The Prevalence and Co-Existence of Psychosocial Factors in Functional Gastrointestinal Disorders and other Functional Somatic Syndromes

by

David Thomas McNaughton

Macquarie University, 2015

Thesis Submitted in Partial Fulfillment

of the Requirements of the Degree of

Master of Research

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Abstract

Functional Somatic Syndromes (FSS) are health conditions for which no apparent biological cause can be identified. Examples of such conditions include Functional Gastrointestinal Disorders (FGIDs; e.g. Irritable Bowel Syndrome), chronic pain and chronic fatigue. Research has shown strong associations between FGIDs and a number of adverse psychological phenomena. Some doubt has been expressed, however, over the specificity of these relationships to the gastrointestinal (GI) system, with similar findings in other FSSs such as chronic pain. As such, the present study sought to test whether adverse psychological phenomena are equally involved in a range of FSSs, using a cross-sectional correlational design with standardized measures and consistent diagnostic criteria. Participants were recruited from various sites around Sydney at which a high prevalence of FSSs were known to exist: hospital and private Gastroenterology consultation rooms, private and university Chiropractic clinics and the Macquarie University Psychology undergraduate student pool. A total of $N = 133$ participants were included in the study: $n = 58$ (43%) met ROME III criteria for FGID diagnosis and $n = 79$ (59%) met the criteria for an extra-GI diagnosis (outside the gastrointestinal tract, e.g. chronic low back pain and fibromyalgia). The data revealed a strong pattern of similar associations between adverse psychological constructs and the symptom burden of GI and extra-GI symptoms. Somatization (the tendency to manifest physical symptoms through psychological distress) was most strongly and consistently correlated with GI and extra-GI symptoms. In addition, significant comorbidity was found between different FSSs. The current study identifies an analogous role of adverse psychological phenomena in a range of FSSs, suggesting that the influence of psychological phenomena may be manifested in multiple physical expressions, as well as concluding that their presence significantly impacts the symptom burden of GI and extra-GI disorders.

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Table of Abbreviations

FGID	Functional Gastrointestinal Disorder
GI	Gastrointestinal
IBS	Irritable Bowel Syndrome
FD	Functional Dyspepsia
FMS	Fibromyalgia Syndrome
CLBP	Chronic Low Back Pain
CFS	Chronic Fatigue Syndrome
CS	Central Sensitization
QoL	Quality of Life

Chapter 1: Functional Gastrointestinal Disorders and other Functional Somatic Syndromes

An Overview

Functional Gastrointestinal Disorders (FGIDs) such as Irritable Bowel Syndrome (IBS) and Functional Dyspepsia (FD) are prevalent within society and impose a high socioeconomic burden (Talley, 2008). Despite their frequency, no consistent biochemical, psychological or physiological abnormalities have been identified as pathognomonic. Psychological factors such as mood, personality, somatization and dysfunctional cognitions play a crucial role in FGIDs via their effects on gut motility, symptom severity, quality of life and therapeutic approach (Budavari & Olden, 2003; Fukudo, 2013). This absence of organic pathology and high psychological co-morbidity is not gastrointestinal (GI) specific, for other extra-GI syndromes, such as chronic somatic pain, have delineated similar conclusions (Wessely, Nimnuan, & Sharpe, 1999). The aim of the current study is to test the specificity of the relationship between adverse psychological constructs and the symptom burden of FGIDs and other extra-GI functional somatic syndromes (FSSs).

Functional Somatic Syndromes

Due to a high proportion of patients with FGIDs reporting multiple GI and extra-GI symptoms, the notion of FGIDs as a distinct disorder group has been challenged (Whitehead., Palsson., & Jones., 2002). It is postulated that FGIDs are a particular

instance of a disorder that sits within the broader class of FSSs (Wessely et al., 1999). Other FSSs include fibromyalgia syndrome (FMS), chronic fatigue syndrome (CFS), chronic low back pain (CLBP) and migraine (Barsky & Borus, 1999).

Similar underlying psychological and neurobiological mechanisms have been identified in the development and symptom expression of FGIDs and other FSSs. In addition, multiple observational similarities can be found in the literature, which suggest that the co-existence of these symptoms is beyond chance. This aetiological and clinical overlap provides substantial evidence that FGIDs and other FSSs are on a diagnostic continuum, rather than separate clinical entities. Due to the similarities outlined below, it is hypothesized in the current study that the relationship between psychological constructs and increased symptom burden of GI and extra-GI complaints will be comparable, irrespective of the specific FSS classification.

Clinical Overlap. The co-occurrence of GI and extra-GI symptoms is well established, with Whitehead et al (2002) identifying many IBS patients meet the criteria for other FGIDs, such as FD. In addition, greater than 50% of FGID patients experience at least one comorbid somatic complaint, such as musculoskeletal pain (Whitehead. et al., 2002), which is more common than in non-FGID populations. Although this overlap between FGIDs and other FSSs is commonly stated in the literature, significant variation in the exact extent exists. Table 1 displays this overlapping prevalence, with the most notable existing within FMS: Almost all FMS patients have at least one co-morbid FGID. In contrast the co-existence of less extreme somatic syndromes, such as low back pain,

headache or neck pain is comparably less. Whilst there is evidence of clinical overlap with localized somatic complaints (Frissora & Koch, 2005), this process is poorly described throughout the literature. Therefore, the current study will add to the literature by identifying the levels of co-morbidity within FSSs, as well as evaluating the extent to which negative psychological phenomena play a common role in their symptom burden. It is hypothesized that individuals with higher symptom burden or diagnostic overlap will display more adverse psychological states.

Table 1

Overlapping Prevalence of FSSs.

	Prevalence of FGID in patients with the disorder.	Prevalence of the disorder in patients with FGID.
CFS	52-59% (Aaron et al., 2001)	14% (Whitehead. et al., 2002)
FMS	98% (Almansa, Rey, Sánchez, Sánchez, & Díaz-Rubio, 2009)	32% (Sperber & Dekel, 2010)
CLBP	12.2% (Davis, 2011)	38% (Whitehead. et al., 2002)

Note: (Functional Gastrointestinal disorder "FGID". Chronic Fatigue Syndrome "CFS", Fibromyalgia Syndrome "FMS" and Chronic low back pain "CLBP").

Gender. Female gender is a common demographic risk factor identified in the development of chronic conditions (Gerdle, Björk, Henriksson, & Bengtsson, 2004) and is consistently observed throughout epidemiological and prognostic studies regarding

FSSs. Females are more likely to be diagnosed with IBS and FD than males (L. Chang, 2006), are nine times as likely to suffer from FMS (Arnold, Clauw, & McCarberg, 2011), and three times as likely to have CFS (Kim & Chang, 2012). Finally, females exhibit a higher prevalence of CLBP, as well as being more likely to transition from acute to CLBP than males (Thomas et al., 1999). The role of female gender in the development or diagnosis of FSSs may relate to peripheral and central pain enhancement processes due to the increased presence of estrogen (Gatchel, Peng, Peters, Fuchs, & Turk, 2007), increased visceral hypersensitivity, and socioeconomic processes, such as an increased health care seeking behavior (Heitkemper, 2008).

Treatment. Similarities in treatment approaches among all FSSs provide another commonality potentially unifying a shared pathophysiology. Treatment of these conditions involves a plethora of therapy options (Henningsen, Zipfel, & Herzog, 2007), which include behavioral therapies, manual and physical therapies, as well as central pharmacological agents, such as anti-depressants and antioxyltics (Gatchel et al., 2007; Grover & Drossman, 2009). While the current study does not address treatment of these conditions, it does strengthen the biopsychosocial model underpinning the management of these complex and costly conditions. The following section describes modern concepts of the pathophysiology of FSSs, with a particular emphasis on functional GI symptoms and chronic pain, as these are the focus of the study.

The Biopsychosocial Model

The Biopsychosocial Model (BPM) presents a holistic framework, which proposed that disease (anatomical pathology) and illness (the perception of disease) are the result of simultaneously interacting systems at a biological, interpersonal and environmental level (Engel, 1977, 1981). The BPM is juxtaposed with the Cartesian Model of Medicine, which describes a reductionist and linear relationship of illness and disease (Mehta, 2011). Similar representations of this model have been identified within all FSSs. Examples of such included the "Brain-Gut" axis, for FGIDs and the pain neuromatrix for somatic conditions. This thesis appreciates the complexity of the BPM by addressing its involvement in a number of FSSs, as well as evaluating a potential core psychological pathway through empirical path modelling. The following suggest a common neurobiological and psychological theme throughout selected FSSs which has important implications regarding the pathophysiology of these inherently separate non-organic disorders.

The brain-gut axis. A unifying model conceptualizing the link between limbic areas of the brain and the enteric nervous system is known as the "Brain-Gut" axis. This is identified as another illustration of the BPM and recognizes the importance of multi-causality of symptom expression. The "Brian-Gut" axis has been extensively studied and is highlighted in FGIDs, with psychological stressors influencing gut motility via altered neurotransmitter release, and vice versa (see Figure 1) (Olden, 2002). This thesis will expand on the concepts identified in the "Brain-Gut" axis by identifying whether adverse

psychological phenomena will influence GI and extra-GI disorders in a similar fashion. The process can be explained through an interconnection between the bran-gut axis and the pain neuromatrix.

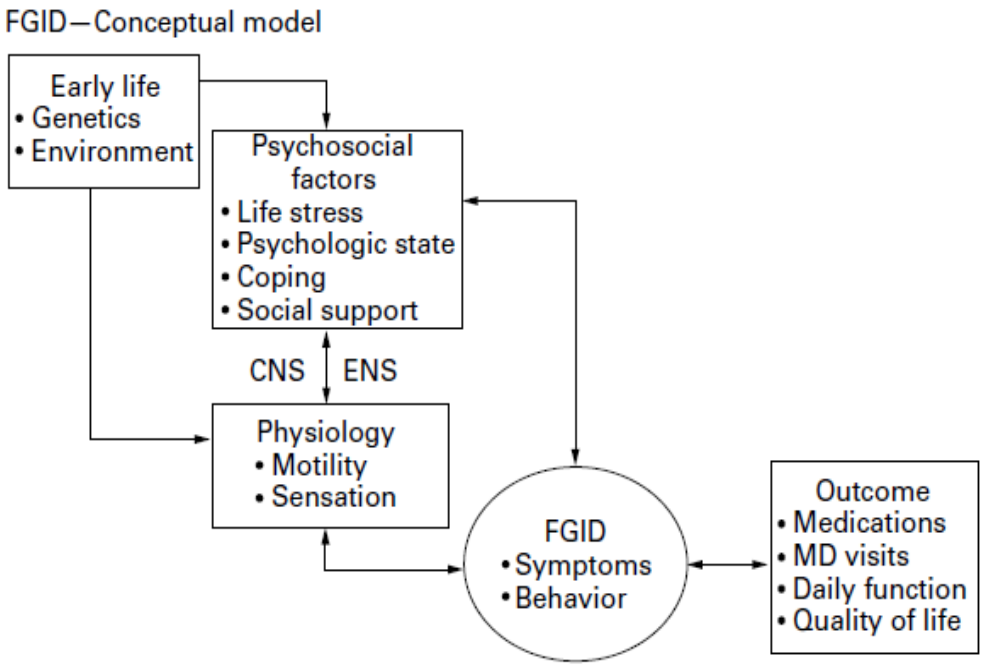

Figure 1. A biopsychosocial conceptualization of the pathogenesis and clinical expression of Functional Gastrointestinal Disorders (FGIDs).
(Central Nervous system "CNS" and Enteric Nervous System "ENS"). Source: Drossman, D. A., Creed, F. H., Olden, K. W., Svedlund, J., Toner, B. B., & Whitehead, W. E. (1999). Psychosocial aspects of the functional gastrointestinal disorders. Gut, 45,p.1126. Copyright 1999 by BMJ Publishing

Biopsychosocial model of Chronic Somatic Pain. Pain is generally synonymous with tissue damage, injury or nociception. However, in the case for chronic somatic syndromes, there may no longer be any demonstrable structural impairment (Waddell, 1992). This lack of identifiable pathology has led to the inclusion of a BPM in the conceptualization and treatment of somatic pain syndromes, in particular chronic low back pain (Gatchel et al., 2007)

Recent advances in neuroscience have extended the understanding of the biopsychosocial involvement of pain and identified specific cortical structures responsible (Moseley, 2003). This neurophysiological mapping is known as the pain neuromatrix and, as described in the current study, shares similar neurological pathways with the experience of visceral symptoms. Whilst the co-existence chronic somatic pain and FGIDs is well documented (Whitehead. et al., 2002), their psychological and symptom influences on each other is poorly understood. Re-conceptualizing the 'brain-Gut" axis and Pain neuromatrix as extensions of one another has important implications for understanding, diagnosis and treatment of multiple FSSs.

A gastrointestinal focus. Although causality has not been established, bi-directionality of symptom expression has been postulated in the brain-gut axis (Koloski et al., 2012b) with some individuals suffering brain-directed abdominal symptoms and other gut-directed. Some doubt has been expressed however over the specificity of these finding to the gastrointestinal system with similar findings in other functional somatic syndromes (FSS) such as chronic pain, FMS and CFS (Bellato et al., 2012; Cella, White,

Sharpe, & Chalder, 2013). The commonality of the mind-body relationships among all FSSs may aid in the understanding of these costly and complex disorders.

This thesis will extend on previous research by identifying the role of specific psychological phenomena in the symptom burden of the selected FSSs. Specifically, it will define and describe FGIDs and other FSSs, as well as explore psychological similarities between the conditions that re-conceptualize their inclusion on a diagnostic continuum, rather than as single, separate clinical entities. Expanding on the biopsychosocial nature of the disorders, this introduction will provide psychological and neurobiological evidence, supporting the argument these clinically distinct disorders are more similar than previously thought.

The Selected Functional Somatic Syndromes

Functional Gastrointestinal Disorders. FGIDs represent a collection of symptoms attributed to the gastrointestinal tract and are classified in to six domains; Esophageal, Gastroduodenal, Bowel, Functional Abdominal Pain Syndrome, Biliary and Anorectal. Currently, FGID are diagnosed via the ROME III criteria, which is a symptom based classification in the absence of organic pathology (Douglas A. Drossman, 2006). These disorders are prevalent, affecting up to 22% of the general population (Boyce,

Talley, Burke, & Koloski, 2006). They are costly to the health system (Talley, 2008) and impact heavily on the quality of life of those affected (L. Chang, 2006).

A previous notion of FGIDs is that of symptom confinement to the GI tract. This leads to an isolated focus on specific GI symptoms and inheritably disregard influences from outside GI system. This research will identify the widespread consequences, GI symptoms have on QoL, extra-GI symptomatology and psychological state.

Irritable Bowel Syndrome (IBS). The worldwide prevalence of IBS is estimated around 10-20%, is most commonly seen in females and those with underlying psychological disturbances (Drossman, Camilleri, Mayer, & Whitehead, 2002). In Australia, IBS accounts for a large proportion of primary care consultations and is the largest diagnostic group within Gastroenterology clinics (Talley, Boyce, & Jones, 1997). The current Rome III criteria, the diagnostic standard, for IBS entails recurrent abdominal pain or discomfort at least 3 days per month in the last 3 months associated with 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 (appearance) of stool (Soares, 2014).

Functional Dyspepsia (FD). The prevalence of FD has been noted worldwide between 11-29%, and is also more common in females and those with underlying psychological disturbances (Mahadeva & Goh, 2006). The current Rome III criteria dictate FD to have one of the following: Bothersome postprandial fullness, early satiation, epigastric pain or epigastric burning in conjunction with a negative upper

endoscopy. The criteria must be present for the last 3 months with symptoms onset at least 6 months prior to diagnosis (Mearin & Calleja, 2011).

Extra-Gastrointestinal Disorders. Chronic pain is a common and disabling condition, estimated to affect 10-55% of the world's adult population (Harstall & Ospina, 2003) and is considered a major social and economic burden (Gustavsson et al., 2012). The inclusion of a continuum of pain describes a process of localized chronic pain, such as Chronic Low Back Pain (CLBP) in contrast to that of Fibromyalgia Syndrome, which is identified as chronic widespread syndrome. The spectrum of severity within this continuum is associated with greater psychological distress (Viniol et al., 2015) and is hypothesized to be related to an increased amount of GI symptomatology.

Fibromyalgia Syndrome. FMS represents the most common cause of chronic widespread pain with an estimated prevalence between 2-5%, worldwide (Queiroz, 2013). FMS is defined as chronic widespread somatic pain which is commonly associated with fatigue, anxiety, sleep disturbances and/or cognitive impairment (Wolfe, 2010). The inclusion of FMS serves as a functional end spectrum somatic illness, in which a large diagnostic overlap with FGIDs exists (Almansa et al., 2009).

Chronic Low Back Pain. CLBP is defined as pain in the area on the posterior aspect of the body from the lower margin of the twelfth ribs to the lower gluteal folds with or without pain referred into one or both lower limbs, which has been present for at least 3 months (Koes, van Tulder, & Thomas, 2006). Low Back Pain is extremely

prevalent and is one of the most costly and disabling causes of musculoskeletal pain (Hoy et al., 2014). Low back pain will affect 80-90% of people, at some point in their lives (Shekelle, Markovich, & Louie, 1995b) and majority of patients will recover from low back pain within 3 months. However, a 30-40% will not recover and proceed to develop CLBP (Koes et al., 2006). This subset of patients account for a major expense to health care system and workforce (Shekelle, Markovich, & Louie, 1995a). Due to the sheer prevalence of the condition, CLBP is an ample extra-GI population, to investigate psychological and symptom co-existence.

Chronic Fatigue Syndrome. CFS has an estimated prevalence of between 0.1-1%, is more common in females (Prins, van der Meer, & Bleijenberg, 2006) and full recovery without treatment is rare (Cairns & Hotopf, 2005). CFS is defined as intense fatigue of unknown cause, is permanent and limits patients' functional capacity (Fernandez et al., 2009). Concurrent with other FSS, a substantial proportion of those with CFS experience co-morbid psychological disturbance. The incorporation of CFS, or at least symptomatic fatigue, identifies another potential manifestation of a physical symptom, common among those on the FSS spectrum.

How specific are Psychological Phenomena to Functional Gastrointestinal Disorders and other Functional Somatic Syndromes?

There is a strong overlap between a number of FGIDs and multiple adverse psychological phenomena including aspects of personality (Farnam, Somi, Sarami,

Farhang, & Yasrebinia, 2007), mood (Jones, Oudenhove, Koloski, Tack, & Talley, 2013), somatization (Spiegel, Kanwal, Naliboff, & Mayer, 2005) and dysfunctional cognitions (McKinnon, Van Oudenhove, Tack, & Jones, 2013). These psychological phenomena can influence gut function (Mayer, Naliboff, & Craig, 2006), symptom severity (Thompson, Heaton, Smyth, & Smyth, 2000), illness behavior (Levy et al., 2006) and quality of life (Whitehead, Burnett, Cook III, & Taub, 1996), seen in FGID patients. While causality has not been established, the bi-directional relationship of the 'Brain-Gut' axis has been explored (Koloski et al., 2012a). The specificity of these findings to the gastrointestinal system is unclear, for similar psychological mechanisms underpin other FSSs (Whitehead, Palsson, & Jones, 2002).

