is considered superior to traditional clustering analysis because it allows for a more flexible model specification and provides several goodness-of-fit indices to aid in selecting the optimal number of groups. A series of models with increasing numbers of groups or classes was run and the best fitting model was chosen based on a combination of the following methods: comparing tests of statistical significance, goodness of fit indices, and interpretability of the profiles. Selection of the best fitting model was also based on sizes of groups within models. Specifically, solutions that contained groups with less than 5% of the cases was examined with caution (Flaherty & Kiff, 2012).

The log likelihood (LL) is the probability the data given the parameter estimates to find the set of parameter estimates that make the data most likely. The LL always be negative, with higher values (closer to zero) indicating a better fitting model. Then, classes with best model fits were identified by evaluating five tests including the (a) the lowest Akaike's Information Criteria (AIC) (b) the lowest Bayesian information criterion (BIC) as well as the sample size adjusted BIC (SSA-BIC), (c) the lowest Vuong–Lo–Mendel–Rubin likelihood ratio test (VLMR), (d) the lowest parametric bootstrapped likelihood ratio test (BLRT), and (e) entropy to be 0.80 or greater, which indicates a measure of classification uncertainty (from '*0 = low certainty'* to '*1 = high certainty'*). The model that fits the data best has the lowest AIC, BIC, or SSA-BIC, VLMR and/or BLRT, and higher entropy (Doong et al., 2014; Illi et al., 2012).

Aim 2) Chi-square test for categorical variables and analysis of variance (ANOVA) was used to evaluate associations of patient characteristics with the identified latent classes.

Aim 3 and 4) To test genetic associations a) with fatigue, abdominal pain, depression and anxiety, ANOVA test was used; and b) with latent class membership, Chi-square was used.

When age and study designs (Study-1 and Study-2) were adjusted as covariates, since they were associated with symptoms, the results were unchanged. Thus, data are presented without controlling all covariates. Pairwise comparisons with Bonferroni corrections of the *p*-values were conducted.

### 3.3. Results

#### Preliminary analysis

Before conducting LCPA, we conducted preliminary analysis of this study's data, among the 26 daily diary symptoms. Fatigue, abdominal pain, depression, and anxiety were shown to be strongly and positively correlated with each other, using a Pearson correlation ($0.681 \leq r \leq 0.895$).

#### Latent Class Membership

Using an LCPA, three distinct latent classes of IBS patients were identified. The results of indices for determining the candidate models are shown in Table 3-1. The three-class model was selected based on the fit indices of model selection: The LL was highest in the three-class model. The AIC, BIC, and SSA-BIC were lower for the three-class model than for the two- and four-class models. The VLMR suggested that the three-class model fit the data better than the two-class model, and the four-class model was not significantly better than the three-class model. The entropy values from the two- and three-class models were similar, but the highest entropy

was shown in three-class model, indicating that the three groups were highly discriminative. Ultimately, the three-class model was selected over the two- and four-class models.

Thus, the final model consisted of three latent classes (Table 3-2, Figure 3-3). There was no clinical cut point for interpreting the levels of symptom severity, so the subgroups were assigned names based on tertiles of percentage of days with moderate to very severe symptoms (0 % $\leq$ *low* < 33%, 33% $\leq$ *medium* < 66%, and 66% $\leq$ *high* $\leq$ 100%). Class 1 (n = 158, 53.2% of total participants) was labeled "low severity," Class 2 (n = 70, 23.6%) was labeled "medium severity," and Class 3 (n = 21, 7.1%) was labeled "high severity." Classes 1 and 2 had a relatively low level of depression compared to fatigue, abdominal pain, and anxiety.

**Differences in Patient Characteristics**

**Demographic and clinical characteristics.** As presented in Table 3-3, several differences in demographic characteristics were found among the latent classes. Patients in Classes 1 and 2 had similar demographic characteristics, but patients in Class 3 (the high severity class) were less often married or partnered compared to patients in the low and medium severity classes ($p$ =.032). In addition, annual personal income was higher among patients in Class 1 (low severity) than in Classes 2 and 3 ($p$ = .004). Age, education, employment status, and type of job were not statistically significantly different across the classes. For clinical characteristics, no significant across-class differences were found for bowel pattern subtypes, history of mental disorders (Table 3-3), or use of medications (e.g., tricyclic antidepressants, serotonin selective reuptake inhibitors, or oral contraceptives; data not shown).

**Severity of GI symptoms and psychological distress.** Differences between latent classes in GI symptoms and psychological distress, as well as in retrospective (recalled) psychological distress over 7 days, are shown in Table 3-4. Significant differences between

latent classes were observed for most of the symptoms. Of these, the symptoms of stress ($F$ = 98.9), sleepiness ($F$ = 42.3), and GSI ($F$ = 61.6) differed significantly across the latent classes.

**Life impact variables.** Significant differences in IBS-related cognitive beliefs, HRQOL, and work and life interference were found among the three latent classes (Table 3-5). The most negative cognitive beliefs, the lowest QOL scores, and the highest work and life interference were found in Class 3 (high severity). Of note, the overall HRQOL score ($F$ = 33.1) and the subscales for sleep ($F$ = 59.4) and social role ($F$ = 49.4) differed most significantly across the classes. The sleep and social role subscale scores were markedly poorer in the high severity class (Class 3) compared to the other two classes.

**Genetic Associations with Single Symptoms and with Identified Latent Class Membership**

There were significant mean differences in severity of fatigue by polymorphism of TPH2 SNP rs4570625 (Table 3-6). Fatigue severity was higher in patients with TT homozygous, compared to the G allele carriers (i.e., GG and GT genotype). Abdominal pain differed significantly by polymorphism of TPH1 SNP rs4537731. Abdominal pain was higher in G allele carriers (AG and GG genotype) than in the patients with AA homozygous. No significant differences were observed in the severity of single symptoms (i.e., fatigue, abdominal pain, depression, or anxiety) by SERT and COMT genotype (Table 3-7). To confirm these findings, we examined genetic associations with history of mental disorders (i.e., major depression and global anxiety) and with retrospective psychological distress (i.e., depression and anxiety), but, we could not find significant associations (data not shown). In addition, none of the genetic polymorphisms of SERT, TPH, or COMT were significantly associated with identified latent class membership (data not shown).

**Post Hoc Analysis**

Since diarrhea and constipation are common disabling and clinically important symptoms of IBS (Drossman & Dumitrascu, 2006), a post-hoc LCPA was conducted that added these two symptoms to fatigue, abdominal pain, depression and anxiety. Three latent classes - “all symptoms low,” “all symptoms high except for constipation,” and “all symptoms high except for diarrhea” - were selected. Constipation and diarrhea were not significant factors for identifying latent classes. None of the genes were significantly associated with latent class membership based on the severity of the six symptoms fatigue, abdominal pain, depression, anxiety, constipation, and diarrhea (data not shown).

**3.4. Discussion**

This is the first hypothesis-generating study in IBS (a) to identify three distinct subgroups of women with IBS based on the severity of fatigue, abdominal pain, depression, and anxiety using an LCPA; and (b) to explore the linkages of potential genetic markers with fatigue and with the latent class subgroups.

Three latent classes of patients reporting fatigue were identified: patients with all symptoms of low severity (Class 1), patients with all symptoms of medium severity (Class 2), and patients with all symptoms of high severity (Class 3). Patients in Class 3 (high severity symptoms) were less likely to be married or partnered and less likely to have higher annual personal income than patients in the low and medium severity classes. Previous IBS studies have reported that marital status and income were indicative of social support, and researchers reported a protective effect of this social support against the symptom burden (Coulson, 2005; Lackner et al., 2010; Martin, Davis, Baron, Suls, & Blanchard, 1994). Lackner et al. (2010) found social support to be positively associated with less severe pain and less global severity of

overall symptoms of IBS. Thus, our result suggests that the high symptom group should be targeted for intervention to increase social support.

This study found that the three latent classes did not differ by bowel pattern subtypes (data not shown). In a post hoc analysis of this study, the severity of daily diarrhea and constipation were not found to be significant contributing factors in distinguishing the latent classes. There were no statistically significant differences regarding psychological and somatic symptoms, including fatigue, by IBS bowel pattern subtypes (Farzaneh, Ghobakhlou, Moghimi-Dehkordi, Naderi, & Fadai, 2012; Si, Wang, Chen, Sun, & Dai, 2004; Spiegel et al., 2010). Furthermore, the severity of abdominal pain differed by subgroups based on pain but not by those based on IBS bowel pattern subtypes in Caucasian women (Heitkemper et al., 2011). Although these previous IBS studies using different data, we can therefore conjecture that interventions for fatigue and co-occurring symptoms may be applicable for all patients with IBS regardless of bowel pattern subtypes.

Significant increases of severity in many GI symptoms, in stress, and in sleepiness during the day, as well as psychological symptoms, were observed in the expected direction from the low to high severity class. Of note, stress and sleepiness during the day were the symptoms most significantly different across the latent classes. The life impact variables differed significantly among the latent classes, and in particular, sleep and social role QOL scores were very low in the high severity class. Previous researchers with different data from current study have also found that poorer self-reported sleep quality significantly predicted higher next-day abdominal pain, anxiety, and fatigue in IBS (Buchanan et al., 2014; Jarrett, Heitkemper, Cain, Burr, & Hertig, 2000). These results highlight the need to improve sleep quality, social support, and stress

reduction to manage the symptom cluster of fatigue, abdominal pain, depression, and anxiety in IBS.

Given the fact that serotonin and catecholamine are associated with fatigue (Landmark-Høyvik et al., 2010), pain (Colucci et al., 2013; Schmahl et al., 2012), and psychological distress (Desmeules et al., 2012) in chronic diseases, this study examined associations of relevant genetic polymorphisms with specific symptoms (i.e., fatigue, abdominal pain, depression, and anxiety) as well as identified latent class membership. TPH2 (rs4570625) was found to be positively associated with severity of fatigue. Patients with the TT genotype reported higher fatigue compared to G allele carriers. This finding is particularly interesting because TPH2 rs4570625 was either not evaluated or not identified as a candidate gene of fatigue in previous IBS studies as well as other chronic diseases. Only two studies have reported positive associations of fatigue with other TPH2 SNPs: a study of SNP rs12229394 in Caucasian women with depression (Utge et al., 2010), and a study of SNP rs10879355 in Korean men and women with stroke (Choi-Kwon, Ko, Choi, & Kim, 2014).

This study's TPH2 (rs4570625) finding associated with fatigue could be accounted for by the following pathway: mRNA expression for TPH2 rs4570625, in the transcriptional control region of chromosome 12, is decreased in TPH2 T allele carriers relative to G allele carriers (Scheuch et al., 2007), which leads to reduced TPH2 concentrations throughout serotonergic neurons, including axonal terminal sites (Gutknecht et al., 2007). This may lead in turn to reduced serotonin biosynthesis and in consequence to reduced transmitter levels. As a potential compensatory response for deficits in serotonin functions, this decreased serotonin increases amygdala responsiveness to emotional regulation and cognitive controls in the brain (Gutknecht et al., 2007; Reuter et al., 2008; Waider, Araragi, Gutknecht, & Lesch, 2011). In particular, TT

carriers also have been shown to have increased prefrontal cortex activity as measured by functional magnetic resonance imaging in healthy Caucasians (Reuter et al., 2008). In addition, there was a positive association between the TPH2 TT genotype and psychological distress and somatic disorders (i.e., fatigue) (Mossner et al., 2006). One study also found decreased concentrations of serotonin levels in patients with chronic fatigue syndrome (Nakatomi et al., 2014). However, the associations between TPH2 rs4570625 polymorphism and the risk of fatigue have not yet been elucidated. Further research is warranted to explore the effects of this SNP on fatigue.

As a confirmatory analysis of previous studies (Andreou et al., 2010; Camilleri, 2011), this study found a significant and positive association of TPH1 SNP rs4537731 with abdominal pain, in particular in G allele carriers. The A allele of TPH1 SNP rs4537731 has been associated with better cognition and higher QOL with lower serotonin levels as compared to those with G allele carriers in healthy participants (Andreou et al., 2010) and to symptom improvement including abdominal pain in patients with IBS (Camilleri, 2011).

However, this study did not find significant genetic associations between TPH and depression or anxiety, or between SERT, COMT, and the four single symptoms (fatigue, abdominal pain, depression, and anxiety). The lack of genetic associations with symptoms found in this study are consistent with previous studies in patients with IBS. There were no significant associations between TPH and depression or anxiety in Caucasian women (Jun, Kohen, Cain, Jarrett, & Heitkemper, 2014); between SERT and daily diary depression and anxiety in Caucasian men and women (Jarrett et al., 2007); and another IBS study also found no associations between COMT, abdominal pain, depression and anxiety in Caucasian men and women (Karling et al., 2011). Although the COMT Met/Met genotype has been associated with

the symptoms phenotypes of IBS, the mechanisms of how COMT is involved in symptom phenotypes are still unknown in IBS (Hall et al., 2012; Karling et al., 2011). In contrast, this lack of association is inconsistent with the findings of other studies in patients with IBS, which have shown (a) significant associations between SERT and abdominal pain in Indian women and men (Kumar et al., 2012); (b) significant associations between SERT and the life time history of depression or anxiety in Caucasian women and men (Jarrett et al., 2007); and (c) significant associations between COMT and abdominal pain in Caucasian men and women (Hall et al, 2012).