A key concept throughout the "brain-gut" axis is while peripheral aspects of nociception, such as inflammation or trauma in the gut are appreciated, some individuals suffer brain driven gut symptoms. A simplistic explanation of this process is state anxiety and stress, induced in public speaking, exacerbating gut symptoms (Elsenbruch et al., 2006). While these temporal effects of induced psychological trauma on gut symptoms exist, sustain psychological insults may lead to visceral syndromes, such as FGIDs. This process is hypothesized to be similar in other FSSs, as comparable aspects of personality, mood, somatization and dysfunctional cognition have all been identified throughout the literature, as the following suggests.

Personality: Neuroticism

Personality can be defined as dynamic organisations inside the person that create a person's characteristic pattern of behaviors, thoughts and feelings (Carver, Scheier, & Scheier, 1996). The Five Factor Model of personality is a common conceptualization of personality, which has proposed five broad traits to summarize an individual's disposition, each of which exist on a continuum: agreeableness (kindness and trust vs. selfishness and distrust), conscientiousness (thoroughness and reliability vs. negligence and unreliability), extraversion (sociability vs. passivity or reserve), neuroticism (emotional reactivity vs. stability) and openness to experience (curiosity and creativity vs. shallowness or imperceptiveness) (Costa & McCrae, 2008; Goldberg et al., 2006). Neuroticism in particular is a central focus to the current thesis.

A neurotic personality is linked with the expression of medically unexplained symptoms, as well as being a key driver in the health care seeking nature of FSS patients (De Gucht, Fischler, & Heiser, 2004). A lack of emotional resilience (high neuroticism) leads to a tendency to seek help earlier and more often, in an effort to satisfy a fundamental emotion and physical need for support. This thesis hypothesizes through a path modelling analysis that neuroticism underpins other maladaptive psychological phenomena, such as negative affect and somatization, as a core pattern of behavior.

The negative thoughts and feelings associated with a neurotic personality can exacerbate and sustain brain driven symptoms of the gastrointestinal tract (Hansel et al., 2010). Neuroticism is frequently identified in IBS patients at higher levels than that in the

general population (Alireza Farnam, Somi, Sarami, & Farhang, 2008), as well as those suffering from Inflammatory Bowel Disorders (Tkalcic, Hauser, & Stimac, 2010). Other FGIDs, such as FD, also experience increased levels of neuroticism when compared to the general population (Filipovic et al., 2013). Neuroticism is thought to influence coping mechanisms, eventually leading to compromised therapy outcomes (Tanum & Malt, 2000) and a decreased quality of life (Surdea-Blaga, Băban, & Dumitrascu, 2012).

Neuroticism is associated with FMS, with increased levels compared to healthy subjects (Malin & Littlejohn, 2012). When compared with other chronic pain control groups, such as osteoarthritis, FMS exhibits greater levels of neuroticism (Zautra et al., 2005), which is likely due to FMS being furthest along the FSS spectrum. This further explores the notion of a spectrum of severity in the continuum of pain, with psychological distress a key feature in its symptom development and expression. Similar to FGIDs, neuroticism in FMS is thought to mediate mal-adaptive coping strategies, such as catastrophizing as well as exacerbate symptom specific anxiety (Martinez, Sanchez, Miro, Medina, & Lami, 2011).

Psychological factors play an important role in the chronicity and reoccurrence of low back pain. Neuroticism is associated with short term pain outcomes, such as pain severity and functional impairment (BenDebba, Torgerson, & Long, 1997), and long term repercussions from emotional instability have been noted. Finally, neuroticism is significantly associated with an elevated risk for the disability pension, due to low back pain (Ropponen et al., 2012).

Neuroticism is described in all selected FSSs and its effect on symptom severity is well documented. On a spectrum of severity, a highly neurotic co-morbidity is correlated in the extreme of both FGIDs and extra-GI syndromes. While neuroticism is clearly linked with both FGIDs and extra-GI disorders, its relationship with other psychological constructs is unknown. As personality is a stable trait that develops relatively early on in life, in contrast to aspects of negative affect and somatization, which are state constructs. A proposed path modelling, similarly hypothesized by (McKinnon et al., 2013), with neuroticism as a foundation, will directly and indirectly correlate with the symptom burden of both somatic and gastrointestinal symptoms.

Mood: Negative Affect

Mood can be described as a temporary state of mind or feeling and is a common behavioral reaction to real or perceived stimuli (Zelman, Howland, Nichols, & Cleeland, 1991). However, sustained and prolonged negative mood states reflect clinical affective illnesses, such as depression and anxiety. In the context of the Brain–Gut axis, mood negatively impacts FGIDs via augmentation of sensory signals at a cortical level and alteration of endogenous hormones and stimulation of the immune system (Forsythe, Sudo, Dinan, Taylor, & Bienenstock, 2010). In the thesis, it is predicted all those with a FSS will experience more negative mood states than those without. This hypothesis has been informed by the evidence reviewed below.

Affective disorders, such as depression and anxiety, have been implicated in the onset and development of FGIDs (Surdea-Blaga et al., 2012). Depression is commonly comorbid with IBS, with greater depression scores noted when compared to healthy controls (Savas et al., 2009; Whitehead et al., 2003). In contrast, the prevalence of depression is greater in IBS patients, when compared to those with organic IBD (Whitehead et al., 2003). Anxiety disorders, such as generalized anxiety disorder, panic disorder and post-traumatic stress disorder, are commonly observed in IBS patients (Lee et al., 2009). Anxiety has been identified as a strong predictor of the healthcare seeking and development of new onset IBS (Koloski et al., 2012a).

In FD, similar observations have been found, identifying a higher comorbidity of anxiety, compared to those with organic gastroduodenal disease (Mahadeva & Goh, 2011). The association with depression has been established, with depressed individual three times more likely to suffer from FD (Silva et al., 2006). Concurrent with the concept of this thesis, the effect of negative affect is non-specific to sites within the GI tract.

Anxiety and depression have been observed in FMS (Buskila & Cohen, 2007) with 74.8% of 150 American College of Rheumatology diagnosed FMS patients met the criteria for DSM-IV axis 1 conditions (Thieme, Turk, & Flor, 2004). This is also observed in CLBP, with a high co-morbidity of anxiety and depressive symptoms (Gore, Sadosky, Stacey, Tai, & Leslie, 2012). The comorbid diagnosis of Axis-1 psychiatric illness in CFS is prevalent and results from a large population based study, indicate the

prevalence of major depressive disorder in CFS patients to be 57% (Cella et al., 2013; Dansie et al., 2012). While this thesis does not address causality and a paucity of quality longitudinal studies attending to a directionality of pain or fatigue with psychiatric illness is unknown, it is hypothesized that the relationship between mood and somatic symptom burden is strong, regardless of the body system involved.

Aspects of mood, especially anxiety and depression, can lower neurobiological thresholds allowing for increased and amplified transmission of somatic and visceral sensations (Simons, Elman, & Borsook, 2014). This thesis aims to extend this statement, by examining the strength of association between negative affect and GI and extra-GI symptom burden via the precision of correlation and consistency of effect sizes, with respect to regression slopes. It is hypothesized that aspects of mood will correlate similarly with gastrointestinal and other somatic symptoms, questioning the specificity of negative affect to FGIDs.

Somatization

Somatization is a tendency to experience physical symptoms as a manifestation of psychological distress (Lipowski, 1988). There is often a large overlap with other psychological conditions, such as anxiety and depression, as well as having a significant relationship with all FSSs selected (Fishbain, Lewis, Gao, Cole, & Steele Rosomoff, 2009). This is particularly evident within FGIDs as somatization is commonly seen in patients with IBS and is thought to represent a key psychological feature in the extra-GI

symptom co-morbidity (Whitehead. et al., 2002). Along with IBS, somatization is an important risk factor in the impairment of quality of life, severity of pain, and weight loss experienced by FD patients (Van Oudenhove et al., 2011). Associating disproportionate distress to normal or dysfunctional bodily sensations, may explain the large co-morbidity of symptoms, as well as exacerbate the experience of symptomatology. Given this, the identification of somatization in FGIDs is important to gain perspective on why there is a high psychological morbidity occurring with the patients' symptomatology.

As in extra-GI disorders, the prevalence of somatization is greater in those with chronic fatigue compared to those without, as well as being associated with deficits in health related quality of life (Martin, Chalder, Rief, & Braehler, 2007). Within a spectrum of chronic pain, (Häuser & Henningsen, 2014) somatization is common in patients who experience FMS, chronic widespread pain and chronic localized pain (Licciardone, Gatchel, Kearns, & Minotti, 2012; McBeth, Macfarlane, Benjamin, & Silman, 2001), as well as lead to an increase health seeking behavior and relate to greater symptom severity (Gupta et al., 2007). While, multiple and distinct illness states may confound this observation, this thesis hypothesizes the maladaptive tendency to somatize is common among all FSSs and its effect on symptom burden is non-specific.

Somatization overlap is prevalent among all identified FSSs, however it is unknown whether it, like many other psychological constructs is antecedent to, or a consequence of, a chronic illness process. Manifesting disproportionate stress to normal or abnormal bodily symptoms can exacerbate underlying sub-clinical conditions (Koloski

et al., 2012b). This can be extrapolated via a bi-directional neurophysiological relationship, lowering visceral and/or somatic stimuli thresholds at various levels of the nervous system, as seen in Central Sensitization (Simons et al., 2014). The process and importance of central sensitization in FSSs is described in the current study.

Dysfunctional Cognitions

Throughout sustained visceral and/or somatic symptom expression, dysfunctional cognitions such as catastrophizing, pain hypervigilance, fear avoidance and psychological inflexibility may develop (Keefer & Mandal, 2015). These dysfunctional cognitions relating to the experience of pain are associated with a number of pain related outcomes. They include increased severity of pain, increased disability due to symptoms, disruption of social support networks and greater affective responses (Sullivan et al., 2001).

Pain catastrophizing is conceptualized as a negative cognitive–affective response to anticipated or actual pain (Quartana, Campbell, & Edwards, 2009). This process is a maladaptive coping strategy identified in, although not limited to, a number of FSSs and is thought to amplify pain intensity, irrespective of the severity of initial stimuli (Garland, 2012). Pain catastrophizing and other dysfunctional cognitions can predict chronicity in musculoskeletal disorders (Vlaeyen & Linton, 2000), as well as contribute to the maladaptive psychosocial profile in FGIDs identified earlier (Budavari & Olden, 2003).

Patients with IBS report a greater tendency to catastrophize when compared to those with organic GI disorders (Drossman et al., 2000). Catastrophizing is identified in

FD, with greater levels of this dysfunctional cognition noted compared to controls, as well as increased symptom severity (Levy et al., 2006). In IBS, catastrophizing mediates the contribution of other affective responses, such as depression, to the severity of symptoms (Lackner, Quigley, & Blanchard, 2004). This illustrates the complex nature of direct and indirect pathways, psychological factors exhibit in FGIDs.

Catastrophizing in FMS patients is associated with increased activation of cortical regions of cerebral structures (Gracely et al., 2004). Even controlling for factors of mood, such as anxiety and depression, FMS patients, who identified catastrophic thoughts, experience lower thresholds to mechanical and thermal stimuli (Geisser et al., 2003). Pain catastrophizing has been associated with greater pain severity and disability in CLBP (Wertli et al., 2014) and it is hypothesized in this thesis, a spectrum of severity will exist and those with a greater somatic symptom burden, will experience more dysfunctional cognitions.

In CFS, catastrophizing significantly predicts multiple clinical outcomes. These include somatic pain experienced, depressive symptoms, kinesophobia and decreased in quality of life (Nijs, Van de Putte, Louckx, Truijen, & De Meirleir, 2008). Catastrophizing was an immediate and long term predictor of pain expression in CFS patients with chronic widespread musculoskeletal pain (Meeus, Nijs, Van Mol, Truijen, & De Meirleir, 2012). Therefore, dysfunctional cognitions play a pivotal role in the symptom expression and disease burden in those with CFS. Pain catastrophizing has been associated with greater pain severity and disability in CLBP. Therefore, the importance of

identifying catastrophizing early in clinical practice has been proposed, due to its effects on delaying recovery (Wertli et al., 2014).

Pain catastrophizing is greater in FGIDs and other FSSs than healthy controls. Dysfunctional cognitions mediate the effects of mood and personality in multiple clinical pain outcomes, such as pain severity, duration and disability (Lackner et al., 2004; Mira Meeus & Nijs, 2007). Their identification is targeted in the behavioral treatment of FSSs and their reduction is associated with symptom improvement (Mayer et al., 2006; Wertli et al., 2014). As these processes are integrated with all somatic or visceral sensations, it is hypothesized that they will be associated with the GI and extra-GI symptom burden experienced. Substantial cross over will exist and the dysfunctional cognition output will be non-specific in nature, irrespective of the initial GI or extra-GI stimuli.

Summary of the Psychological Involvement in FGIDs and other FSSs

In summary, the negative psychological phenomena of personality, mood, somatization and dysfunctional cognitions have all been identified within the literature as a common co-morbidity with the selected FSSs. Within FSSs, a spectrum of severity exists and the association of adverse psychological phenomena in FGIDs and extra-GI disorders is recognized more in the extreme (Levy et al., 2006; Viniol et al., 2015). A defining feature of this project is the broad inclusion of historically distinct clinical entities and addressing their psychological state in parallel and together. All individuals were subject to the same measures and diagnostic criteria ensuring comparability, which

has been lacking in previous research. It is hypothesized that the aspects of negative psychological phenomena, which have been shown to drive brain directed gut symptoms (Koloski et al., 2012a), may play a similar role in other common physical symptoms, such as somatic pain and fatigue.

Neurobiological Aspects of Functional Somatic Syndromes: A Potential Explanation

A neurobiological explanation of the widespread and multi-system expression of symptoms experienced in FSSs is the notion of Central Sensitization (CS). Sustained nociceptive input via the gut or somatic sites can trigger a prolonged increase in excitation and synaptic efficacy in central nociceptive pathways. This is manifested through hyperalgesia (increased sensitivity to a painful stimuli) and allodynia (painful experience to a normally no-painful stimuli), with secondary changes identified in cortical activity through neuroimaging studies (Woolf, 2011). Specifically, this is an increased activation of somatosensory processing regions (e.g., thalamus, insula), cognitive and affective processing regions (e.g., anterior cingulate cortex [ACC]), and limbic and paralimbic regions (e.g. Amygdala) (Moseley, 2003).The process of CS is common throughout all FSSs, as is shown below, and is hypothesized to be independent of the initial somatic, visceral or psychological stimuli driving the altered sensory processing state.

Peripheral and Central Sensitization

Visceral hypersensitivity in FGIDs has been extensively studied and is considered a potential biomarker of FGIDs, with majority of IBS patients experiencing decreased pain thresholds in distention of a rectal barostat (Mertz, Naliboff, Munakata, Niazi, & Mayer, 1995). Visceral hypersensitivity is seen in FD with decreased tolerance to gastric distention observed when compared to control subjects (Azpiroz et al., 2007). In addition to visceral changes, somatic hypersensitivity to thermal, ischemic and cold pressure nociceptive stimuli has been identified in diarrhea-predominant IBS patients (Zhou, Fillingim, Riley, Malarkey, & Verne, 2010). Therefore, while not limited to a specific organ or the entire GI tract, both visceral and somatic hypersensitivity has been identified among FGID patients (Azpiroz et al., 2007). Amplification of peripheral pain nociception at shared spinal cord origins, decreased pain inhibitory pathways and aberrant pain processing is postulated as potential mechanisms behind these widespread observations (Azpiroz et al., 2007; Zhou et al., 2010).

Widespread somatic hyperalgesia and allodynia is the hallmark of FMS (Dadabhoy, Crofford, Spaeth, Russell, & Clauw, 2008). Visceral hypersensitivity in fibromyalgia patients, with or without IBS, has been studied using a balloon catheter in rectum and descending colon, demonstrating visceral perceptions to be greater than in healthy controls (Chun et al., 1999). In addition, significantly greater perceptions of pain are identified in patients with both IBS and FMS, compared to IBS patients alone. Therefore, due to the central changes being non-discriminatory to a particular peripheral

stimuli, central mechanisms may play an important role in the etiology and perpetuation of symptoms in FSSs (Chang et al., 2003).

The up regulation of somatic and visceral pathways has been experimentally studied in CFS, through rectal barostat and noxious thermal stimuli, with results similar to that of FMS and FGIDs (Nijs et al., 2012). Etiological theories behind enhanced pain perception include altered descending pain inhibiting pathways (Van Oosterwijck et al., 2010), abnormal afferent nociceptive pathways (Aaron, Burke, & Buchwald, 2000), increased blood oxidative stress (Vecchiet et al., 2003) and augmented brain activation, most notably in the Anterior cingulate cortex (ACC), insula and pre frontal cortex (Nijs et al., 2012).

Early changes in somatosensory function are associated with axial spine pain, providing evidence of augmented central pain processing, similar to other FSSs (Giesecke et al., 2004). CLBP patients reported higher pain intensity, duration and referral of peripheral nociception, when compared to age and gender matched controls (O'Neill, Manniche, Graven-Nielsen, & Arendt-Nielsen, 2007). These neuroplastic changes in pain circuits begin immediately after a nociceptive or neuropathic insult, driving a central sensitizing sequela in CLBP.

In summary, central changes to visceral and somatosensory processing has been observed in multiple FSSs and concurrent to CS. These sustained insults from the somatic or gut periphery lead to a non-specific and maladaptive facilitation of body sensations and illness behaviors. It is the authors' opinion that the FSSs studied in this thesis are

fundamentally problems with pain or sensory processing, rather than abnormalities confined to regions where the symptoms are experienced. This research addresses FSSs co-morbidity through validated epidemiological identification and hypothesizes that substantial overlap in syndromes will exist. This overlap is identified on a continuum of symptom expression and negative psychological phenomena will relate to the extreme.

The Current Study

FGID, FMS, CFS and CLBP all exhibit similarities in demographics, clinical overlap and treatment options. Psychological aspects of personality, mood, somatization and dysfunctional cognition have all been associated with the development and symptom expression of multiple FSSs. In addition, the literature suggests the biological mechanism of central sensitization similarly underpins their etiology. The findings of past research could be interpreted to suggest that the selected FSSs can be viewed as manifestations of a similar underlying mechanism and their symptom expression is strongly associated with psychological state (Afari et al., 2014; Lackner et al., 2014). However this remains an untested hypothesis and is the underlying purpose of this study. In doing so this study will further extend the knowledge regarding multiple FSSs, isolating specific psychological factors associated with their symptom expression. Consequentially examining whether similarities exist that might change our approach to their study and treatment.