Furthermore, this study did not observe association with genetic variation among the three identified latent classes. Different underlying mechanisms, with various etiologies, may come into play when it comes to complex symptoms in IBS (Jun et al., 2011). The phenotypes of symptom cluster of fatigue and co-occurring symptoms may be more dependent on sociodemographic and clinical characteristics than on genetic variations. In addition, the evidence of common shared etiology of abdominal pain, fatigue, depression and anxiety may be weak, or it could be another common underlying mechanisms of these symptoms. Fatigue must be regarded as a complex condition of probable multifactorial etiology and possibly involving multiple mechanisms and factors (Landmark-Høyvik et al., 2010).

The strengths of this study are its use of an LCPA. The benefits of LCPA, compared to cluster analysis and/or factor analysis, are that LCPA is probabilistic and gives inter-individual variability in the classification of patients based on their symptoms (Williams & Kibowski, 2016). In addition, the current targeted genetic study has the advantage of using prospective data from a well-phenotyped group of women with IBS.

**Limitations**

This study has a few potential limitations. Overall, the reasons for the negative findings regarding genetic associations may be the small sample size, or may be the result of a different dataset in terms of race, population, and sample size; different study methods (e.g., study designs and symptom measurements); as well as different SNPs and haplotypes of genes, compared to previous studies. Thus, a replication study to examine the relationships between fatigue and other candidate genes (e.g., cytokines, serotonin receptor) as well as genome-wide association studies (GWAS) will be further required. Second, the majority of participants were middle-aged and Caucasian women. This limits the generalizability of the findings to the general population. Third, only limited numbers of single SNPs of the four candidate genes were addressed in this study. The study did not cover all of the haplotypes of possible candidate genes. Finally, it should also be noted that the current analyses do not rule out the possibility that the genetic associations observed in this study's IBS patients may be partly attributable to gene x gene and gene x environment interactions.

**3.5. Conclusions**

This study uses an LCPA to provide strong support for presence of subgroups of IBS patients with fatigue and co-occurring symptoms and to explore genetic associations in IBS with both fatigue alone and in a symptom cluster that includes fatigue. The patients in the high severity symptom class had lower annual incomes; were less likely to be married or partnered; had more severe levels of psychological distress, more sleepiness during the day, and more stress; and were more likely to experience work and daily life interference as well as lower QOL. Indeed, this study suggests a comprehensive assessment for IBS patients with fatigue and co-occurring symptoms. For example, comprehensive assessment and intervention may focus on

reducing the overall symptom burden within a cluster, improving social support, making referrals to mental health professionals, and managing patient QOL. Future studies are needed to further understand the underlying fatigue mechanisms and to develop and test new approaches in fatigue management that incorporate multiple factors (e.g., social support, symptom burden, QOL and genetics).

Table 3-1. Latent Class Solution and Fit Indices for Two-Class through Four-Class Solutions

| Model | LL | AIC | BIC | Adjusted BIC | VLMR | Entropy |
|---|---|---|---|---|---|---|
| Two Class | -731.39 | 1488.78 | 1533.01 | 1491.82 | 12.28* | 0.862 |
| Three Class | -649.38 | 1344.77 | 1423.03 | 1350.14 | 12.10* | 0.892 |
| Four Class | -667.65 | 1371.29 | 1432.54 | 1375.52 | 12.12 | 0.863 |

Note.
N = 249.
AIC = Akaike information criterion. BIC = Bayesian information criterion. LL = Log-likelihood.
VLMR = The Vuong-Lo-Mendel-Rubin likelihood ratio test for the K versus K-1 model.
*p <.05.

Table 3-2. Symptom Severity Scores by Latent Class

| Mean (SD) | Class 1, Low | Class 2, Medium | Class 3, High | *F, p, pairwise*[a] |
|---|---|---|---|---|
| Percent of days with moderate to very severe | | | | |
| Fatigue | 23.8 (20.0) | 50.6 (23.9) | 66.4 (28.5) | 95.2, <.001, 1<2<3 |
| Abdominal pain | 27.6 (19.4) | 49.9 (27.4) | 66.9 (26.7) | 65.5, <.001, 1<2<3 |
| Depression | 10.5 (6.3) | 33.1 (15.4) | 65.5 (36.4) | 113.2, <.001, 1<2<3 |
| Anxiety | 13.7 (7.6) | 38.6 (20.3) | 65.9 (30.2) | 140.2, <.001, 1<2<3 |
| Daily symptom severity | | | | |
| Fatigue | 0.88 (0.5) | 1.41 (0.6) | 2.14 (0.7) | 156.9, <.001, 1<2<3 |
| Abdominal pain | 0.93 (0.4) | 1.48 (0.6) | 2.23 (0.6) | 93.8, <.001, 1<2<3 |
| Depression | 0.22 (0.2) | 0.70 (0.4) | 1.77 (0.9) | 201.9, <.001, 1<2<3 |
| Anxiety | 0.39 (0.3) | 1.21 (0.4) | 2.17 (0.8) | 242.4, <.001, 1<2<3 |

Note.
SD = standard deviation.
N = 249 (Class 1 n = 158, 53.2%, Class 2 n = 70, 23.6%, Class 3 n = 21, 7.1%).
*F, p* = testing differences of mean symptom severity by latent classes.
[a]pairwise group comparisons among three latent classes
(The notation '1 <2< 3' indicates that the mean symptom severity of Class 1 is less than the mean of Class 2, the mean symptom severity of Class 2 is less than the mean of Class 3, and the p-value of each pairwise comparison was statistically significant).

Table 3-3. Differences in Demographic and Clinical Characteristics by Latent Classes

| | Class 1 Low | Class 2 Medium | Class 3 High | $F/\chi^2$, *p, pairwise*[a] |
|---|---|---|---|---|
| Age in years, mean (SD) | 42.6 (14.9) | 42.3 (13.3) | 42.7 (13.7) | $F$= 1.53, $p$ =.986 |
| Married/Partnered, n (%) | 71 (44.9) | 36 (51.4) | 8 (38.0) | $\chi^2$ = 19.2, $p$ =.032, 1 = 2 > 3 |
| ≥ Bachelor's degree, n (%) | 111 (70.3) | 42 (60.0) | 15 (71.4) | $\chi^2$= 0.43, $p$ =.105 |
| Income ≥ $ 60,000/yr., n (%) | 64 (40.2) | 30 (42.8) | 4 (16.0) | $\chi^2$ = 16.7, $p$ =.004, 1 = 2 > 3 |
| Professional job, n (%) | 44 (28.0) | 11 (15.1) | 3 (16.3) | $\chi^2$ = 0.25, $p$ =.623 |
| Bowel pattern subtypes, n (%) | | | | $F$ = 0.86, $p$ =.551 |
| Constipation | 33 (20.9) | 20 (28.6) | 8 (38.1) | |
| Diarrhea | 92 (58.2) | 30 (42.9) | 8 (38.1) | |
| Mixed | 19 (12.0) | 13 (18.6) | 3 (14.3) | |
| History of mental disorder, n (%) | | | | $X^2$= 2.93, $p$ =.462 |
| Major depression disorders | 18 (11.4) | 8 (11.4) | 2 (9.5) | |
| General anxiety disorders | 10 (6.3) | 5 (7.1) | 1 (5.2) | |

Note.
SD = standard deviation. N = 249 (Class 1 n = 158, 53.2%, Class 2 n = 70, 23.6%, Class 3 n = 21, 7.1%). $F/\chi^2$, $p$ = testing differences of demographic and clinical characteristics by latent classes. [a]pairwise group comparisons among three latent classes (The notation '1 = 2' indicates that the difference between the values of Class 1 and Class 2 was not statistically significant; The sign '>' indicates that the values of Class 1 and Class 2 were each greater than the value of Class 3 with a statistical significance).

Table 3-4. Differences in Symptom Severity Scores by Latent Classes

| | Class 1 Low | Class 2 Medium | Class 3 High | *F, p, pairwise*[b] |
|---|---|---|---|---|
| Percent of days with moderate to very severe | | | | |
| Abdominal pain after eating | 21.2 (19.1) | 42.1 (29.2) | 52.2 (33.3) | $F$ = 24.7, $p$ <.001, 1<2<3 |
| Constipation | 15.3 (18.9) | 29.1 (27.1) | 35.9 (28.2) | $F$ = 11.1, $p$ <.001, 1<2<3 |
| Diarrhea | 12.1 (17.3) | 21.0 (25.8) | 21.7 (27.9) | $F$ = 6.1, $p$ <.001, 1<2=3 |
| Bloating | 25.2 (26.2) | 39.7 (34.7) | 44.9 (30.8) | $F$ = 12.4, $p$ <.001, 1<2<3 |
| Intestinal gas | 31.9 (27.5) | 50.2 (27.8) | 62.3 (32.5) | $F$ = 12.6, $p$ <.001, 1<2<3 |
| Stressed | 13.1 (6.3) | 24.8 (18.5) | 65.5 (33.2) | $F$ = 98.9, $p$ <.001, 1<2<3 |
| Sleepiness during the day | 16.6 (10.3) | 32.4 (21.2) | 50.8 (31.4) | $F$ = 42.3, $p$ <.001, 1<2<3 |
| Retrospective psychological distress[a] | | | | |
| Depression | 0.3 (0.3) | 0.6 (0.5) | 1.7 (0.8) | $F$ = 53.8, $p$ <.001, 1<2<3 |
| Anxiety | 0.4 (0.4) | 0.8 (0.6) | 1.8 (0.8) | $F$ = 45.0, $p$ <.001, 1<2<3 |
| Global Severity Index (GSI) | 0.4 (0.2) | 0.6 (0.4) | 1.3 (0.6) | $F$ = 61.6, $p$ <.001, 1<2<3 |

Note. N = 249 (Class 1 n = 158, 53.2%, Class 2 n = 70, 23.6%, Class 3 n = 21, 7.1%). [a]recalled symptoms over 7 days using a Brief Symptom Inventory (BSI). *F, p* = testing mean differences of symptoms by latent classes. [b]pairwise group comparisons among three latent classes (The notation '2 = 3' indicates that the difference between the means of Class 2 and Class 3 was not statistically significant; The notation '1 <2< 3' indicates that the mean symptom severity of Class 1 is less than the mean of Class 2, the mean symptom severity of Class 2 is less than the mean of Class 3, and the p-value of each pairwise comparison was statistically significant).

Table 3-5. Differences in Life Impact Variables by Latent Classes

| Mean (SD) | Class 1 Low | Class 2 Medium | Class 3 High | *F, p, pairwise*[a] |
|---|---|---|---|---|
| IBS-related cognitive beliefs | 3.3 (1.0) | 4.1 (1.0) | 5.4 (0.9) | $F = 17.9$, $p = .041$, 1<2<3 |
| Health-Related Quality Of Life (HRQOL) | | | | |
| Overall QOL | 72.2 (13.9) | 58.2 (18.0) | 41.6 (19.9) | $F = 33.1$, $p < .001$, 1>2>3 |
| Emotional QOL | 83.4 (13.3) | 70.4 (18.2) | 63.1 (21.6) | $F = 31.8$, $p < .001$, 1>2>3 |
| Mental health QOL | 86.2 (11.3) | 66.3 (15.2) | 58.9 (19.4) | $F = 21.8$, $p < .001$, 1>2>3 |
| Physical functioning QOL | 98.7 (12.5) | 94.7 (17.6) | 84.0 (24.7) | $F = 11.3$, $p = .011$, 1=2>3 |
| Physical role QOL | 95.2 (13.5) | 91.3 (16.6) | 56.0 (19.2) | $F = 16.9$, $p = .032$, 1=2>3 |
| Sleep QOL | 83.7 (13.5) | 76.2 (17.1) | 35.6 (24.0) | $F = 59.4$, $p < .001$, 1>2>3 |
| Energy QOL | 95.7 (12.2) | 79.1 (14.2) | 55.4 (20.1) | $F = 60.9$, $p < .001$, 1>2>3 |
| Social role QOL | 68.6 (11.9) | 59.3 (19.7) | 22.2 (27.1) | $F = 49.4$, $p < .001$, 1>2>3 |
| Work and Life Interference | | | | |
| Overall work impairment (%) | 37.1 (25.9) | 52.6 (33.6) | 60.4 (31.2) | $F = 3.4$, $p = .035$, 1<2<3 |
| Work time missed (%) | 2.3 (7.2) | 1.9 (3.8) | 3.2 (5.5) | $F = 0.3$, $p = .778$ |
| Impairment while working (%) | 24.4 (18.9) | 28.8 (20.6) | 39.7 (27.2) | $F = 3.9$, $p = .020$, 1<2<3 |
| Daily activity impairment (%) | 27.1 (18.9) | 35.6 (24.9) | 45.2 (27.9) | $F = 8.7$, $p < .001$, 1<2<3 |

Note.
SD = standard deviation. N = 249 (Class 1 n = 158, 53.2%, Class 2 n = 70, 23.6%, Class 3 n = 21, 7.1%).
*F, p* = testing mean differences in life impact variables by latent classes. [a]pairwise group comparisons among three latent classes (The notation '2 = 3' indicates that the difference between the means of Class 2 and Class 3 was not statistically significant; The notation '1 <2< 3' indicates that the mean of Class 1 is less than the mean of Class 2, the mean of Class 2 is less than the mean of Class 3, and the p-value of each pairwise comparison was statistically significant; The notation '1 >2> 3' indicates that the mean of Class 1 is greater than the mean of Class 2, the mean of Class 2 is greater than the mean of Class 3, and the p-value of each pairwise comparison was statistically significant).