The objectives and hypotheses of this thesis are as follows:

- Aim One: Determine whether the strength of association (correlation) and effect size (regression slope) between psychological constructs of personality, mood, somatization and dysfunction cognitions with GI and extra-GI symptom burden is similar between FGID and extra-GI FSSs.
    - Hypothesis 1a: The precision of association (correlation) between psychological constructs and the symptom burden of both GI and Extra-GI disorders will be similar.
    - Hypothesis 1b: The effect sizes (regression slopes) of psychological constructs on symptom burden will be similar across GI and Extra- GI disorders.
- Aim Two: To determine whether levels of QoL and disease specific symptom burden are similar in FGIDs and other FSS.
    - Hypothesis 2a: The levels of QoL will be similar for GI and Extra- GI disorders.
    - Hypothesis 2b: The levels of somatic pain symptom burden will be similar across GI and Extra- GI disorders.
    - Hypothesis 2c: The levels of GI symptom burden will be similar across GI and Extra- GI disorders.
    - Hypothesis 2d: The levels of fatigue symptom burden will be similar across GI and Extra- GI disorders.

- Aim Three: Evaluate whether previously identified path models of the role of psychological constructs in the severity of GI and extra-GI symptoms applies equally well in FGIDs and extra-GI FSSs.
    - Hypothesis 3: A single path model relating psychological constructs to GI and extra-GI symptom burden will provide adequate fit for both gastrointestinal and extra-gastrointestinal populations.
- Aim Four: Estimate the overlap of the selected FSSs.
    - Hypothesis 4: Significant overlap will exist in those who meet the criteria for gastrointestinal and extra-gastrointestinal functional somatic syndromes.

Chapter 2: Methodology

Procedure

This preliminary study employed a cross-sectional correlational design based primarily on questionnaire data collection, via an online survey platform. Study participants were identified from multiple sources that were likely to yield predominant GI and non-GI conditions. They were analysed to identify similarities or differences in GI and extra-GI somatic symptom burden, health specific QoL and adverse psychological phenomena. In addition, measures used for the clinical classification of FGIDs and extra-GI disorders were implemented to identify those who meet the criteria for a specific FSS. All individuals were subject to the same measures and diagnostic criteria to ensure comparability, which has been lacking in previous research.

Recruitment was organized through three groups; Chiropractic clinics for Chronic Somatic pain, Gastroenterology clinics and specialists rooms for Functional GI disorders and Psychology undergraduate student pool for Functional GI disorders as well as a range of other somatic conditions common in young adults. This study was approved by the Macquarie University medical sciences (5201500188) and Northern Sydney Local Health District (HREC/15/HAWKE/175) ethics committees.

Participants

Participants who experience functional GI and extra-GI symptoms were actively identified throughout a variety of locations around Sydney. The Gastroenterology department at Royal North Shore Hospital (RNSH) and associated private specialist

consultation rooms aided recruitment by actively screening patients for FGIDs. A similar process was implemented throughout university and private Chiropractic clinics, with practitioners actively identifying participants with chronic somatic pain. Advertisements (see Appendix A) with a URL link were disseminated throughout the various healthcare locations directing participants to the online questionnaire.

Macquarie University Student Pool. The Macquarie University psychology pool has a high prevalence of GI symptom burden (McKinnon et al., 2013) and in return for course credit, selected participants could complete the online questionnaire. To ensure participants from the Macquarie University student pool had sufficient gastrointestinal symptoms, a modified ROME III screening criteria was implemented (see Appendix B) which was designed to ensure that participants had at least some degree of gastrointestinal symptoms. Previous research by the Psychology Department has identified this sample population high in FGID prevalence (McKinnon et al., 2013). In addition, the students were also asked whether they had ever been diagnosed with GI cancer, Crohn's disease or any other serious organic bowel or stomach disease. Organic GI disease is comparatively rare in the community; therefore, the lack of a physician consultation is unlikely to result in many if any misclassification. Those who answered 'yes' were automatically excluded at screening.

This sample proved to be an ample source of participants, with 97 respondents all with varying levels of GI symptom burden. The validity of the source is strengthened with 40% of the sample meeting the criteria for at least one FGID.

Royal North Shore Hospital. Participants sampled from RNSH Gastroenterology clinic were subject to the following inclusion criteria: aged between18 and 65, not pregnant at the time of study, experience Gastrointestinal Symptoms, in the absence of any organic disease, which was excluded following, rigorous investigatory procedures, such as serum blood analysis and colon/endoscopy. This site provided a logical source of healthcare seeking functional GI population, however recruitment was slower than initially expected. Hence, due to time constraints only 5 participants were included into the analyses.

Chiropractic Outpatient Clinics. Participants throughout the various Chiropractic clinics were actively screened to comply with a predetermined inclusion criteria: between the ages of 18 and 65, not pregnant, and experienced functional somatic pain for at least 3 months. Research suggests this is an appropriate sample location, with majority of all consultations are for musculoskeletal conditions (French et al., 2013). Participants with previously diagnosed organic pathology that can manifest as chronic pain, such as Cancer, inflammatory arthritis and/or autoimmune disorders were excluded at screening. Similar to that of RNSH, recruitment as these site proved much slower than anticipated. Therefore, only 31 patients were included into the analyses.

Measures

The constructs considered in this study all have well-validated questionnaire instruments available (see Appendix B). The measures included in the study can be

separated into three groups; diagnostic criteria, psychological constructs and symptom burden. In addition, demographic data (age and gender) were collected.

Diagnostic Criteria

The Rome III Criteria (Drossman, 2006). The IBS and FD modules of the Rome III integrative questionnaire (Drossman, 2006) were administered to participants, which assess the diagnostic criteria for FGIDs with 18 questions and 10 questions, respectively. The response options all ask for frequency of symptoms but differ in the scale utilized, with some in yes/no format and others with frequency selections, for example, never [0] to everyday [6] and never or rarely [0] to always [4].

Classification was carried out according to standard Rome III criteria (Drossman, 2006). The Rome III symptom based criteria performs well (sensitivity 0.4 - 0. 9) compared with a clinical diagnoses by experienced clinicians and previous fulfillment of the Rome II criteria (Whitehead & Drossman, 2010). The Rome criteria have long been the most well-established and widely used method of FGID identification in epidemiological studies (Drossman, 2006; Thompson, Irvine, Pare, Ferrazzi, & Rance, 2002).

Participants meet the criteria for IBS if they had recurrent pain or discomfort at least 3 days/month for the last 3 months associated with two or more of the following: Improvement with defecation, onset associated with a change in frequency of stool and/or onset associated with a change in form (appearance) of stool.

Participants met the criteria for FD is they had one or more of the following symptoms; Bothersome postprandial fullness, early satiation, epigastric pain and/or epigastric burning. In addition, symptoms must be present for at least 3 months.

The Wide Spread Pain Index (WPI) and Symptom Severity Scale (SSS) (Wolfe, 2010). The American College of Rheumatology (ACR) developed simple and practical criteria for the Diagnosis of Fibromyalgia, which entails the use of the WPI and SSS in tandem. This revision of the 1990 ACR diagnostic criteria is both sensitive (88.1%) and specific (81.1%) in identifying those with FMS. In addition, it excludes the need for a physical examination, allowing a greater use in epidemiological studies (Wolfe, 2010; Wolfe et al., 1990).

The WPI identifies the number of areas a participant has experienced pain in. With the aid of a mannequin to label the body areas, the number of painful areas out of 19 is totaled. This component was introduced to eliminate the need for a physical examination counting tender points. The WPI correlates more strongly with the SSS (r_s = .73) than a physical tender point count (r_s = .68)[1].

The SSS is divided into two parts: Part A focused on three domains; fatigue, waking unrefreshed and cognitive symptoms. These domains are rated from No Problem [0] to Severe: pervasive, continuous, life disturbing problems [3]. Part B displays 41 "other symptoms", such as, headache, painful urination and blurred vision. The summation of the other symptoms is categorized into 4 categories: no symptoms [0], 1-10

[1] r_s = Spearman correlation co-efficient

symptoms [1], 11-24 symptoms [2] and 25 or more symptoms [3]. Therefore, in combining part A and B, the SSS scores from 0-12. Therefore, in combining part A and B, the SSS scores from 0-12. Criteria thresholds for the diagnosis of Fibromyalgia include one of the following: either a WPI greater than or equal to 7 and a SSS greater than or equal to 5; or, a WPI between 3-6 and a SSS greater than or equal to 9.

To further explore the continuum of chronic pain, the WPI is presently used to distinguish participants with Chronic Widespread Pain. The ACR defines this as pain in the left and right side of the body as well as above and below the waist, plus pain in the axial skeletal. In addition, these symptoms are to be present for greater than 3 months (Wolfe et al., 1990).

Localized Somatic Pain (Dionne et al., 2008). The Dionne et al. consensus paper constructed a standardized reporting of Low Back Pain in epidemiological studies to increase comparability of data. The present study incorporated the Chronic Low Back Pain module, which includes four items, as well as the use of a mannequin to orientate the participant. Questions included the presence of Low Back Pain in the past 4 weeks, its effect on Activities of Daily living (ADLs), chronicity of the pain and a Visual Analogue Scale (VAS). Modified versions of the Dionne et al measure were used to incorporate chronic functional headache and neck pain. Participants were considered to have Chronic Localized Somatic Pain at that region if they met the criteria of a) the presence of pain and b) duration greater than 3 months.

The Chalder Fatigue Scale (Cella & Chalder, 2010). The Chalder Fatigue Scale was developed to measure fatigue in both a clinical and community setting. The items contain aspects of both physical (e.g., "Do you lack energy?") and mental fatigue ("Do you have difficulties concentrating?"). Ten of the 11 items are responded to from Less than usual [0] to Much more than usual [3], with the 11th responded to from Better than usual [0] to Much worse than usual [3]. Scores range from 0-33, with a score equal to or greater than 29 discriminative of CFS (Cella & Chalder, 2010). This Chalder Fatigue Scale reveals good internal consistency: Cronbach's alpha = .89 (Chalder et al., 1993). The Chalder Fatigue Scale is used widely in clinical and occupational research and allows for straight forward comparisons between studies and populations (Jackson, 2015).

Psychological

The International Personality Item Pool (IPIP) (Goldberg et al., 2006). The IPIP neuroticism scale consists of 10 items that assess the tendency to experience distressing or negative emotions. A 5-point response scale was used, from Very inaccurate [1] to Very accurate [5]. Scores range from 10 to 50, with higher scores indicating greater neuroticism. IPIP scales are highly correlated with the NEO Personality Inventory Revised (NEO-PI-R, a well-established and highly utilized measure of the five factor personality model), with correlations ranging from r = .85 to .92 and an overall

mean correlation of .90 (Costa, 1996). IPIP scales have good internal consistency, with Cronbach's alphas ranging from .77 to .86 (Goldberg et al., 2006).

Depression Anxiety Stress Scales 21 (DASS-21) (Lovibond & Lovibond, 1995). The DASS-21 is a quantitative measure of distress along the axis of depression, anxiety and stress. Although, not a categorical measure of a clinical diagnosis, the 21 item scale is a useful tool to identify and categorize depressive thoughts and feelings among the sampled population. It includes items such as, "I find it hard to wind down", "I felt I was close to panic" and "I fell down-hearted and blue". The items are rated from did not apply to me at all [0] to Applied to me very much, or most of the time [3]. In addition, for the purposes of Aim 4, aspects of depression, anxiety and stress, were incorporated together as DASS total score. The overall score serves as a broad measure of negative affect, which is commonly used in clinical and epidemiological investigations (Lovibond & Lovibond, 1995).

The DASS-21 demonstrated strong psychometric properties, correlating distinguishing clinical (Brown, Chorpita, Korotitsch, & Barlow, 1997) and non-clinical samples (Henry & Crawford, 2005). The reliability of the DASS-21 is well established with Cronbach's alpha .88 for depression, .82 for anxiety and .90 for stress (Henry & Crawford, 2005).

Patient Health Questionnaire -15 (PHQ-15) (Kroenke et al., 1994). The PHQ-15 is a somatic symptom severity subscale derived from the full PHQ, which identifies levels of somatization (Kroenke et al., 1994). It assesses symptoms, such as stomach

ache, dizziness and chest pain, which account for more than 95% of physical complaints reported by outpatients (Han et al., 2009). Each symptom is rated on a scale ranging from Not bothered at all [0] to Bothered a lot [2], with total scores ranging from 0 to 30. The measure has been previously validated in a clinical setting (Kroenke, Spitzer, & Williams, 2002), as well as demonstrating a good internal consisting, with α =.80 (Han et al., 2009).

Pain Catastrophizing Scale (Sullivan, Bishop, & Pivik, 1995). The Pain Catastrophizing Scale (PCS) is a 13-item self-report questionnaire that assesses catastrophic thinking related to pain. It includes items such as 'I worry all the time about whether the pain will end'. It utilizes a 5-point response scale, from not at all [0] to all the time [4]. Scores range from 0 to 52, with higher scores reflecting higher degrees of catastrophizing. The PCS has demonstrated good construct and criterion-related validity, test retest reliability and high internal consistency, with Cronbach's alpha coefficients ranging from 0.87 to 0.92 (Osman et al., 2000; Osman et al., 1997; Sullivan et al., 1995).

Visceral Sensitivity Index (Labus et al., 2004). The Visceral Sensitivity Index (VSI) is a 15-item self-report questionnaire that captures GI symptom-specific anxiety. It includes items such as 'As soon as I feel abdominal discomfort I begin to worry and feel anxious'. It utilizes a 6-point scale, labelled from strongly agree [1] to strongly disagree [6]. Items are reverse-scored so that scores range from 0 to 75, with higher scores reflecting higher GI symptom-specific anxiety. The VSI has demonstrated strong psychometric properties, including good content, convergent, divergent and predictive

validity, as well as excellent internal consistency with Cronbach's alpha coefficients ranging from .90 to .93 (Labus et al., 2004; J. S. Labus, Mayer, Chang, Bolus, & Naliboff, 2007).

The Tampa Scale for Kinesiophobia (Kori, Miller, & Todd, 1991). The Tampa Scale of Kinesiophobia (TSK), consisting of 17 items, is designed to measure fear avoidance behavior as it relates to movement. Each item is evaluated on a 4-point Likert scale with response options ranging from "strongly disagree" to "strongly agree". The total score can vary from 17 to 68. The scale reports two constructs, a somatic focus, such as "Pain always means I have injured my body" and activity avoidance, such as "I'm afraid that I might injury myself if I exercise". When combined these constructs give a single score of fear avoidance related to movement. The TSK exhibits good internal consistency: $\alpha = .80$ in CLBP patients and .82 in FM patients (Goubert et al., 2004).

Symptom Burden

Short Form 12v2 Health Survey (Maruish, 2012). Developed from the SF-36, The SF12v2 was constructed to yield a quantitative measure of both the physical and mental burden of chronic disease. Items are used to measure eight domains of health: physical functioning, role participation with physical health problems (role- physical), bodily pain, general health, vitality, social functioning, role participation with emotional health problems (role-emotional), and mental health. This project will display the condensed physical and mental component summaries, as well as eight specific health

domains. Standardized T-scores of the condensed variables range from 0-100, with higher scores relating to a better health state. The SF12v2 demonstrates good reliability with Cronbach alpha of 0.88 for the physical and 0.92 for the mental health component summaries (Maruish, 2012).

Gastrointestinal Symptom Rating Scale (GSRS) (Svedlund, Sjodin, & Dotevall, 1988). The GSRS was developed based on reviews from the literature and clinical expertise, to assess common symptoms of the gastrointestinal tract. The measure contains 15 items, scored on a 7-point Likert scale, from no discomfort to very severe discomfort. The GSRS can be broken down into 5 syndromes, which clusters common symptoms together: abdominal pain, reflux syndrome, diarrhea syndrome, indigestion syndrome and constipation syndrome. Average scores are computed for each symptom cluster; higher scores reflect a greater symptom burden. High test-retest reliability has been demonstrated (r = .55 - .70; (Hunt, Moshier, & Milonova, 2009) as well as adequate internal consistency, with Cronbach's alpha co-efficient ranging from .61 - .87 (Kulich et al., 2008; Revicki, Wood, Wiklund, & Crawley, 1997; Svedlund et al., 1988).

Chronic Pain Grading Scale (CPGS) (Dixon, Pollard, & Johnston, 2007; Von Korff, Ormel, Keefe, & Dworkin, 1992). The CPGS is a multidimensional measure that assesses two dimensions of chronic pain; pain intensity, "In the past 6 months, on average, how intense was your pain rated on a 0-10 scale? (That is your usual pain at times you were experiencing pain)" and pain related disability "In the past 6 months, how has this pain changed your ability to work (including housework)?" Items are scored on

an 11-point Likert scale, with responses ranging from 0–10. Scores are calculated for 3 subscales: The characteristic pain intensity score, which ranges from 0–100, is calculated as the mean intensity ratings for reported current, worst, and average pain; the disability score, which ranges from 0–100, calculated as the mean rating for difficulty performing daily, social, and work activities; and the disability points score, which ranges from 0–3, is derived from a combination of ranked categories of number of disability days and disability score.

The three sub-scale scores are then used to categories participants into 1 of 5 pain severity grades; [0] for no pain to [5] for high disability/severely limiting. The CPGS demonstrates good internal consistency, with Cronbach's alphas ranging from .74-.89 (Salaffi, Stancati, & Grassi, 2006; Von Korff et al., 1992). In addition, adequate construct validity has been identified, with higher CPGS scores significantly associated with higher rates of un-employment, greater pain impact scale scores, greater use of opioid analgesics and physician visits, depressed mood, and lower self-rated health status (Penny, Purves, Smith, Chambers, & Smith, 1999; Von Korff et al., 1992).

Statistical Analysis

Disorder specific measures were coded to identify those who met the criteria for all outlined FSSs. Informed by the study's hypotheses, the sample was stratified into four disorder groups; (1) No FSS, (2) FGID only (IBS and/or FD), (3) extra-GI only (FMS, CWP, CFS and/or Chronic Localized Pain) and (4) Both GI and Extra-GI. Groups two

and three explore the relationship between FGIDs and extra-GI disorders against a control, while group four yields further insights into the additive effects of multiple FSS. This facilitates the study's hypotheses addressing the specificity of psychological and symptom burden relationships among FGIDs and extra-GI conditions. All participants were screened for some level of GI or extra-GI symptom burden. However, due to the spectrum of severity exhibited in FSSs, some participants did not meet the required thresholds for the classification of a selected FSSs. This group was used as an internal control against those with a defined FSS.