Table 3-6. Differences in Percent of Days with Moderate to Very Severe Symptoms by TPH Genotypes

| TPH1 (rs4537731) | AA (n = 75) | AG (n =143) | GG (n = 29) | *p* |
|---|---|---|---|---|
| Fatigue | 34.0 (27.9) | 32.7 (24.8) | 37.1 (32.4) | .482 |
| Abdominal pain | 30.3 (23.1) | 37.9 (26.3) | 42.1 (28.9) | .043;<br>AA≠ AG $p^a$ = .008<br>AA ≠ GG $p^a$ =.005 |
| Depression | 9.9 (18.4) | 9.2 (15.0) | 11.9 (20.9) | .255 |
| Anxiety | 17.9 (24.5) | 20.6 (21.8) | 18.4 (23.5) | .080 |
| TPH1 (rs684302) | CC (n = 88) | CT (n = 123) | TT (n = 38) | |
| Fatigue | 31.2 (27.8) | 33.7 (26.5) | 38.8 (27.9) | .747 |
| Abdominal pain | 39.2 (25.4) | 34.9 (27.2) | 32.5 (22.3) | .423 |
| Depression | 9.0 (16.3) | 10.2 (16.9) | 10.6 (20.0) | .582 |
| Anxiety | 17.6 (20.4) | 19.9 (23.6) | 20.1 (26.1) | .137 |
| TPH1 (rs211105) | TT (n = 129) | GT (n =79) | GG (n = 35) | |
| Fatigue | 36.7 (28.3) | 29.7 (24.6) | 30.8 (31.0) | .094 |
| Abdominal pain | 35.7 (24.9) | 36.9 (27.9) | 27.2 (18.0) | .062 |
| Depression | 10.8 (19.9) | 8.6 (12.4) | 8.9 (14.6) | .413 |
| Anxiety | 21.4 (25.3) | 16.6 (19.6) | 12.5 (15.0) | .599 |
| TPH1 (rs1800532) | CC (n = 72) | AC (n = 134) | AA (n = 37) | |
| Fatigue | 31.5 (27.3) | 33.8 (26.7) | 38.9 (28.3) | .944 |
| Abdominal pain | 40.9 (26.2) | 33.2 (26.5) | 33.3 (22.1) | .321 |
| Depression | 9.4 (16.1) | 9.9 (17.0) | 10.8 (20.3) | .757 |
| Anxiety | 18.9 (21.1) | 19.1 (23.2) | 20.3 (26.4) | .172 |
| TPH2 (rs4570625) | GG (n = 149) | GT (n = 74) | TT (n =12) | |
| Fatigue | 31.8 (27.5) | 30.4 (25.5) | 43.6 (32.7) | .032<br>GG ≠ TT $p^a$ = .024<br>GT ≠ TT $p^a$ =.009 |
| Abdominal pain | 34.8 (25.8) | 36.9 (25.6) | 44.3 (29.5) | .532 |
| Depression | 10.4 (17.7) | 8.3 (16.3) | 13.5 (17.2) | .574 |
| Anxiety | 19.7 (22.9) | 18.0 (24.4) | 20.6 (16.1) | .434 |

Note.
TPH = tryptophan hydroxylase. N = 249.
Data are presented as means and standard deviations for symptom severity.
*p* = testing differences in mean percent of days with moderate to very severe symptoms by TPH genotypes.
$p^a$ = pairwise group comparisons among TPH genotypes.

Table 3-7. Differences in Percent of Days with Moderate to Very Severe Symptoms by SERT and COMT Genotypes

| SERT (rs25531) | s/s (n = 52) | s/l (n = 108) | l/l (n = 81) | *p* |
|---|---|---|---|---|
| Fatigue | 28.1 (24.9) | 34.2 (26.1) | 35.9 (29.9) | .827 |
| Abdominal pain | 38.8 (26.4) | 32.1 (23.9) | 38.0 (28.0) | .799 |
| Depression | 10.4 (16.7) | 9.3 (19.1) | 10.3 (15.3) | .710 |
| Anxiety | 20.2 (24.8) | 17.6 (22.9) | 20.1 (22.4) | .670 |
| COMT (rs4680) | Val/Val (n = 61) | Val/Met (n = 113) | Met/Met (n = 64) | *p* |
| Fatigue | 30.1 (24.7) | 34.9 (27.8) | 37.5 (28.5) | .177 |
| Abdominal pain | 37.2 (27.7) | 35.1 (24.3) | 38.9 (27.5) | .653 |
| Depression | 7.6 (11.9) | 11.7 (19.4) | 9.6 (16.9) | .188 |
| Anxiety | 19.4 (20.8) | 19.1 (24.9) | 19.6 (20.9) | .933 |

Note.
COMT = catechol-O-methyltransferase. SERT = serotonin transporter.
N = 249. Data are presented as means and standard deviations for symptom severity.
*p* = testing differences in mean percent of days with moderate to very severe symptoms by SERT and COMT genotypes.