Data was analyzed with SPSS and AMOS, both v23. To assess normality of the variables of interest, descriptive statistics were calculated and the Shapiro-Wilk test used as a formal evaluation (see Appendix C) (Shapiro & Wilk, 1965) . As a number of statistically significant violations of normality were identified, spearman's rho was used to assess correlations and the nonparametric bootstrap was employed in most other formal statistical inference. To assess whether effect size (regression slope) is different across disorder groups the interaction of psychological variables and disorder group was evaluated using General Linear Models. Due to bootstrapping of the omnibus test of interaction not being available, data transformation, using Log10, Square Root or forced "Rank" normality was implemented to obtain a non-significant Shapiro – Wilk test. The interaction between a given psychological construct and disorder group was evaluated using both the untransformed and transformed dependent variables as a sensitivity analysis. Since the rejection or acceptance of the statistical null hypothesis was never

altered by transformation, the un-transformed variables were displayed as these are easier for the reader to interpret.

Statistical analyses for Aim 1. Stratified by disorder groups, all psychological constructs were correlated with GSRS, CPGS (intensity), CPGS (disability) and Chalder Fatigue Scale because they represent a range of GI and extra-GI symptom burden measures.

1a – Precision of association. To determine the precision of the association psychological phenomena exhibit on the symptom burden of GI and extra-GI complaints, Spearman Correlation Coefficients were calculated as descriptive measures. Bootstrapped regression analyses were implemented to determine the strength of association between psychological constructs and the GI and extra-GI symptom burden. This was described through Beta (β) coefficients and 95% CI.

1b – Consistency of Effect sizes (regression slopes). Formal tests of the specific hypotheses were undertaken via multiple regression which included the interaction between psychological constructs and disorder groups. An Omnibus F-test was used to determine whether there was any evidence of variation between disorder groups, in contrast to the specific associations between pairs of groups.

All interactions of association with p-values less than 0.1 were subject to a sensitivity analysis via omitting the no FSS disorder group. This was implemented on the basis that the no FSS group suffer sub-syndromal levels of symptoms whose association with psychological constructs may be limited.

Statistical analyses for Aim 2. To determine similarities of symptoms burden and Quality of Life (QoL) between GI and extra-GI disorders, a nonparametric approach was adopted. The SF12v2 provided the mental and physical QoL variables, while the GSRS, CPGS and Chalder fatigue scale identified GI and extra-GI symptom burden. Kruskal – Wallis pairwise tests were implemented as the non-parametric test and it is hypothesized non-significant relationships will exist, suggesting health specific QoL, GI and extra-GI symptom burden is similar across disorder groups, irrespective of GI or extra-GI diagnosis.

2a - Quality of Life. Descriptive statistics of the SF12v2 component summaries and health domains were used to describe the Quality of life reported among our data set. Mean t-scores were displayed against a normative value of 50 (SD 10), which is described in 2009 US general population (Maruish, 2012).

The SF12 physical and mental component summaries were analyzed using non-parametric Kruskal-Wallis testing to determine differences of health specific QoL between disorder groups. The remaining physical and mental component summaries had a normal distribution between disorder groups.

2b - Chronic Somatic Pain Symptom Burden. Descriptive statistics of the CPGS describes the chronic somatic pain symptom burden experienced by the sample. Stratified by disorder group, the level of chronic somatic pain was identified through subgrouping participants into one of five categories, consistent to that of the CPGS: No Pain, low

disability/low intensity, low disability/high intensity, high intensity/moderately limiting and high disability/severely limiting.

A Kruskal – Wallis test was implemented to determine any significant differences between Somatic pain symptom burden and the GI and extra-GI disorder groups.

***2c - Gastrointestinal Symptom Burden*.** Descriptive statistics of the GSRS were used to help understand the samples characteristics of the gastrointestinal symptom burden. Five domains were measured (diarrhea, constipation, abdominal Pain, indigestion and reflux). Non-parametric testing of the overall mean GSRS with GI and extra –GI disorder groups determined any significant differences between disorder groups. Kruskal –Wallis testing was implement for the purpose of consistency, as normality was evident through Shapiro –Wilk testing.

2d - Fatigue Symptom Burden. Descriptive statistics of the Chalder fatigue scale were used to describe the fatigue symptom burden of the sample. Stratified by disorder group, the mean fatigue scores were displayed to identify the effect of fatigue across multiple FSSs. Non- parametric testing of fatigue symptom burden determined any significant differences between disorder groups.

Statistical analyses for Aim 3. Previous research (McKinnon et al., 2013) found support for a proposed pathway of the role of psychological constructs influence FGIDs. The purpose of this aim is to examine whether a hypothesized path model, fashioned for FGIDs, applies to extra-GI symptoms. Path modelling of a combination of key elements

of the previously identified path models was carried out using AMOS (v23) software (see Figure 3).

Path analysis was implemented using the whole sample, as well as stratifying the sample into two FSS populations; 1) those who met the criteria for FGID (IBS and FD) and 2) those who met the criteria for extra-GI disorders (Localized pain, Chronic Widespread Pain, CFS and FMS) and refitting the model on each of these strata. These FSS populations differ from the stratified disorder groups, as they do not account for symptom overlap. Bootstrapping was employed as a non-parametric method of estimating parameter standard errors, and hence p-values due to non-normal distribution of several variables in the model.

Path coefficients and model fit statistics for the three path analyses were tabulated. Any missing data was discarded to produce a complete data set (n=133 to n=109). This was done to be able to use the bootstrap in formal statistical inference in the path analysis. Both n=133 and n=109 were run to compare path co-efficient and model fit and both parameter estimates the model fit were very similar. Given this, the smaller sample was retained as it was decided that no substantial information was lost and this enabled the bootstrap approach to statistical inference to be utilized.

Statistical analyses for Aim 4. Descriptive statistics of diagnostic specific measures identified the level of co-morbidity among FGIDs and extra-GI syndromes. Cross tabulation of FGIDs (IBS and FD) and extra-GI Disorders (FMS, chronic widespread pain, chronic localized pain and CFS) examined this relationship and was

displayed as a Venn diagram to show an assumed large overlap among FSSs. The overlap of the individual extra-GI disorders with FGIDs was also tabulated. This was compared to that of the existing literature, which is outlined in Table 1.

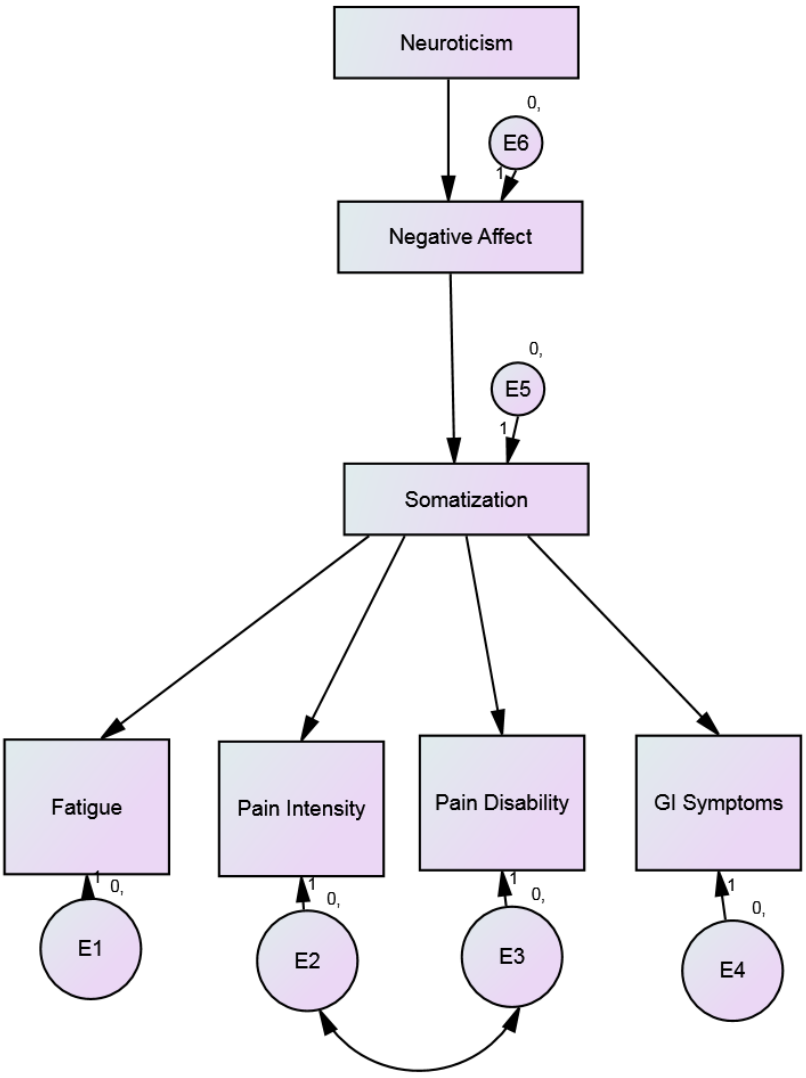

Figure 2. Base Path Model

Chapter 3: Results

Descriptive Statistics

There were 133 responses in total, of which 97 were from the Psychology Student Pool, 31 from Chiropractic outpatient Clinics and 5 from Public and Private Gastroenterology specialist rooms (see table 2). The recruitment sites performed well, in terms of achieving the objective of a range of functional somatic syndromes (FSSs) and some sub-syndrome participants, sampling a total of 58 (43% of total sample) participants who met ROME III criteria for FGID diagnosis and 79 (59% of total sample) participants who met the criteria for an extra-GI diagnosis. Within the FGIDs, IBS predominated (n=57) compared to that of FD (n=3). This FGID diagnosis is larger than previous research of the psychology student sample (McKinnon et al., 2013), however the inclusion of a screening questionnaire enriched the FGID population. Within the extra-GI diagnoses, chronic localized somatic pain predominated with 77 participants identified, of which headache was the most prevalent (n=55). The extra-GI breakdown was follow by 10 participants with chronic widespread pain, 9 with CFS and 6 with FMS. This breakdown, successful represents a spectrum of chronic somatic pain, which has been previously described in this thesis.

The disorder grouping identified a total of 31 (23%) participants who did not meet the criteria for any FSS, 20 (15%) participants met the ROME III criteria for a FGID only, 40 (30%) participants met the criteria for an extra-GI disorder only and 38 (28%) participants met the criteria for both a FGID and an extra-GI disorder. This breakdown is used to describe descriptive and correlational observations referred to in the corresponding hypotheses.

Female respondents dominate the sample (85%) (see Table 2). This is due to majority of results drawn from an undergraduate psychology pool, which is typically female predominant. However, as explained in Chapter 1, females are more likely to be diagnosed with all FGID and extra-GI disorders included in the study (Arnold et al., 2011; L. Chang, 2006; Gerdle et al., 2004; Kim & Chang, 2012).

Descriptive statistics of the symptom Burden, psychological and diagnostic criteria measures are outlined (see Table 2) and show comparability among the recruitment sites. The symptom burden and QoL constructs varied in the GI clinics when compared to that of the Psychological and Chiropractic samples, however this may well be due to random sampling variability given the small size of the GI clinic sample. This was similar for the diagnostic criteria of the FSS within the GI clinics, with majority of the FSS diagnosis originating from the psychology student and Chiropractic clinic samples. The psychological constructs performed consistently across all three sampling groups irrespective of sample size, with no large differences noted. This analysis suggests that the sample sources differ only in respects that are part of the research design.

Table 2

Characteristics of the samples

	Psychology Student Pool (n=97)	**Chiropractic Clinic (n=31)**	**GI clinic (n=5)**	**Whole Data Set (n=133)**
	Demographics (n / %)			
Aged 18 – 25	93 / 96%	6 / 19%	1 / 20%	100 / 75%
Aged 26 – 34	2 / 2%	5 / 16%		7 / 5%
Aged 35 – 54	2 / 2%	17 / 53%	2 / 40%	21 / 16%
Aged 54 – 65	-	4 / 13%	2 / 40%	6 / 5%
Male	17 / 18%	1 / 3%	2 / 40%	20 / 15%
Female	80 / 82%	31 / 97%	3 / 60%	114 / 85%
Bowel Hx	1 / 1%	3 / 9 %	-	4 / 3%
Pain Hx	3 / 3.1%	5 / 16%	-	8 / 6%
	Symptom Burden (M / SD)			
SF12 **Mental Component**	37 / 6.5	39.8 / 6.1	50.3 / 4	37.9 / 10.6
SF12 **Physical Component**	53.6 / 10.8	46.6 / 9.3	51.7 / 2.6	51.9 / 6.9
GSRS	34.9 / 13.4	38.2 / 15.8	33.2 / 9.7	35.5 / 13.8
CPGS Intensity	33.4 / 19.5	48.6 / 21.1	21.9 / 16.2	36.4 / 20.8
CPGS Disability	21.3 / 20.1	29.9 / 22.8	10.1 / 10	22.8 / 20.8
Fatigue	19.59 / 5.21	18.86 / 5.68	18.4 / 6.66	19.38 / 5.34
	Psychological (M / SD)			
IPIP	32.4 / 7.2	28.5 / 7.2	20.4 / 3.7	31.1 / 7.6
DASS Total	41.1 / 11.7	34.5 / 9	31.2 / 6.2	39.3 / 11.4
Depression	13.3 / 4.7	11 / 3.3	8.8 / 1.8	12.6 / 4.5
Anxiety	12.7 / 4.1	10.2 / 3	9.8 / 4.7	12 / 4.1
Stress	15.1 / 4.6	13.3 / 3.9	12.6 / 2.4	14.6 / 4.5
VSI	33.5 / 13.7	34.8 / 12.5	28.2 / 12.1	33.6 / 13.5
TSK	33.5 / 5.5	35.1 / 7.3	28.4 / 5.9	33.6 / 6
PCS	27.7 / 11.4	24.7 / 10.6	25.6 / 11.3	27 / 11.2
PHQ	26 / 4.8	25.9 / 4.4	25.6 / 7.5	26 / 4.8
	Diagnostic Criteria (n / %)			
FGID diagnosis	39 / 40%	17 / 53%	2 / 40%	58 / 43%
Irritable Bowel Syndrome	38 / 39%	17 / 53%	2 / 40%	57 / 43%
Functional Dyspepsia	2 / 2%	1 / 3%	0	3 / 2%
Extra-GI diagnosis	54 / 56%	21 / 66%	4 / 80%	79 / 59%
Fibromyalgia	3 / 3%	0	0	3 / 2%
Chronic Widespread Pain	5 /5%	5 / 16%	0	10 / 8%
Localised Chronic Pain	52 / 54%	21 / 66%	4 / 80%	77 / 58%
Headache	36 / 37%	16 / 50%	3 / 40%	55 / 41%
Neck Pain	26 / 27%	18 / 56%	2 / 60%	46 / 34%

Low Back Pain	24 / 25%	11 / 34%	3 / 60%	38 / 28%
Chronic Fatigue Syndrome	6 / 6%	2 / 6%	1 / 20%	9 / 7%
Both FGID + extra-GI Diagnosis	23 / 24%	13 / 41%	2 / 40%	38 / 28%

Normality of Measures

The Shapiro – Wilk test of normality found nine of the thirteen measures used to be non – normally distributed, and inspection of histograms showed substantial skewness (nine of the thirteen measures; Appendix C.). DASS: Depression ($W = 0.923$, $p < 0.001$), DASS: Anxiety ($W = 0.921$, $p < 0.001$), DASS: Stress ($W = 0.972$, $p = 0.002$), DASS Total ($W= 0.946$, $p < 0.001$), PHQ ($W= 0.976$, $p = 0.042$), VSI ($W= 0.95$, $p < 0.001$), TSK ($W = 0.974$, $p = 0.034$), PCS ($W = 0.934$, $p < 0.001$), GSRS ($W = 0.927$, $p < 0.001$) CPGS Disability ($W = 0.873$, $p < 0.001$) were not consistent with a normal distribution. Given the number of violations, all analyses were conducted using non-parametric methods or applying normalizing transformations.

Results for Aim 1

Comparisons between disorder groupings are made with respect to a) precision of the relationship between psychological constructs and symptom burden measures via Spearman rank correlation coefficients and b) effect size of the relationship between psychological constructs and symptom burden measures via the slope of regression line in which the dependent variable is symptom burden and the independent variable is a psychological construct.

Spearman's Rho correlations are used in (a) and statistical inference in via the non-parametric bootstrap of the regression coefficients (β) in (b) (see Table 3). The statistical significances of the Spearman Correlation coefficient are denoted in red, while the statistical significance of the regression slopes of significance are denoted in green.

Table 3 reports findings within-disorder groups and comparing disorder groups for both precision of relationship (correlation) and effect size (regression slopes) with respect to the involvement of adverse psychological phenomena on GI and extra-GI (somatic pain intensity, somatic pain disability and fatigue) symptom burden. The table is organized with respect to a) the precision of correlations through spearman rank coefficients (*rho*), b) the effect size (β) of the relationship between psychological constructs and symptom burden measures via the slope of the regression line and c) the test of equality of slopes across disorder groups (p-value). The columns of the table express the GI and extra-GI symptom burden measures, while the rows represents the psychological constructs, stratified by disorder groups. A separate item on the last row represents the test of equality between the slopes across disorder groups, within that psychological construct.

Table 3

Association and Interaction of Psychological Constructs and Symptom Burden within Disorder Groups

	GI Symptom Burden			Somatic Pain Intensity			Somatic Pain Disability			Fatigue Symptom Burden		
Neuroticism	*rho*	*β*	*95% CI*	*rho*	*β*	*95% CI*	*rho*	*β*	*95% CI*	*rho*	*β*	*95% CI*
No FSS	0.315	1.0**	0.19 – 1.46	0.263	1.19	-.97 – 2.91	0.341	0.13	-3.02 – 2.00	0.338	0.81**	0.4 – 1.18
FGID Only	0.398	-1.02	-3.26 – 0.10	-0.382	-0.19	-3.07 – 5.04	-0.180	0.62	-3.12 – 3.4	0.437	-0.32	-0.84 -0.19
Extra-GI Only	0.191	0.08	-0.65 - .58	0.105	0.69	-1.07 – 2.01	0.036	0.43	-1.73 – 2.07	0.525**	0.46**	0.32 - 0.74
FGID and extra - GI	0.232	0.52	-1.0 – 2.0	0.286	1.7	-0.39–4.09	0.372*	1.9	-0.2 – 4.03	0.498**	0.64**	0.02 –1.26
Test of Equality	F(3,113) = 0.62, p = 0.12			F(3,113) = 2.0, p = 0.12			F (3,106) = 1.97, p = 0.12			F (3,114) = 1.3, p = 0.28		
Depression	*rho*	*β*	*95% CI*	*rho*	*β*	*95% CI*	*rho*	*β*	*95% CI*	*rho*	*β*	*95% CI*
No FSS	0.513**	1.01**	0.41–1.76	0.567**	2.81**	1.2- 4.39	0.415*	1.69	-0.92 – 3.6	0.350	0.38	-0.14 - .83
FGID Only	0.349	1.59	-0.1 –3.65	-0.294	-1.17	-3.38-1.2	-0.160	-1.0	-3.24 –1.44	0.093	0.04	-0.41 - .42
Extra-GI Only	0.203	0.04	-0.69 - 0.87	0.203	0.12	-1.06 - 1.49	0.038	-0.40	-1.43 – 1.20	0.490**	0.44*	0.66 - .78
FGID and extra - GI	0.504	0.02	-0.96 –1.34	0.131	0.88	-0.52 –2.17	0.441**	1.73*	0.49 – 3.47	0.539**	0.77**	0.41–1.15
Test of Equality	F (3,114) = 1.2, p = 0.31			F (3,113) = 2.9*, p = 0.04			F (3,106) = 2.14, p = 0.1			F (3,114)=1.34, p = 0.26		
Anxiety	*rho*	*β*	*95% CI*	*rho*	*β*	*95% CI*	*rho*	*β*	*95% CI*	*rho*	*β*	*95% CI*
No FSS	0.268	0.89*	-0.12 – 1.62	0.468*	2.58*	0.65–4.59	0.408*	2.5	0.05 – 5.32	0.385*	0.58*	-0.01 –1.05
FGID Only	0.448	2.75**	0.77 –3.97	-0.329	1.73	-3.51–1.35	0.008	-0.17	-1.94–2.69	0.430	0.46*	-0.02-0.78
Extra-GI Only	0.347*	0.88	-0.1 – 1.97	0.144	0.15	-1.63–2.1	0.260	0.89	-0.63 – 3.08	0.676**	0.90**	0.55–1.15
FGID and extra - GI	0.351*	0.73	-0.28 – 2.4	-0.032	0.32	-1.79–1.52	0.124	0.81	-0.71 – 2.57	0.641**	0.94**	0.66 – 1.47
Test of Equality	F (3,114) = 1.94, p = 0.13			F (3,113) = 2.36, p = 0.08			F (3,106) = 0.87, p = 0.36			F (3,114)= 1.83, p = 0.79		
Stress	*rho*	*β*	*95% CI*	*rho*	*β*	*95% CI*	*rho*	*β*	*95% CI*	*rho*	*β*	*95% CI*
No FSS	0.227	0.64	-0.26 –1.33	.533*	2.7**	1.09 -4.21	0.479*	1.8	-0.45 – 3.9	0.447*	0.60*	0.7 – 1.01
FGID Only	0.506*	2.56*	-0.07–4.45	-.236	-1.86	-4.38–1.87	-0.156	-1.51	-3.88–2.61	0.537*	0.64*	0.22 –1.34
Extra-GI Only	0.310	0.76	-0.08 – 1.69	.277	1.05	-0.27–2.33	0.389*	1.47	0.1 – 2.9	0.611**	0.56**	0.25 – 0.82
FGID and extra - GI	0.187	0.56	-0.36 – 1.65	.133	0.50	-0.96–1.94	0.234	0.78	-0.64 – 2.3	0.457**	0.64**	0.37 - 0.90
Test of Equality	F (3,114) = 1.25, p = 0.3			F (3,113) = 2.36, p = 0.08			F (3,106) = 1.09, p = 0.36			F (3,114)= 0.35, p = 0.79		

Somatization	*rho*	*β*	*95% CI*	*rho*	*β*	*95% CI*	*rho*	*β*	*95% CI*	*rho*	*β*	*95% CI*
No FSS	0.449*	0.88*	0.26 – 1.62	0.629**	2.26**	1.58 – 3.63	0.417	1.26	-0.1 – 2.87	0.569*	0.54**	0.26 - 0.91
FGID Only	0.522*	1.83*	0.63 –3.39	0.413	2.77*	0.18–4.56	0.451	2.14	-0.54–4.17	0.226	0.24	-0.27 - 0.52
Extra-GI Only	0.551**	0.98*	0.26 – 1.76	0.378*	1.17*	0.06-2.14	0.288	0.67	-0.59 – 1.94	0.669**	0.63**	0.38 - 0.92
FGID and extra - GI	0.447**	0.99	0.07 – 2.49	0.213	0.98	-0.69 – 2.3	0.293	1.15	-0.54 – 2.46	0.525**	0.78**	0.51 – 1.16
Test of Equality	F (3,109) = 0.53, p = 0.66			F (3,108) = 1.4, p = 0.25			F (3,101) = 0.32, p = 0.81			F (3,109)=1.25, p = 0.3		
Visceral Specific Anxiety	*rho*	*β*	*95% CI*	*rho*	*β*	*95% CI*	*rho*	*β*	*95% CI*	*rho*	*β*	*95% CI*
No FSS	.605**	.47**	.23 - .68	.259	2.26**	1.58 – 3.63	.417	1.26	-.1 – 2.87	0.569*	0.54**	0.26 - 0.91
FGID Only	.134	.13	-.54 - .67	-.102	2.77*	.18–4.56	.451	2.14	-.54–4.17	0.226	0.24	-0.27 - 0.52
Extra-GI Only	.392*	.38**	.11 - .57	-.144	1.17*	.06-2.14	.288	.67	-.59 – 1.94	0.669**	0.63**	0.38 - 0.92
FGID and extra - GI	.508**	.55**	.26 - .85	.407*	.98	-.69 – 2.3	.293	1.15	-.54 – 2.46	0.525**	0.78**	0.51 – 1.16
Test of Equality	F (3,113) = 1.09, p = 0.36			F (3,108) = 2.33, p = 0.08			F (3,105)=1.77, p = 0.16			F (3,113) =1.1, p = 0.36		
Kinesiophobia	*rho*	*β*	*95% CI*	*rho*	*β*	*95% CI*	*rho*	*β*	*95% CI*	*rho*	*β*	*95% CI*
No FSS	-0.202	-0.16	0.86 - 0.35	0.096	0.36	-0.25 - 0.91	0.012	-0.1	-0.82 - 0.51	0.212	0.07	-0.09 - 0.23
FGID Only	0.185	0.18	-1.03 –1.24	0.028	-0.17	-1.12-0.79	-0.062	0.11	-0.64 - 0.88	0.182	0.03	-0.14 - 0.15
Extra-GI Only	0.332	0.26	-0.36 - 0.86	0.280	-0.2	-0.61 - 0.21	-0.132	-0.24	-0.69 - 0.15	0.213	0.08	-0.07 - 0.22
FGID and extra - GI	-0.203	-0.33	-0.99 - 0.30	0.186	0.64*	0.14 –1.14	0.472**	0.61	-0.08 – 1.18	0.392*	0.19*	0.03 - 0.37
Test of Equality	F (3,109) = 2.0, p = 0.16			F (3,108) = 0.27, p = 0.84			F (3,101) = 0.26, p = 0.85			F (3,109)=0.2, p = 0.9		
Pain Catastrophizing	*rho*	*β*	*95% CI*	*rho*	*β*	*95% CI*	*rho*	*β*	*95% CI*	*rho*	*β*	*95% CI*
No FSS	0.052	0.10	-0.32 - 0.39	0.251	0.96*	-0.31– 1.68	0.292	0.95*	0.02 – 1.99	0.205	0.01	-0.42 - 0.32
FGID Only	-0.151	-0.10	-0.93 - 0.65	-0.173	-0.29	-1.84 – 1.72	0.117	0.06	-1.10 – 1.63	0.412	0.12	-0.18 - 0.33
Extra-GI Only	0.035	0.06	-0.37 - 0.42	0.310	0.69	-0.38 – 1.83	0.339	0.23	-0.94 – 1.53	0.287	0.23*	0.03 - 0.44
FGID and extra - GI	0.053	0.10	-0.27 - 0.63	0.287	0.65	-0.12–1.29	0.293	1.1*	0.11 – 2.04	0.128	0.01	-0.35 - 0.35
Test of Equality	F (3,114) = 0.1, p = 0.92			F (3,110) = 1.21, p = 0.31			F (3,103) = .42, p = 0.74			F (3,111)= 2.03, p = 0.11		

Note: ** $p < .005$, * $p < .05$, B = Beta Co-efficient, rho = Spearman Correlation Coefficients

The precision of the relationship between psychological constructs and symptom burden measures. Hypothesis 1a is partially supported: The degree of associations between psychological constructs and symptom burden measures were identified as being substantially invariant with disorder grouping, in many cases including the no FSS group. The most consistent of these psychological constructs involved somatization. Spearman correlations associated with all GI and extra-GI symptom burden measures were quite similar. Majority of these correlations were between *rho* = 0.3 - 0.5 across disorder groups, however due to outliers, the full range was *rho = 0.2 -0.7* and β = 0.2 – 2.8. Another common pattern identified was that the association of the burden of GI and fatigue with a number of psychological constructs, e.g. Neuroticism and anxiety were quite similar across disorder groups. There were however a number of association that did appear to vary across disorder groups such as depression and somatic pain intensity (see Table 3).

The effect size of the relationship between psychological constructs and symptom burden measures. To determine the consistency of effect size between psychological factors and symptom burden (hypothesis 1b), the interaction between the psychological constructs and disorder groups in a regression model predicting a symptom burden measure was tested (see table 3). If the interaction is not statistically significant then we cannot differentiate between disorders with respect to the effect size of the relationship between psychological constructs and symptom burden.

Hypothesis 1b was substantially supported since in only one case did the effect size differ between disorder groups, this was for depression and somatic pain intensity (F (3,113) = 2.9, p-value = 0.04) (see table 3). This interaction is displayed on a scatter plot (see figure 3) and shows a strongly positive correlation within the No FSS participants, compared to a modernly negative correlation within the FGID only participants, minimal positive correlation with the extra-GI only participants and a moderate positive correlation within the combined FGID and extra-GI participants. However, once the no FSS group is omitted from the omnibus test, this interaction become clearly non-statistically significant; F(2, 86) = 0.92, p = 0.400.

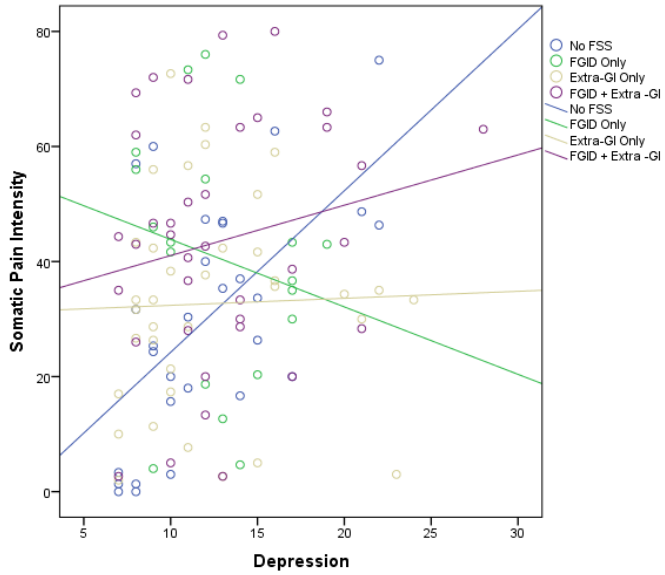

Figure 3. Depression – Somatic pain intensity scatter plot

This phenomenon of omitting the no FSS disorder group was implemented on all interactions of association with p-values less than 0.1, as a sensitivity analysis on the basis that the no FSS group suffer sub-syndromal levels of symptoms whose association with psychological constructs may be limited. The interaction of psychological constructs of anxiety and stress with somatic pain intensity became definitively non-significant; $F(2, 86) = 0.86$, $p = 0.4$ and ($F(2, 86) = 1.25$, $p = 0.29$), respectively. However, in the 4th case, visceral specific anxiety and somatic pain intensity, due to a strongly positive FGID + Extra- GI group, the interaction become marginally significant; $F(2,85) = 3.4$, $p = 0.04$.

The interaction of association between all other psychological constructs and GI and extra-GI symptom burden did not differ to a statistically significant extent between disorder groups. The similarity of correlations and effect sizes between psychological factors and GI as well as extra-GI symptom burden is most clearly illustrated by somatization and is displayed in scatter plots (see Figures 4 and 5). Somatization shows similar strengths of correlation and similar regression slopes for the GI and extra-GI symptom burden, regardless of disorder group and is supportive of Hypothesis 1b.

This suggests there is no clear evidence of a difference between disorder groups with respect to the effect size of the association between psychological constructs and GI or extra-GI symptoms burden.

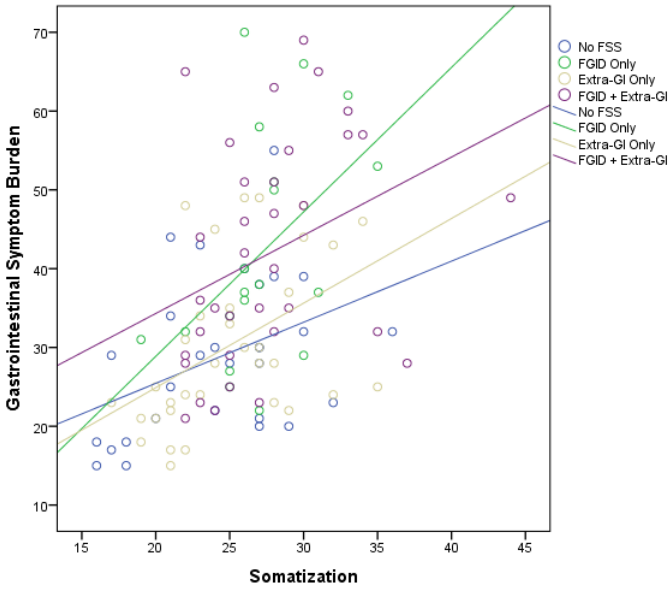

Figure 4. Somatization – Gastrointestinal symptom burden scatter plot

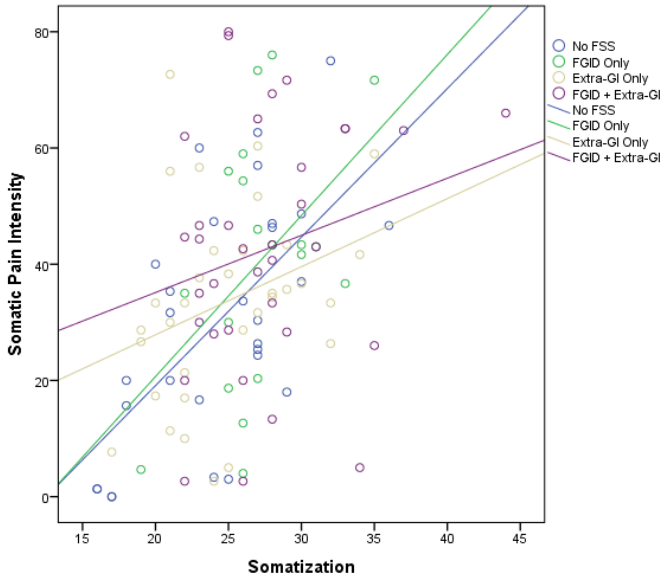

Figure 5. Somatization – Somatic pain intensity scatter plot

Results for Aim 2

Quality of Life. Descriptive statistics of the SF12 determined the health specific QoL experienced throughout the sample. Mean T score values, stratified by disorder group is displayed on a clustered bar chart (see Figure 6). The mental health component summery and vitality health domain are identified as being lower than that of a normative population (mean 50, SD 10) (Maruish, 2012). However, when compared between disorder groups no difference in QoL was identified.

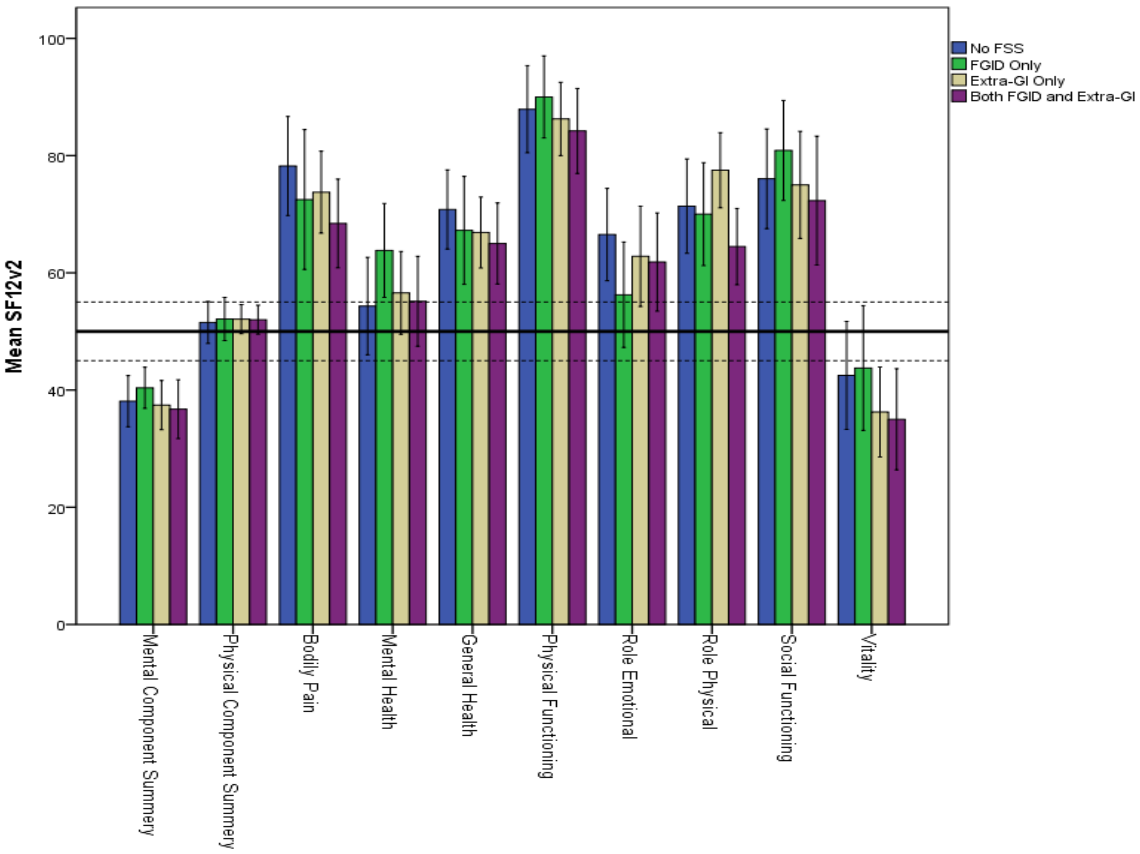

Figure 6. SF12v2 Quality of Life

Kruskal-Wallis tests were implemented to determine if there were any differences in health specific QoL between GI and extra-GI disorder groups. Hypothesis 2a was supported as no significant differences in Physical ($H(3) = 0.199$, $p = 0.978$) or Mental ($H(3) = 0.652$, $p = 0.884$) component summaries are noted between disorder groups. This suggests a similar level of QoL exists within both FGID and extra-GI disorders, irrespective of FSS diagnosis.