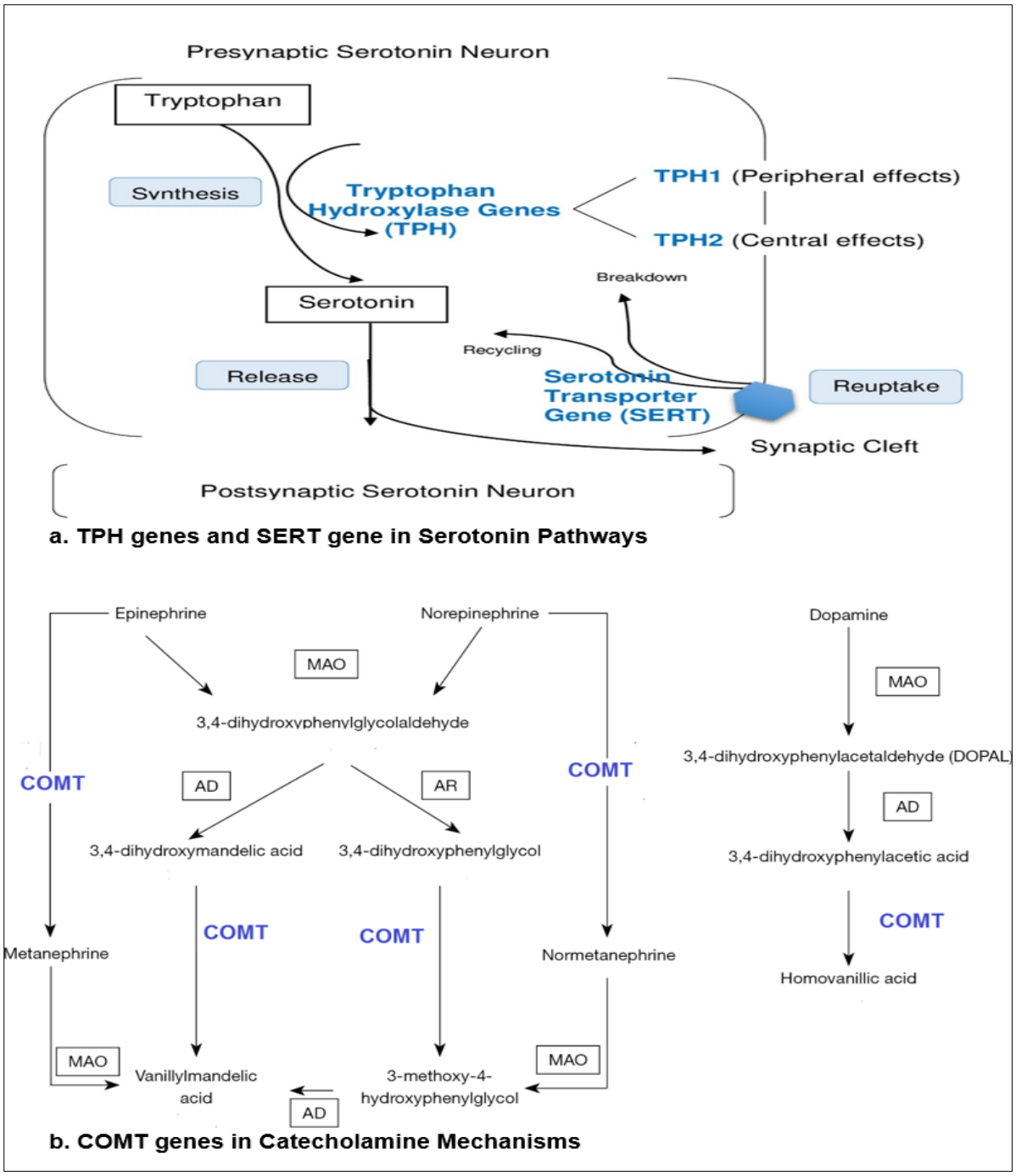


Figure 3-1. Serotonin and Catecholamine Pathways.
Figure 3-1a. SERT = serotonin transporter. TPH = tryptophan hydroxylase. TPH genes are involved in serotonin synthesis, and SERT gene is involved in serotonin reuptake into the presynaptic neuron (Allegri et al., 2012).
Figure 3-1b. AD = aldehyde dehydrogenase. AR = aldehyde reductase. COMT = catecol-O-methyl transferase. MAO = monoamine oxidase. The adrenal medulla and the post-ganglionic fibers of the sympathetic nervous system are the main sites of production, storage, and release of catecholamine. The COMT operates catecholamines inactivation (Bisogni et al., 2015).