Chronic Somatic Pain Symptom Burden. The distribution of somatic pain scores of the sample is displayed through a cluster bar chart (see Figure 7). All disorder groups experienced varying levels of chronic pain symptom burden. All disorder groups experience some level of chronic pain and the greatest somatic pain distribution was noted in the combined FGID + extra-GI group. Kruskal – Wallis testing was implemented to determine any differences in somatic pain symptoms between GI and extra – GI disorder groups. Hypothesis 2b is supported with no significant differences of somatic pain symptom burden between disorder groups $H(3) = 4.75$, $p = 0.191$. This suggests a similar level of somatic pain exists within all disorders, irrespective of FSS diagnosis.

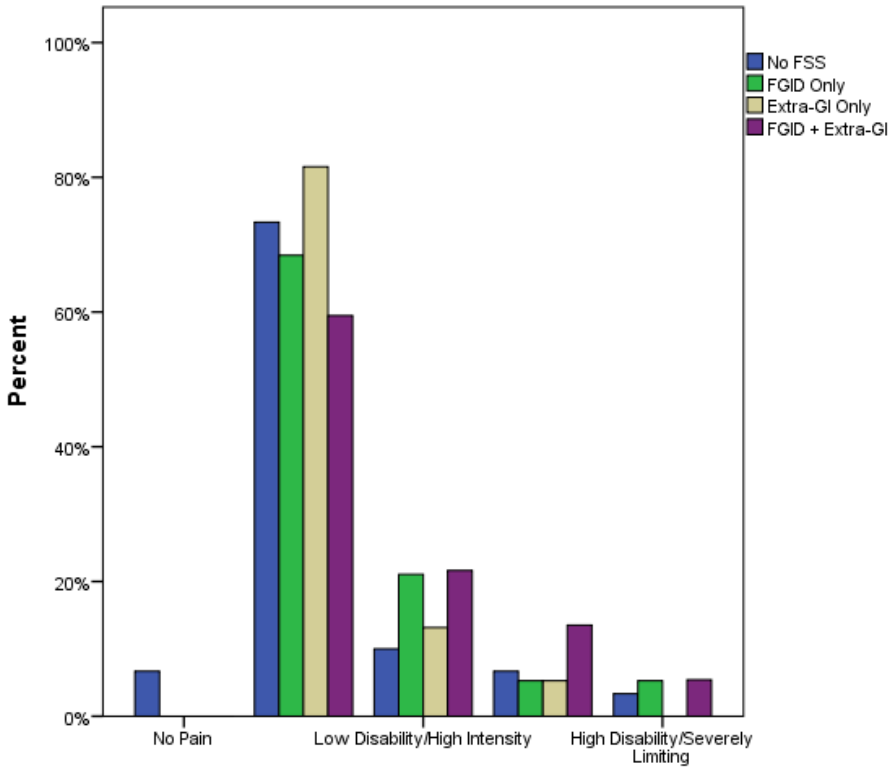

Figure 7. Chronic Somatic Pain Symptom Burden

Gastrointestinal Symptom Burden. Gastrointestinal symptom burden was determined using the Gastrointestinal symptom Rating Scale (GSRS) and the overall mean of the whole data set was 35.5 (*SD* = 13.8). An error bar chart, stratified via disorder group, displays the GSRS subscales (see Figure 8). Both FGID and combined FGID and extra-GI groups yielded the highest means in each subscale syndrome. Indigestion and Constipation account for the highest syndromes across the sample and there was a similar level of GI symptom burden between the No FSS and extra-GI only disorder groups, throughout all GI syndromes.

Kruskal - Wallis testing was implemented to determine whether any differences in GI symptom burden exist between FGID and extra-GI disorder groups. Hypothesis 2c was not supported as there was a significant difference in GSRS scores between disorder groups, $H(3) = 22.06$, $p < 0.001$. No FSS ($r = 46.28$) individuals showed significantly lower GSRS scores than FGID individuals (adjusted $p = 0.011$, $r = 78.55$) and combined FGID and extra-GI individuals other group (adjusted $p = 0.002$, $r = 77.38$). In addition, the extra-GI only group (r = 48.86) showed significantly lower GSRS scores than the FGID only individuals (adjusted p = 0.018, r = 29.69) and combined FGID and extra-GI individuals (adjusted p = 0.003, r = -28.52).

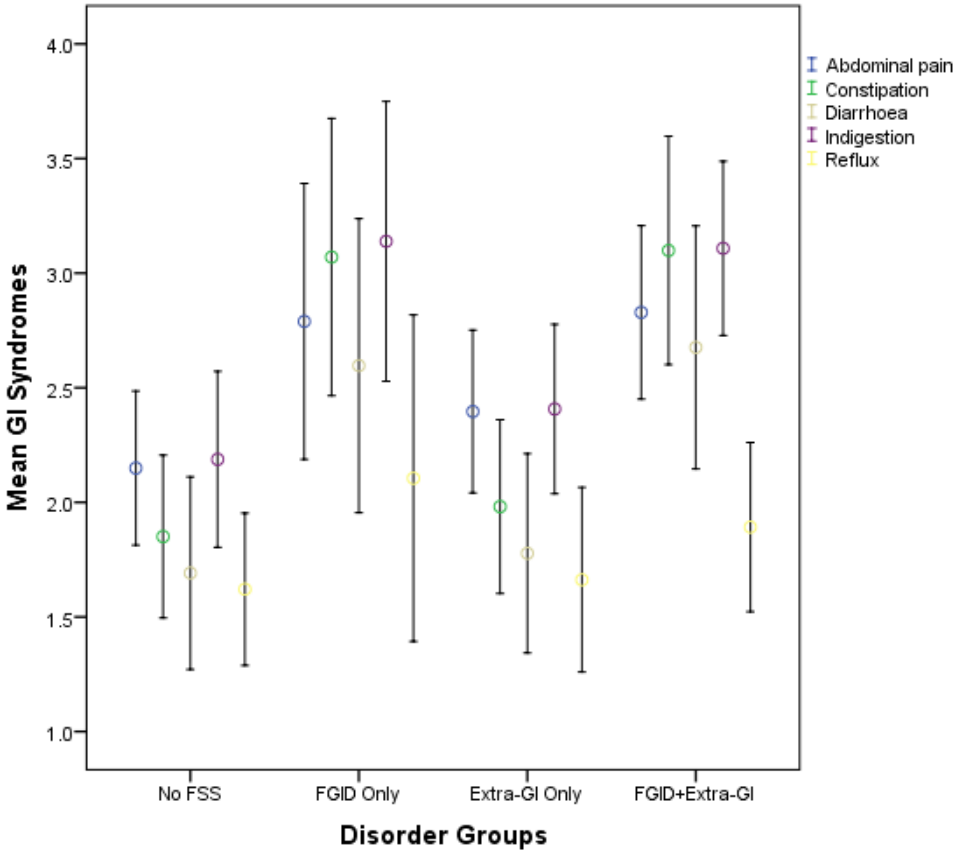

Figure 8. Gastrointestinal Symptom Burden

Fatigue Symptom Burden. Fatigue symptom burden was determined using the Chalder fatigue scale and the overall mean of the whole data set was 19.38 (SD 5.34). Similar levels of fatigue were noted in both FGID and extra-GI disorder groups (19.20, SD 5.17). This relationship is displayed on an error bar chart (see Figure 9). Kruskal-Wallis tests were implemented to determine there was any difference in fatigue symptom burden between FGID and extra-GI disorder groups. Hypothesis 2d was supported with was no significant differences in fatigue symptom burden between disorder groups, $H(3) = 4.034$, $p = 0.258$. This suggests a similar level of fatigue exists within all disorders, irrespective of FSS diagnosis.

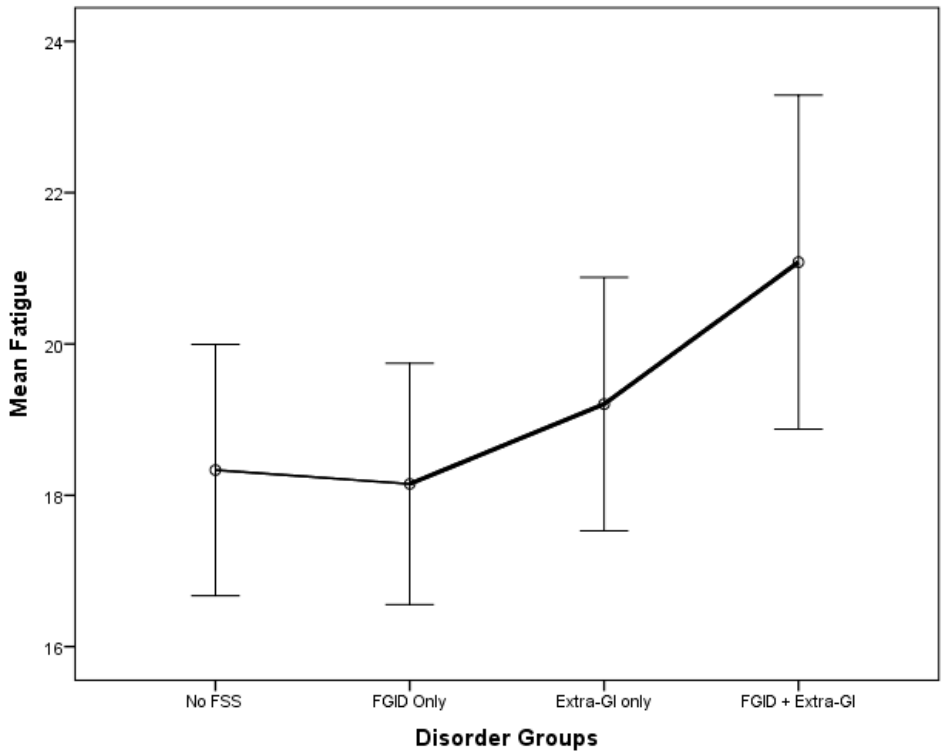

Figure 9. Fatigue Symptom Burden

Results for Aim 3

In order to extend hypothesis 1, this aim evaluates whether a common but complex path model applies to both GI and extra-GI populations. A path analysis is equivalent to fitting number of multiple linear regressions simultaneously. This process can be utilized to determine whether a set of data supports our a priori model concerning psychological associations with symptom burden, although it cannot be used to make definitive casual statements.

The results of the path analysis (n=109: due to removal of incomplete data) of the whole data set is shown in Figure 10. The FGID and extra-GI population path models can be found in Appendix D. Standardized path coefficients (Table 4) and model fit statistics (Table 5) of the three path analyses were tabulated to evaluate the consistency of a psychological pathway for the FSS populations. All the pathways supported by the correlational analysis remain significant and more importantly the consistency of the path coefficients between FSS populations remain similar (see table 4). This supports the idea that psychological constructs, from trait features, such as neuroticism into more state constructs of negative affect and somatization, influence both GI and extra-GI symptomatology in a similar fashion. Hypothesis 3 is supported with a path model evaluating the psychological involvement in GI and extra-GI symptoms is consistent in differing FSS populations.

Table 4

Path Coefficients of whole data set, FGID population and extra-GI population

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	Whole sample (n=109)	FGID Population (n=53)	Extra – GI Population (n=63)
Neuroticism > Negative Affect	0.742**	0.815**	0.791**
Negative Affect > Somatization	0.596**	0.544**	0.676**
Somatization > GI Symptoms	0.459**	0.379 *	0.594**
Somatization > Fatigue	0.543**	0.537**	0.594**
Somatization > Somatic Pain Intensity	0.420**	0.294*	0.313*
Somatization > Somatic Pain Disability	0.295*	0.297*	0.291*

*Note: **=p<0.005, *=p<0.05*

Table 5

Model Fit Statistics of Whole Data Set, FGID population and extra-GI population

	Whole Data Set (n=109)	FGID Population (n=53)	Extra – GI Population (n=63)
Chi Square / DF (p)	20.017 / 14 (.130)	20.640 / 14 (.111)	23.279 / 14 (.056)
Chi Square / DF Ratio	1.430	1.474	1.663
CFI	0.979	0.955	0.955
RMSEA	0.063	0.096	0.103

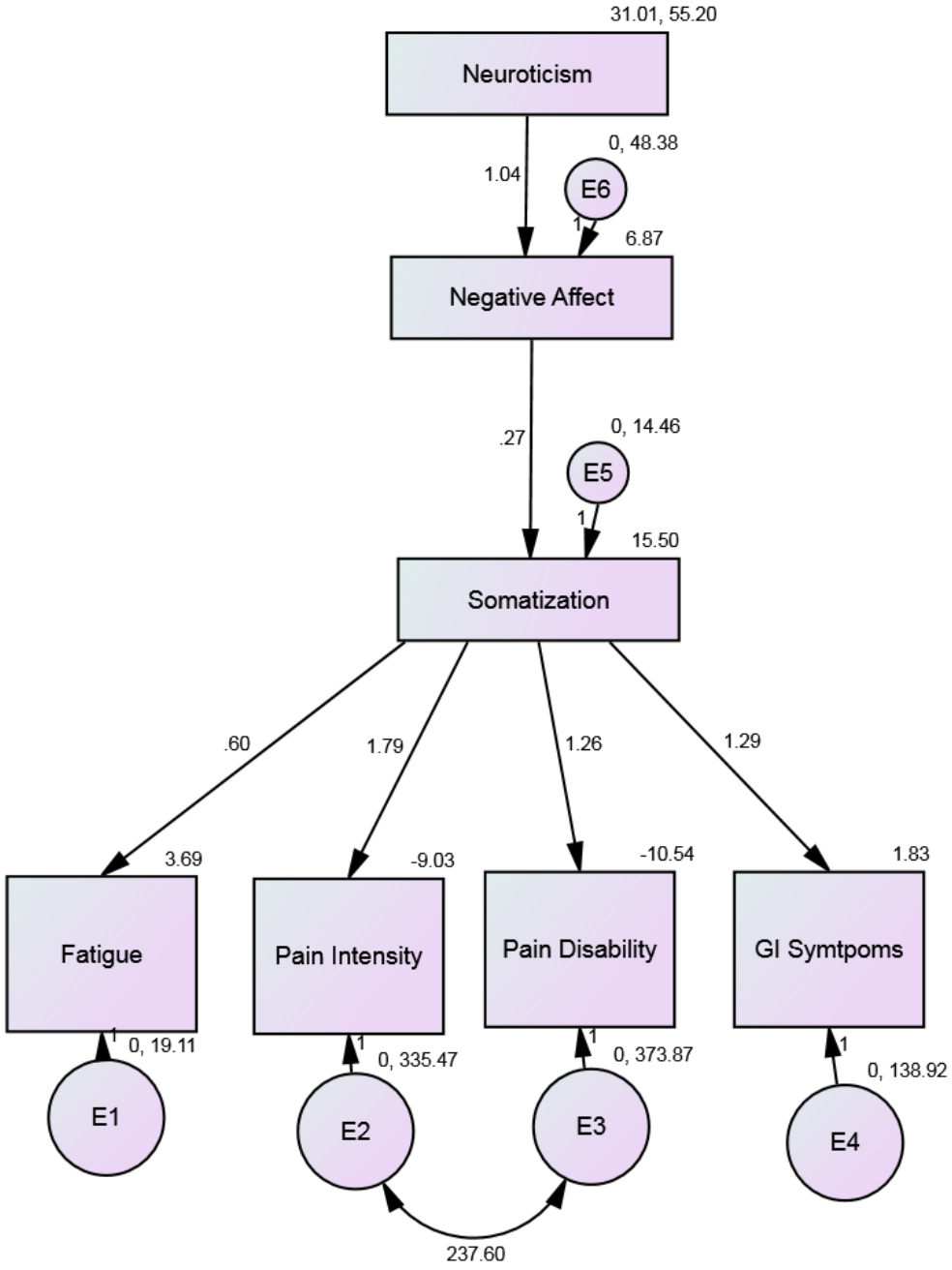

Figure 10. Path Model: Whole Data Set. $\chi 214=20.017$, p=.130, CMIN/df=1.430. CFI=0.979, RMSEA=0.063.

Results for Aim 4

The overlapping prevalence of FGIDs and a spectrum of extra-GI disorders is outlined below (see Table 4). Cross tabulation of the diagnostic specific measures identified the number (n) and the subsequent percentage (%) of FSS overlap. The prevalence of FGIDs within extra-GI disorders was contrasted with the prevalence of extra-GI disorder within FGIDs. Table 4 shows the complexity of diagnostic overlap existing within the selected FSSs.

The overall overlap of GI and extra – GI syndromes is displayed as a Venn diagram (see figure 12). There is some invariance experienced due to non-comparability of the individual disorders (table 4) versus the overall syndromes (figure 11). In general, extra-GI syndromes are more commonly identified in FGIDs (see figure 11).

Hypothesis 4 is supported with significant overlap noted. Individually, the greatest overlap is identified in the end spectrum somatic complaint of FMS, as 100% (n=3) had a FGID. This is concurrent with the literature describes in Table 1, however the prevalence of FMS in FGIDs is relatively smaller, 7%, compared to 32% (Sperber & Dekel, 2010). The overlap with chronic localized pain is greater than that identified in the literature; more than 50% of all low back pain, neck pain or headache suffers experienced a co-morbid FGID.