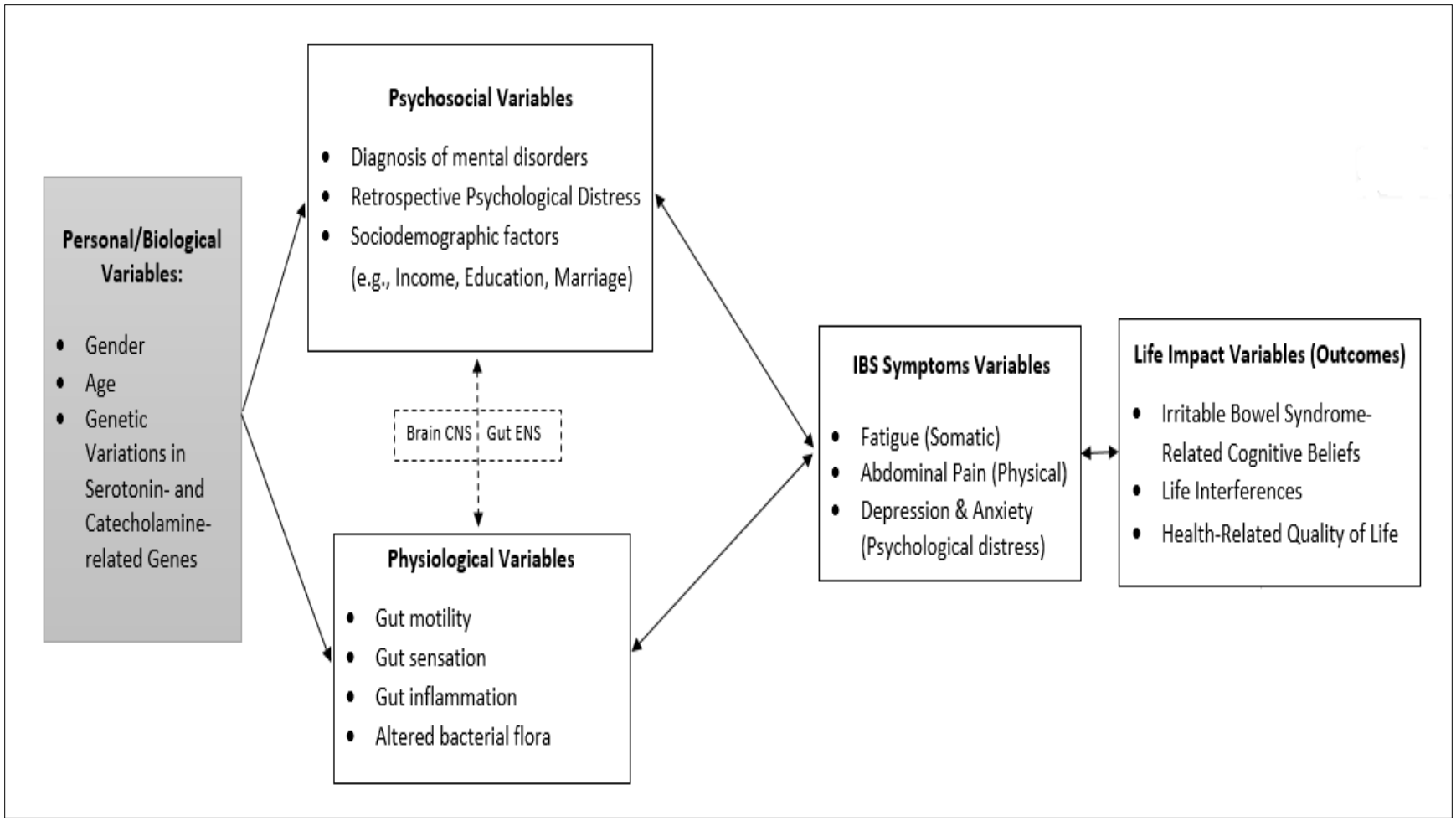


Figure 3-2. Conceptual Framework for Fatigue and Symptom Cluster of Fatigue, Abdominal Pain, Depression, and Anxiety in IBS. CNS = central nervous system. ENS = enteric nervous system. IBS = irritable bowel syndrome. The framework was modified, with permission of Drossman, from "Biopsychosocial Model of Irritable Bowel Syndrome," by Tanaka, Kanazawa, Fukudo, & Drossman, 2011, Journal of Neurogastroenterology and Motility, 17(2), p. 133.

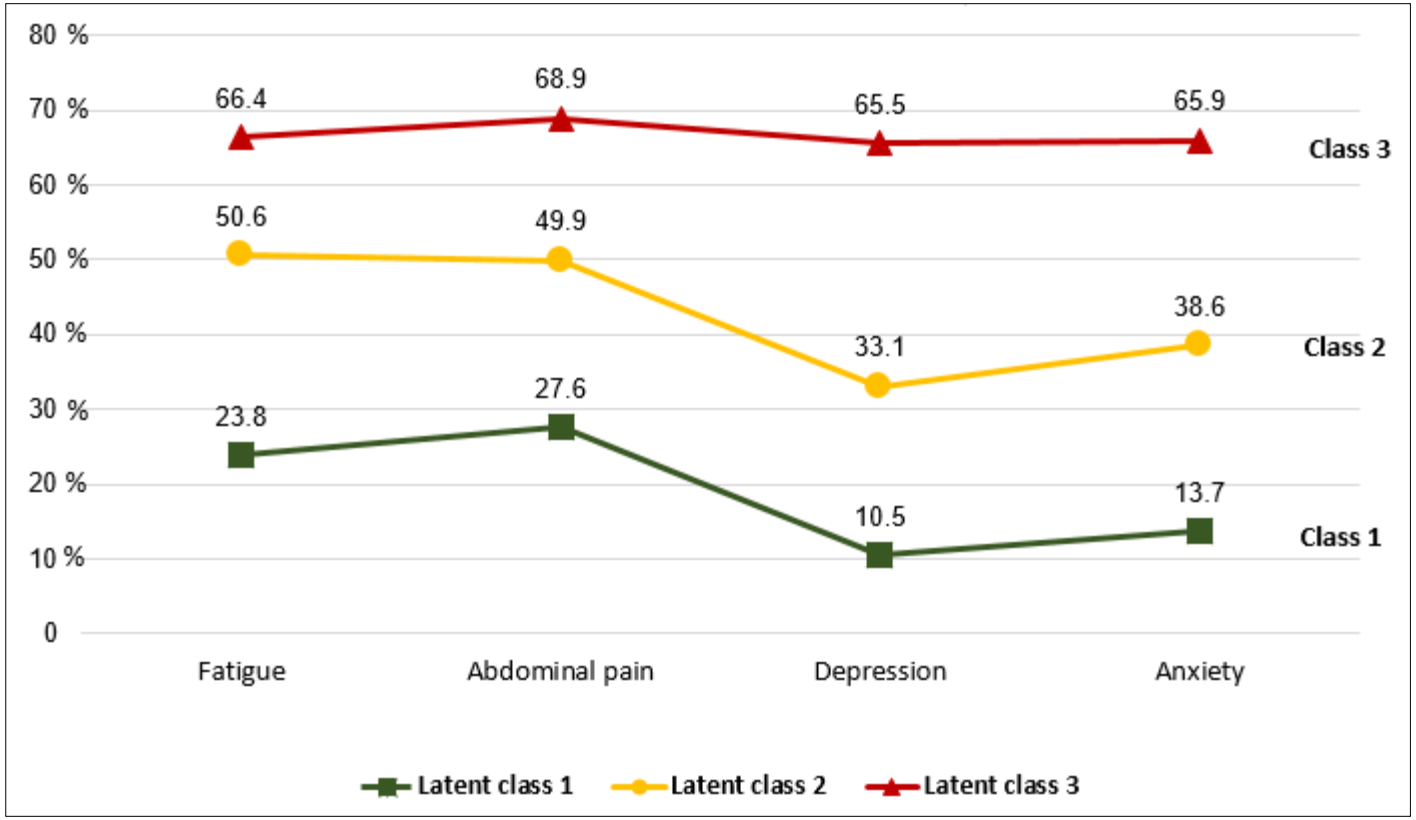


Figure 3-3. Symptom Severity Scores by Identified Latent Classes.
Latent class profile analysis (LCPA) was used to identify three irritable bowel syndrome (IBS) subgroups based on the severity of fatigue, abdominal pain, depression and anxiety in 249 women with IBS.
Bar represents the mean percent of days with moderate to very severe symptoms using a 28-day daily symptom diary, in each latent class. For example, the percent of days with moderate to very severe fatigue was 23.8% (Class 1), 50.6% (Class 2) and 66.4% (Class 3).

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# CHAPTER IV.

# CONCLUSIONS

This chapter summarizes the overall study findings from two manuscripts; then discuss the limitations, implications for research and clinical practice, and recommendations for future studies.

## 4.1. Summary of Findings

This research is the first to investigate (a) the directionality of relationships among fatigue, abdominal pain, and psychological distress in patients with IBS; (b) latent classes of women with IBS defined based on the severity of the symptom cluster with fatigue; and (c) genetic mechanisms of fatigue in IBS.

In Chapter II (manuscript I), data from two randomized controlled trials (Study-1 and Study-2) were used to examine the relationships among symptoms in three models (same-day, prior-day abdominal pain predicting next-day fatigue, and prior-day fatigue predicting next-day abdominal pain). Overall, consistent results were observed in the data from each study individually... Positive and significant across-women relationships between abdominal pain and fatigue were observed in each model. Abdominal pain predicted next-day fatigue within-woman, but the reverse was not found. Psychological distress mediated the effects of abdominal pain on fatigue both across-women and within-woman. Symptom management approaches that incorporate strategies to decrease abdominal pain and psychological distress are likely to also reduce fatigue.

In Chapter III (manuscript II), fatigue, abdominal pain, depression, and anxiety were positively and strongly correlated with each other as a symptom cluster among the twenty-six symptoms recorded in study participants' daily IBS diaries. Three latent classes of women with

IBS were identified based on the severity of the symptom cluster of fatigue, abdominal pain, depression, and anxiety: Class 1, low severity (n = 158); Class 2, medium severity (n = 70); and Class 3, high severity (n = 21). Women with high severity symptoms (Class 3) had lower social support, higher stress levels, poorer sleep quality, higher symptom burden, poorer QOL, and higher life interference, compared to women with the lowest severity symptoms (Class 1).

As presented in Chapter III (manuscript II), this second part of dissertation research also addressed the genetic associations with fatigue and with latent class membership based on the severity of symptom cluster with fatigue. The polymorphisms of TPH2 rs4570625, in particular TT homozygous, were associated with the severity of fatigue, compared to the G allele carriers (GG and GT genotype). Abdominal pain was higher in G allele carriers of TPH1 rs4537731 (i.e., AG and GG genotype) than in the patients with AA homozygous. No significant differences in the severity of single symptoms (i.e., fatigue, abdominal pain, depression or anxiety) were observed in relation to SERT or COMT genotypes. In addition, none of the genes of TPH, SERT and COMT were significantly associated with patients' identified latent class membership.

These results, taken together, suggest that fatigue may be the dependent symptom, in particular occurring as a sequela of abdominal pain and psychological distress. Abdominal pain significantly influenced fatigue. The TPH2 gene was found to play a role in fatigue, but common shared genetic associations among fatigue, abdominal pain, depression, and anxiety were not found. The genetic polymorphisms of TPH2 may be related to subjective fatigue ratings in patients with IBS. The results of this dissertation study establish that fatigue does not occur in isolation, but instead affects a number of factors simultaneously.

### 4.2. Limitations

There were several limitations to this dissertation study. First, while the available data provided with instantaneous access to well-phenotyped data, the majority of participants were middle-aged Caucasian women. This limits the generalizability of the findings to general population. Second, the investigator had no influence on the selection of instruments. The original study, which collected the data, used no validated multidimensional fatigue assessment tools such as the Fatigue Impact Scale (FIS) or the Patient-Reported Outcomes Measurement Information System fatigue scale. Thus, a daily symptom diary, as a single dimensional tool, was used to derive data for this dissertation study. The use of a daily symptoms diary was the strength of this dissertation study, which could examine the directionality among the symptoms with day-to-day variations. Using multidimensional fatigue tools would have added to the strength of the findings and supported a more complete assessment of the symptom experience in IBS patients with fatigue.

Third, no definitive conclusions can be made about exact causal relationships within the short time frame (day-to-day). Thus, it was unable to confirm the actual causal mechanisms that link abdominal pain to fatigue, and the results from this dissertation study should be interpreted with caution. Finally, while this research returned negative findings regarding genetic associations, this may be due to the small sample size. Alternatively, the negative findings may be due to differences in the dataset related to race, population and sample size, or different SNPs and haplotypes of the genes compared to the datasets used in previous studies. Since this study selected certain genetic polymorphisms of genes in relation to fatigue from existing data, it did not examine all of the possible candidate genes (i.e., cytokines) in relation to fatigue. It should also be noted that the analyses of this study do not rule out the possibility that the observed

genetic associations may be partly attributable to gene x gene and gene x environment interactions.

### 4.3. Implications for Research and Clinical Practice

This study utilized currently available, well-phenotyped samples from randomized controlled trials of a nurse-delivered self-management program funded by the NINR. The findings make a clear contribution to the development of symptom science research including genetics. In particular, this dissertation study contributes to current understandings of the complexity of comorbid symptoms and of genetic links in relation to fatigue in IBS.

The findings reported in Chapter II shed light on strategies for fatigue management in IBS, including not only self-management for abdominal pain but also psychological interventions that target depression and anxiety. This approach, in which an intervention for one symptom may also modulate other symptoms, may result in reduced therapeutic or pharmacological needs and improved patient outcomes for patients with IBS.

The findings reported in Chapter III contribute to the work of identifying subgroups of women with IBS and fatigue who are at risk of higher symptom burdens. The etiology of IBS is heterogeneous, and symptom characteristics vary. Thus, the generalized approach to treatment can be very successful for some patients yet not so for others. This study identified phenotypes of women with fatigue and co-occurring symptoms and addressed the related clinical and genetic biomarker data. The findings from this study may also contribute to identifying patients who are more likely to have a higher symptom burden, and thus guide cost-effective symptom interventions tailored to an individual's symptom profile. The patients group with high severity of fatigue and co-occurring symptoms should be prioritized for screening by the patient care team and they should be part of the focus of symptom intervention strategies. Clinicians who

treat patients with IBS should be prepared to screen patients for these common symptoms, to intervene when effective interventions are available, and to identify patients with substantial symptom burden who are in need of additional symptom support. The results of this study may benefit patients with IBS whose fatigue puts them at risk for greater reductions in high symptom burden.

In summary, this dissertation study makes a contribution to the development of informed clinical applications and precision medicine for symptom reduction, improvement, and prevention and enhanced health outcomes for patients with IBS.

### 4.4. Recommendations for Future Studies

Based on the aforementioned limitations of this dissertation study, a longitudinal follow-up study of IBS patients, which measures abdominal pain, psychological distress, and fatigue at different time points (i.e., time series analysis), is needed to confirm these findings and to better understand directionality among the symptoms. To better characterize the relationships among abdominal pain, fatigue, and psychological distress and symptom cluster of fatigue and co-occurring symptoms, future studies that explore the underlying mechanisms of these symptoms are also recommended using a well validated multi-dimensional symptom instrument. Replication studies with larger sample sizes, in different populations or ethnic groups, and with different SNPs and genes, are recommended to improve the generalizability of the findings. Further studies are also needed to develop and test new approaches to fatigue management that incorporate multiple factors. For example, a comprehensive assessment and intervention could focus on reducing the overall symptom burden within a cluster, improving social support, making referrals to mental health professionals, and managing patient QOL.