Table 6

Overlapping Prevalence of FGID and extra-GI disorders

	Prevalence of FGID in patients with the disorder n (%)	Prevalence of the disorder in patients with FGID n (%)
FMS	3 / 3 (100%)	3 / 43 (7%)
CFS	6 / 9 (67%)	6 / 57 (11%)
Chronic Widespread Pain	6 / 9 (67%)	6 / 26 (23%)
Chronic Localized Pain		
Low Back Pain	20 / 37 (54%)	20/58 (35%)
Neck Pain	23 / 45 (51%)	23 /58 (40%)
Headache	31 / 54 (58%)	31 / 58 (53%)

Note: FMS = Fibromyalgia syndrome, CFS = Chronic Fatigue Syndrome

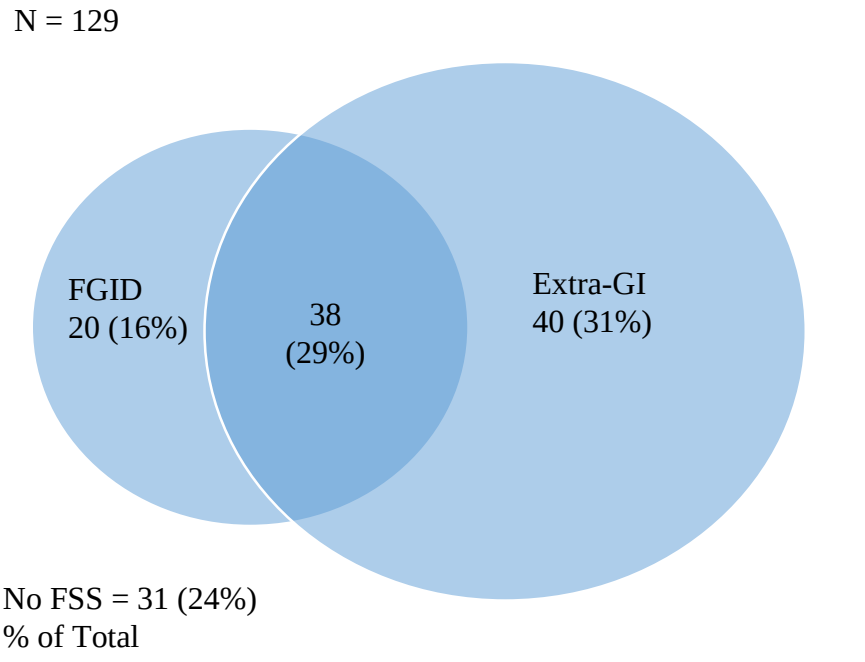

Figure 11. Venn diagram of the overlapping prevalence of FGIDs and extra-GI disorder

Chapter 4: Discussion

Discussion

The current study sought to test the specificity of the relationship between psychological variables and the symptom burden of gastrointestinal (GI) and extra-GI disorders. Past research has demonstrated a strong association between negative psychological phenomena and functional gastrointestinal disorder (FGID) symptom burden (Drossman et al., 1999); however, the present study has demonstrated that similar relationships apply outside the GI tract. Negative psychological aspects of personality, mood, somatization and dysfunctional cognitions were associated with both GI and extra-GI symptom burden, and importantly the precision of relationship and consistency of effect sizes, with respect to regression slopes, was independent of the type of functional somatic syndrome (FSS). These results suggest a common theme of psychological involvement throughout all selected FSSs and has important implications regarding the pathophysiology of these apparently non-organic disorders. This study presents empirical evidence suggesting the co-existence of GI and extra-GI disorders is beyond chance and may share common psychological mechanisms. The study further provides evidence, although not proof, that FGIDs and other FSSs fall on a diagnostic continuum, rather than separate clinical entities, and has helped to deconstruct the psychological nature of FGIDs and other FSSs.

Psychological involvement in FGIDs and other FSSs

Aims 1 and 3 of the present study explored the relationships between psychological factors and GI and extra-GI symptom burden, first by identifying the associations in simple bivariate analyses, and then by exploring the possible pathways to symptom burden using more complex path modeling. The relationship between psychological state and GI and extra-GI symptoms have historically been examined in isolation of one another (Lane, Manu, & Matthews, 1991; Levy et al., 2006; Simons et al., 2014), potentially omitting key factors influencing FSS symptom burden. The current study identified that negative psychological phenomena, in particular somatization and neuroticism, have a similar influence on both GI and extra-GI symptom burden with respect to the correlation and consistency of effect sizes of regression slopes. This questions the specificity of the psychological involvement and expands the current understanding of the biopsychosocial profile of FSSs.

Somatization: The key link? Somatization is a tendency to experience physical symptoms as a manifestation of psychological distress (Lipowski, 1988). In the current study, somatization was more consistently strongly positively associated with GI, somatic and fatigue symptoms, compared to the other psychological constructs. The literature has shown levels of somatization to be higher in FGIDs (van Tilburg, Palsson, & Whitehead, 2013), chronic fatigue (Martin et al., 2007) and chronic somatic pain (McBeth et al., 2001), as well as predictive of a greater symptom burden. The attachment of disproportionate distress to a spectrum of normal or sub-clinical physiological sensations,

such as abdominal distension or spinal movement, may perpetuate the symptomatology experienced in the selected FSSs and is consistent with central sensitization (CS).

CS is identified in the pain neuromatrix and 'brain-gut' axis as an increase in excitation and synaptic efficacy in central nociceptive pathways with an associated increase of sensory processing areas (e.g. prefrontal cortex, thalamus, insula), enhanced cognitive and affective regions (e.g. anterior cingulate cortex) and limbic and para limbic regions (e.g. amygdala) (Mayer et al., 2006; Moseley, 2003). The current study shows that in all selected FSSs, the construct of somatization represents a potential manifestation of the aberrant neuro-psychological involvement within CS.

In the present study, individuals classified as non-FSS (i.e., who did not meet criteria for FGIDs, FMS, CFS chronic localized pain) demonstrated similar associations between symptom burden and psychological state as the FSS individuals: For example, in all disorder groups, increased somatization predicted greater symptom burden. We would have thought that for the non-FSS individuals, (1) level of symptom burden would have been lower, and (2) symptom burden would not have predicted increased psychological distress as strongly compared to FSS participants. Thus, whilst the presence of these negative psychological constructs strongly predicts greater symptom burden in FSS sufferers, they similarly predict symptom burden in sub-syndromal individuals. This is a novel contribution in terms of the role of psychology in the diagnosis of non-organic disease. While a clinical diagnosis of a FSS can provide legitimacy to and a perceived 'road to recovery' for patients, the poor treatment options, respect and understanding of

FSSs within healthcare generally leads to negative health outcomes (Undeland & Malterud, 2007). The current study presents a comprehensive biopsychosocial picture of the symptomology experienced in FGIDs and other FSSs, stressing greater cross-collaboration and exploration into inherently separate clinical entities is necessary and beneficial.

Aim 3 sought to test a model that proposed that trait psychological constructs (e.g. Neuroticism) influence GI and extra-GI symptomatology via more health specific state constructs (e.g., somatization). The data demonstrated that somatization plays an important role in explaining how neuroticism and negative affect predict symptom specific disability, regardless of a FSS classification.

Given our results showed that the combined GI and extra-GI participants experience a greater level of symptom burden compared to that of the other disorder group (Aim 2), we would expect the combined FGID and extra-GI individuals to similarly experience greater psychological co-morbidity. However, this was not the case. The FGID and extra-GI group did not show greater levels of somatization when compared to the other disorder groups. The additive effects of multiple FSS did not influence the psychological co-morbidity. While it is easy to assume multiple illness states predicts a greater psychological co-morbidity, the current study suggest those further down on a hypothesized spectrum of symptom co-morbidity experience the similar levels of somatization.

Maladaptive Psychology and Intensity of Somatic Pain. While Hypothesis 1 was generally supported, with respect to a similar a) strength of correlation and b) effect size of regression slopes, the interaction between four psychological variables (depression, anxiety, stress and visceral specific anxiety) with somatic pain intensity was marginally significant (statistical significance levels of less 0.1), which is counter to the hypothesis. When the No FSS group was omitted from the analyses, however, 3 of 4 interactions became clearly non-significant. Thus, for those with a FSS, increasing negative mood (depression, state anxiety and stress) predicts increased intensity of pain to a similar degree, regardless of where specifically that pain is experienced.

Regarding the fourth case (visceral specific anxiety), due to a strongly positive regression slope in the comorbid GI and extra-GI group, this interaction reached statistical significant. This inconsistency was only identified with somatic pain intensity and demonstrates the subjective nature of self-reported intensity of pain, compared to GI, fatigue or somatic pain disability symptom burden. No previous research has looked at somatic pain intensity and visceral specific anxiety in GI or extra-GI populations and our results suggest that no association exists, except for a positive correlation in the co-morbid disorder group. While these results need to be interpreted with caution given the small sample sizes (n = 133) this could mean that GI specific anxiety may influence the experience of non-GI pain. Despite potential difference in visceral specific anxiety, on the whole, the role of maladaptive psychological was largely similar across FSS disorder groups.

Overlapping prevalence of symptom burden and clinical diagnoses

Aims 2 and 4 explored the symptom burden and diagnostic overlap experienced in our sample. The co-occurrence of GI and extra-GI symptoms was highly prevalent within all disorder groups. In addition, clinical overlap was common, with 39% of those with a FSS meeting the criteria for both an FGID and extra-GI disorder. These aims provided further evidence, although not proof, that FGIDs and other FSSs are on a diagnostic continuum, rather than separate clinical entities. While this concept is not new (Wessely et al., 1999), the trend, clinically and within the literature, to focus solely on the bodily system to which the symptoms are expressed, represents a key weakness in understanding these complex functional diseases.

FGID and other FSS Symptom Burden. It was predicted that the combined FGID and extra-GI disorder group, who represent those further on a hypothesized spectrum of severity, would experience a larger symptom burden. Descriptive statistics (see Figures 9, 10 and 11) support this augment, as this combined disorder group experienced a great level of chronic somatic pain, GI and fatigue symptoms burden. In addition, contrast testing revealed that those in the combined FGID and extra-GI disorder group experienced a greater level of GI symptom burden compared to those without a FGID status. This addresses the additive effects of multiple FSSs and may be a result of CS. A widespread consequence of CS may indirectly lead to a greater experience of symptoms from a site irrespective of the initial stimuli driving a sensitized central

nervous system. This information can educate clinicians and researcher alike, in understanding why suffers of multiple FSSs, may experience a greater severity.

FGID and other FSS overlap. The current study identified that diagnostic overlap of FGIDs and extra-GI disorders is common, which is consistent with the literature (Whitehead. et al., 2002). While our lack of sample size limits the generalizability of our results, there is some evidence extra-GI syndromes are commonly identified in FGIDs. Understanding those with a FGIDs have a high probability of experiencing co-morbid extra- GI syndromes, will translate into a greater consideration for the biopsychosocial process influencing the symptomatology. Appreciating the extensive co-morbidity will lead to more holistic and coordinated treatment options for those living with these debilitating diseases.

Limitations

While the results of the present study are promising, there are certain methodological limitations that need to be addressed. As outlined earlier, the diagnosis of a FSS, in particular FGIDs, chronic pain and chronic fatigue syndrome, is usually accompanied by a physical examination and rigorous investigations to exclude organic pathology. The recruitment from the psychology student pool asked participants for a history of any organic GI disease in order to exclude organic pathology, however as an examination by a physician was not feasible, undiagnosed organic explanations for symptom burden cannot be excluded. In addition, the recruitment from the chiropractic and specialist gastroenterology clinics screen participants for organic illness in their

specialty, they did not account for the co-morbidity of a functional syndrome with an organic disease (e.g. chronic non-specific low back pain and coeliac disease). However, even if some of the participants do have an organic cause of their symptoms, statistics show that the majority do not or this would most likely be a small proportion of the sample. Suffers from organic GI (e.g. Crohn's Disease) and extra-GI illness (e.g. rheumatoid arthritis) experience less psychological distress and show little evidence for psychosocial correlates as compared to their functional counterparts (Drossman et al., 2000; Walker et al., 1997). Thus, the possible inclusion of organic illness suffers may have weakened the investigated associations, leading to potential missing effects and underestimations of relationships, and do not undermine the results found.

Given the extensive nature of the questionnaire and number of variables measured, the study initially aimed to recruit a sample size of 246 participants to address the current aims. Unfortunately though recruitment was slower than expected and due to the time sensitive nature of the Master of Research program, a smaller than anticipated sample was used.

Strengths, Implication and directions for Future research

Despite these limitations, the results of the current study contribute novel findings to the understanding of the psychological factors influencing the symptom burden of FGIDs and other FSSs. In addition, the consistency of psychological measures and disorder specific criteria ensures comparability of samples, which has been lacking in previous research. The pathway identified in the path analysis helps clarify our

understanding of the relationship between psychological factors and various symptoms, in the context of clinically distinct populations. While it necessary for future research to explore this relationship further, by both replicating and extending on the current study's findings, this study successfully demonstrated the commonality of the relevance of psychological distress to a range of physical symptom expressions with no underlying organic pathology, enhancing our understanding of psychosomatic disorders.

Whilst this study cannot speak to the directionality of this association (i.e., whether psychological factors create or exacerbate physical symptoms, or if physical symptoms lead to a change in psychology), it does provide a conceptual platform for future research to address a similar notion of incorporating a spectrum of FSSs in a prospective design. This will ascertain the specific psychological factors involved in the development of non-organic symptoms. Understanding the directionality of symptoms has important clinical consequences regarding the specificity of treatments (e.g., Cognitive Behavioral Therapy for brain-directed symptom burden).

Conclusion

The current study has tested the specificity of aspects of the "brain-gut" axis and hypothesized that it is an extension of other established neurobiological models such as CS and the pain neuromatrix. Substantial similarities were identified with respect to the association of psychological constructs with FGIDs and extra-GI symptom burden, within multiple FSSs. Such findings are supportive of the biopsychological model proposed by Engel (1981), suggesting psychological factors are central to the experience

of symptomatology within FGIDs and other FSSs. At present FSSs represent a poorly understood, costly and debilitating burden on society (Jackson & Kroenke, 2008). Re-conceptualizing these syndromes as a particular point on a FSS spectrum, rather than separate clinical entities, will have an immense impact on both the understanding and treatment of these conditions.

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Appendix A:

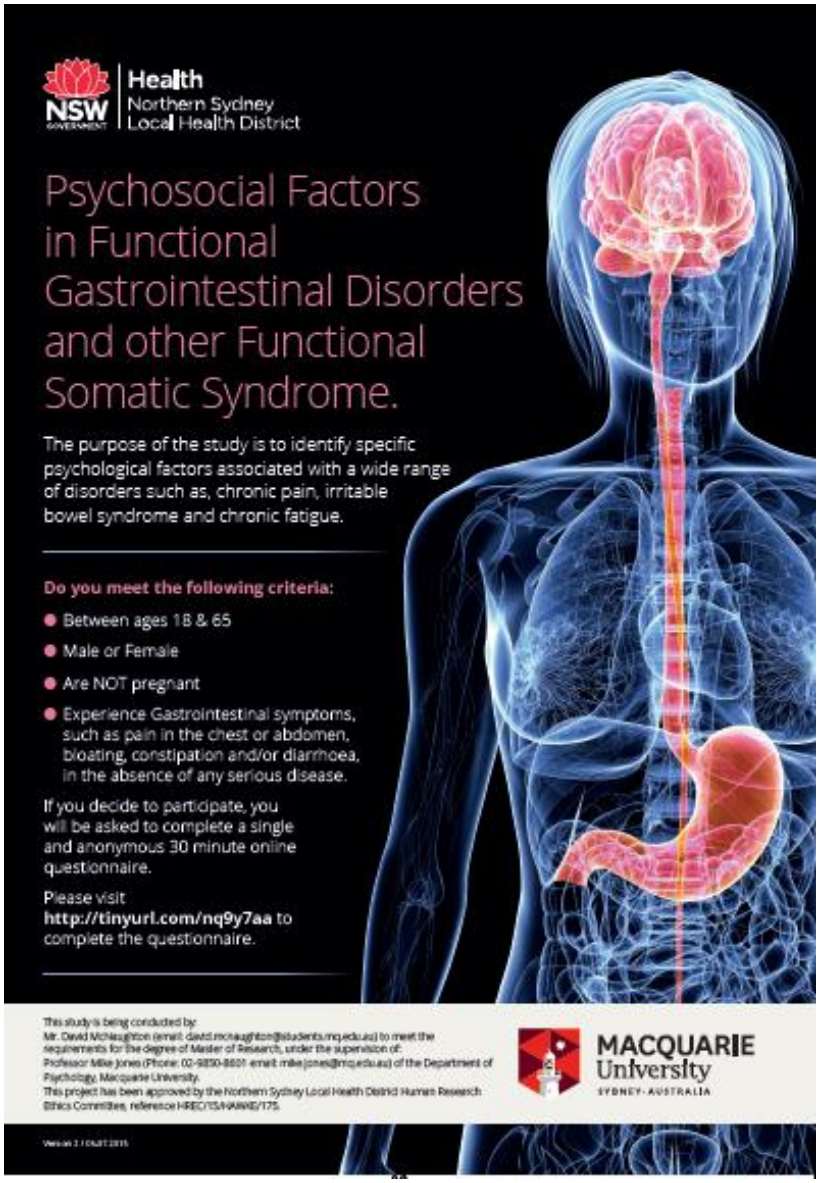

Figure 12. Gastrointestinal symptom Recruitment Flyer

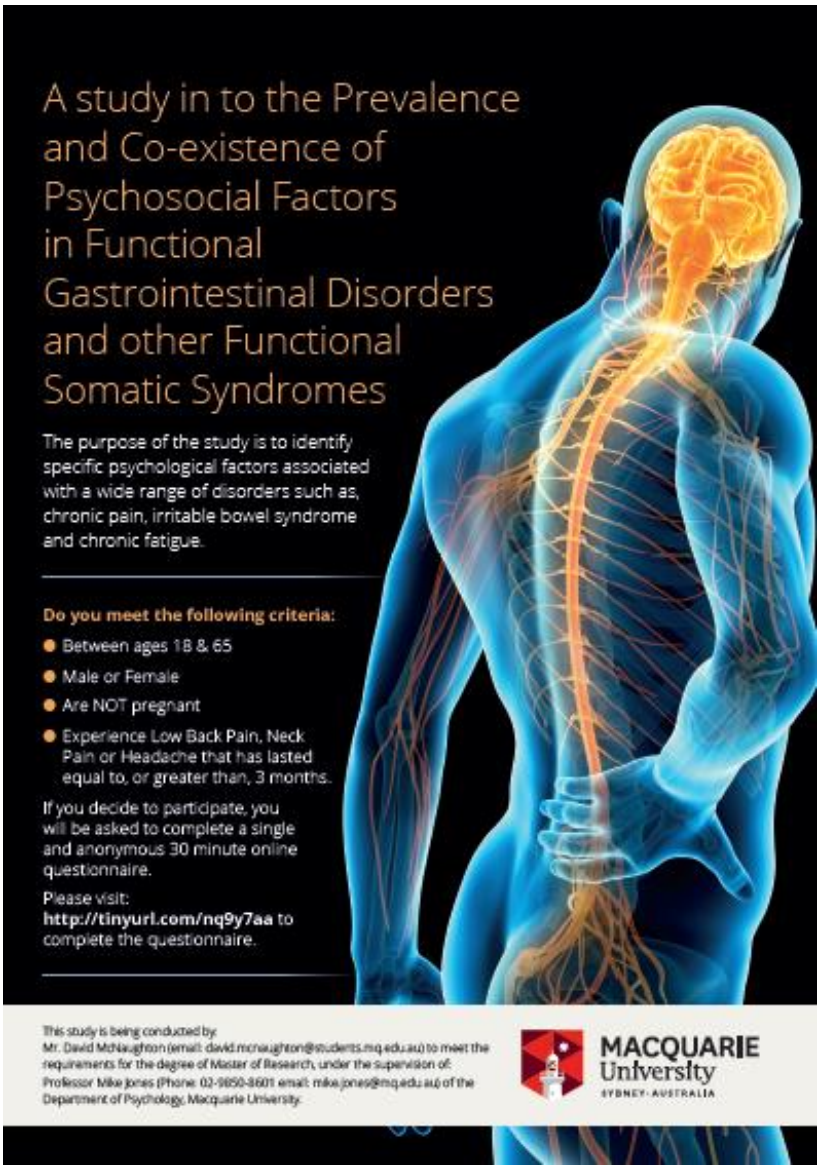

Figure 13.. Gastrointestinal symptom Recruitment Flyer

Appendix B:

Rome III Pre-screener Questionnaire (Drossman, 2006)

1. In the last 3 months, how often did you have discomfort or pain anywhere in your abdomen?

Never

Less than one day a month

One day a month

Two to three days a month

One day a week

More than one day a week

Every day

2. In the last 3 months, how often did you have pain or discomfort in the middle of your chest (not related to heart problems)?

Never

Less than one day a month

One day a month

Two to three days a month

One day a week

More than one day a week

Every day

3. In the last 3 months, how often did you feel uncomfortably full after a regular- sized meal?

Never

Less than one day a month

One day a month

Two to three days a month

One day a week

More than one day a week

Every day

4. In the last 3 months, how often were you unable to finish a regular size meal?

Never

Less than one day a month

One day a month

Two to three days a month

One day a week

More than one day a week

Every day

5. In the last 3 months, how often did you have fewer than three bowel movements (0-2) a week?

Never or rarely

Sometimes

Often

Most of the time

Always

In the last 3 months

6. How often did you have bothersome nausea?

Less than one day a Month

One day a month

Two to three days a Month

One day a week

More than one day a week

Every day

7. In the last 3 months, how often did you have bloating or distension?

Never

Less than one day a month

One day a month

Two to three days a month

One day a week

More than one day a week

Every day

8. In the last 3 months, how often did you have 3 or more bowel movements?

Psychosocial Factors in Functional Gastrointestinal Disorder

Never or rarely

Sometimes

Often

Most of the time

Always

Rome III Criteria IBS Module (citation) (Douglas A. Drossman, 2006)

In the last 3 months, how often did you have discomfort or pain anywhere in your abdomen?

Never

Less than one day a month

One day a month

Two to three days a month

One day a week

More than one day a week

Every day

2. For women: Did this discomfort or pain occur only during your menstrual bleeding and not at other times?

No

Yes

Does not apply because I have had the change in life (menopause) or I am a male

3. Have you had this discomfort or pain 6 months or longer?

No

Yes

4. How often did this discomfort or pain get better or stop after you had a bowel movement?

Never or rarely

Sometimes

Often

Most of the time

Always

5. When this discomfort or pain started, did you have more frequent bowel movements?

Never or rarely

Sometimes

Often

Most of the time

Always

6. When this discomfort or pain started, did you have less frequent bowel movements?

Never or rarely

Sometimes

Often

Most of the time

Always

7. When this discomfort or pain started, were you stools (bowel movements looser?

Never or rarely

Sometimes

Often

Most of the time

Always

8. When this discomfort or pain started, how often did you have harder stools?

Never or rarely

Sometimes

Often

Most of the time

Always

9. In the last 3 months, how often did you have hard or lumpy stools?

Never or rarely

Sometimes

Often

Most of the time

Always

10. In the last 3 months, how often did you have loose, mushy or watery stools?

Never or rarely

Sometimes

Often

Most of the time

Always

Appendix B: Questionnaires (Continued)

Rome III Criteria FD Module (Douglas A. Drossman, 2006)

1. In the last 3 months, how often did you have pain or discomfort in the middle of your chest (not related to heart problems)?

Never

Less than one day a month

One day a month

Two to three days a month

One day a week

More than one day a week

Every day

2. In the last 3 months, how often did you have heartburn (a burning discomfort or burning pain in your chest)?

Never

Less than one day a month

One day a month

Two to three days a month

One day a week

More than one day a week

Every day

3. In the last 3 months, how often did you feel uncomfortably full after a regular sized meal?

Never

Less than one day a month

One day a month

Two to three days a month

One day a week

More than one day a week

Every day

4. Have you had this uncomfortable fullness after meals 6 months or longer?

No

Yes

5. In the last 3 months, how often were you unable to finish a regular size meal?

Never

Less than one day a month

One day a month

Two to three days a month

One day a week

More than one day a week

Every day

6. Have you had this inability to finish regular size meals 6 months or longer?

No

Yes

7. In the last 3 months, how often did you have pain or burning in the middle of your abdomen, above your belly button but not in your chest?

Never

Less than one day a month

One day a month

Two to three days a month

One day a week

More than one day a week

Every day

8. Have you had this pain or burning 6 months or longer?

No

Yes

9. Did this pain or burning occur and then completely disappear during the same day?

Never or rarely

Sometimes

Often

Most of the time

Always

10. Usually, how severe was the pain or burning in the middle of your abdomen, above your belly button?

Very mild

Mild

Moderate

Severe

Very severe

11. Was this pain or burning relieved by taking antacids?

Never or rarely

Sometimes

Often

Most of the time

Always

12. Did this pain or burning usually get better or stop after a bowel movement or passing gas?

Never or rarely

Sometimes

Often

Most of the time

Always

13. How often was this pain or discomfort relieved by moving or changing positions?

Never or rarely

Sometimes

Often

Most of the time

Always

14. In the last 6 months, how often did you have steady pain in the middle or right side of your upper abdomen?

Never

Less than one day a month

One day a month

Two to three days a month

One day a week

More than one day a week

Every day

15. Did this pain last 30 minutes of longer?

Never or rarely

Sometimes

Often

Most of the time

Always

16. Did this pain build up to a steady, severe level?

Never or rarely

Sometimes

Often

Most of the time

Always

17. Did this pain go away completely between episodes?

Never or rarely

Sometimes

Often

Most of the time

Always

18. Did this pain stop you from your usual activities, or cause you to see a doctor urgently or go to the emergency department?

Never or rarely

Sometimes

Often

Most of the time

Always

Appendix B: Questionnaires (Continued)

Widespread Pain Index (WPI)(F. Wolfe, 2010)

Check each area you have felt pain in over the past week.

Shoulder girdle, left	Lower leg left	Abdomen	Lower arm, right
Shoulder girdle, right	Lower leg right	Neck	Hip (buttock) left
Upper arm, left	Jaw left	Upper back	Hip (buttock) right
Upper arm, right	Jaw right	Lower back	Upper leg left
Lower arm, left	Chest	None of these areas	Upper leg right

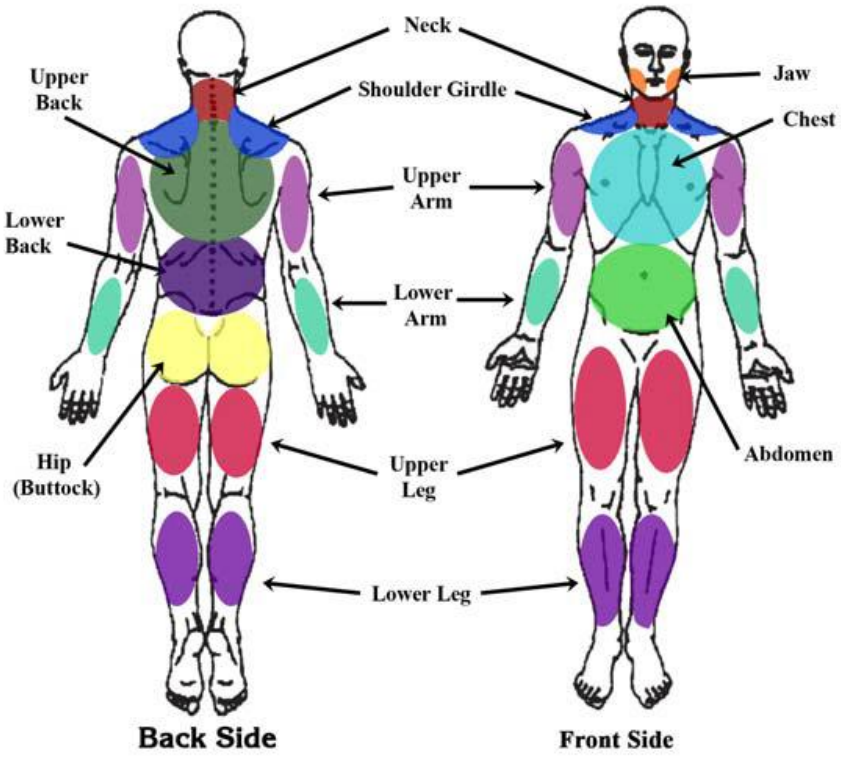

Figure 3. Mannequin depicting body regions. Freely available form google.

Psychosocial Factors in Functional Gastrointestinal Disorder

Symptom Severity Scale (SSS)(F. Wolfe, 2010)

Part A

Indicate your level of symptom severity over the past week using the following scale.

Fatigue

0 = No problem

1 = Slight or mild problems; generally mild or intermittent

2 = Moderate; considerable problems; often present and/or at a moderate level

3 = severe: pervasive, continuous, life disturbing problems

Waking unrefreshed

0 = No problem

1 = Slight or mild problems; generally mild or intermittent

2 = Moderate; considerable problems; often present and/or at a moderate level

3 = severe: pervasive, continuous, life disturbing problems

Indicate your level of symptom severity over the past week using the following scale.

Cognitive symptoms

0 = No problem

1 = Slight or mild problems; generally mild or intermittent

2 = Moderate; considerable problems; often present and/or at a moderate level

3 = severe: pervasive, continuous, life disturbing problems

Psychosocial Factors in Functional Gastrointestinal Disorder

Part B

Check each of the following OTHER SYMPTOMS that you have experienced over the past week?

Muscle pain	Dry mouth	Pain in upper abdomen	Numbness/tingling
Irritable bowel syndrome	Itching	Nausea	Dizziness
Fatigue/tiredness	Wheezing	Nervousness	Insomnia
Thinking or remembering problem	Raynauld's	Chest pain	Depression
Muscle Weakness	Hives/welts	Blurred vision	Constipation
Headache	Ringing in ears	Fever	Rash
Pain/cramps in abdomen	Vomiting	Diarrhea	Hair loss
Oral ulcers	Frequent urination	Heartburn	Loss of appetite
Loss/change in taste	Sun sensitivity	Dry eyes	Easy bruising
Seizures	Hearing difficulties	Shortness of breath	

Appendix B: Questionnaires (Continued)

Localized Somatic Pain Measures (modified for inclusion of Neck Pain and Headache)

(Dionne et al., 2008)

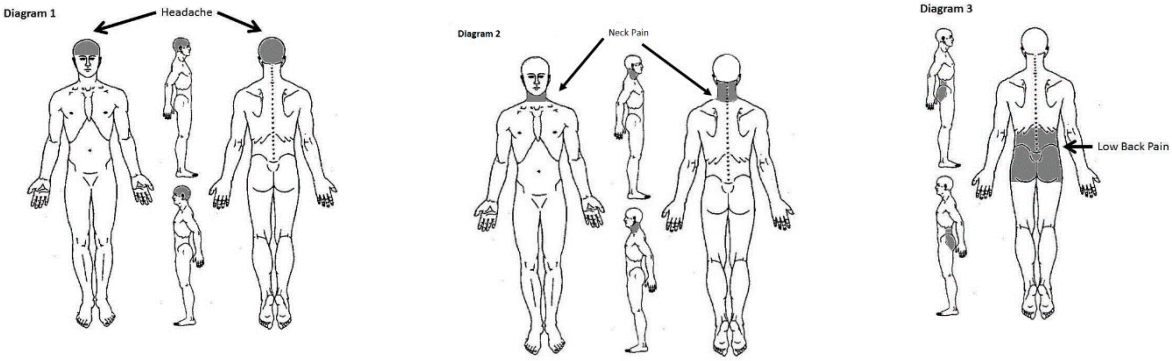

Figure 4. Modified mannequins depicting localized somatic regions. Source: freely available from Dionne, C. E., K. M. Dunn, P. R. Croft, A. L. Nachemson, R. Buchbinder, B. F. Walker, M. Wyatt, J. D. Cassidy, M. Rossignol, C. Leboeuf-Yde, J. Hartvigsen, P. Leino-Arjas, U. Latza, S. Reis, M. T. Gil Del Real, F. M. Kovacs, B. Oberg, C. Cedraschi, L. M. Bouter, B. W. Koes, H. S. Picavet, M. W. van Tulder, K. Burton, N. E. Foster, G. J. Macfarlane, E. Thomas, M. Underwood, G. Waddell, P. Shekelle, E. Volinn and M. Von Korff (2008). "A consensus approach toward the standardization of back pain definitions for use in prevalence studies." Spine (Phila Pa 1976) 33(1): 95-103.

These Questions are about Low back pain

In the past 4 weeks, have you had low back pain (area shown on the diagram)? Please to not report pain from feverish illness or menstruation

Yes (10

No (2)

If yes, was this pain bad enough to limit your usual activities or change your daily routine for more than one day?

Yes (1)

No (2)

If you had low back pain in the past 4 weeks, how long was it since you had a whole month without any low back pain? (Please tick only one box)

Less than 3 months (1)

3 months or more but less than 7 months (2)

7 months or more but less than 3 years (3)

3 years and more (4)

If you had low back pain in the past 4 weeks, please indicate what was the usual intensity of your pain on a scale of 0 to 10, where 0 means “no pain” and 10 means “the worst pain imaginable

0 1 2 3 4 5 6 7 8 9 10

Appendix B: Questionnaires (Continued)

Chalder Fatigue Scale (Chalder et al., 1993)

We would like to know more about any problems you have had with feeling tired, weak or lacking in energy in the last month. Please answer ALL the questions by ticking the answer which applies to you most closely. If you have been feeling tired for a long while, then compare yourself to how you felt when you were last well.

Less than usual No more than usual More than usual Much more than usual

Do you have problems with tiredness?

Do you need to rest more?

Do you feel sleepy or drowsy?

Do you have problems starting things?

Do you lack energy?

Do you have less strength in your muscles?

Do you feel weak?

Do you have difficulties concentrating?

Do you make slips of the tongue when speaking?

Do you find it more difficult to find the right word?

How is your memory?

Better than usual No worse than usual Worse than usual Much worse than usual

Appendix B: Questionnaires (Continued)

International Personality Item Pool scale (neuroticism) (Goldberg et al., 2006)

Please indicate how much you feel each statement applies to you. Describe yourself as you generally are now, not as you wish to be in the future.

Very Inaccurate (1) Moderately Inaccurate (2) neither Accurate nor Inaccurate (3) Moderately Accurate (4) Very Accurate (5)

I often feel blue

I dislike myself

I am often down in the dumps

I have frequent mood swings

I panic easily

I rarely get irritated

I seldom feel blue

I feel comfortable with myself

I am not easily bothered by things

I am very pleased with myself

Appendix B: Questionnaires (Continued)

Pain Catastrophising Scale (Sullivan et al., 1995)

Everyone experiences painful situations at some point in their lives. Such experiences may include headaches, tooth pain, joint or muscle pain. People are often exposed to situations that may cause pain such as illness, injury, dental procedures or surgery.

We are interested in the types of thoughts and feelings that you have when you are in pain. Listed below are thirteen statements describing different thoughts and feelings that may be associated with pain. Using the following scale, please indicate the degree to which you have these thoughts and feelings when you are experiencing pain.

0 – not at all **1** – to a slight degree **2** – to a moderate degree **3** – to a great degree **4** – all the time

When I'm in pain …

I worry all the time about whether the pain will end.

I feel I can't go on.

It's terrible and I think it's never going to get any better.

It's awful and I feel that it overwhelms me.

I feel I can't stand it anymore.

I become afraid that the pain will get worse.

I keep thinking of other painful events.

I anxiously want the pain to go away.

I can't seem to keep it out of my mind.

Psychosocial Factors in Functional Gastrointestinal Disorder

I keep thinking about how much it hurts.

I keep thinking about how badly I want the pain to stop.

There's nothing I can do to reduce the intensity of the pain.

I wonder whether something serious may happen.

Appendix B: Questionnaires (Continued)

Visceral Sensitivity Index (J. Labus et al., 2004)

Below are statements that describe how some people respond to symptoms or discomfort in their in their belly or lower abdomen, such as pain, constipation and diarrhea. Please answer how strongly you agree or disagree with each of these statements, as they relate to you. Please answer all the statements honestly and accurately as you can.

Strongly Disagree (1) Disagree (2) Neither Agree nor Disagree (3) Agree (4) Strongly Agree (5)

I worry that whenever I eat during the day, bloating and distension in my belly will get worse

I get anxious when I go to a new restaurant

I often worry about problems in my belly

I have a difficult time enjoying myself because I cannot get my mind off discomfort in my belly

I often fear that I won't be able to have a normal bowel movement

Because of fear of developing abdominal discomfort, I seldom try new foods

No matter what I eat, I will probably feel uncomfortable

As soon as I feel abdominal discomfort, I begin to worry and feel anxious

When I enter a place I haven't been before, one of the first things I do is look for a bathroom

I am constantly aware of the feeling I have in my belly

Psychosocial Factors in Functional Gastrointestinal Disorder

I often feel discomfort in my belly could be a sign of a serious illness

As soon as I awake, I worry that I will have discomfort in my belly during the day

When I feel discomfort in my belly, it frightens me

In stressful situations, my belly bothers me a lot

I constantly think about what is happening in my belly

Appendix B: Questionnaires (Continued)

Depression, Anxiety and Stress Scale (21) (Lovibond & Lovibond, 1995)

Please read each statement and indicate how much the statement applied to you over the past week. There are no right or wrong answers. Do not spend too much time on any statement.

Never (1) Sometimes (2) Often (3) Almost always (4)

I found it hard to wind down

I was aware of dryness of my mouth

I couldn't seem to experience any positive feelings at all

I experience breathing difficulty (eg. Excessively rapid breathing, breathlessness in the absence of physical exertion)

I found it difficult to work up the initiative to do things

I tended to over-react to situations

I experience trembling (eg. in the hands)

I felt that I was using a lot of nervous energy

I was worried about situations in which I might panic and make a fool of myself

I felt that I had nothing to look forward to

I found myself getting agitated

I found it difficult to relax

I felt down-hearted and blue

I was intolerant of anything that kept me from getting on with what I was doing

I felt I was close to panic

I was unable to become enthusiastic about anything

I felt I wasn't worth much as a person

I felt that I was rather touchy

I was aware of the action of my heart in the absence of physical exertion (eg. sense of heart rate increase, heart missing a beat)

I felt scared without any good reason

I felt that life was meaningless

Appendix B: Questionnaires (Continued)

Tampe Scale for Kinesiphobia (Kori et al., 1991)

Please indicate how much you agree or disagree with the following statements

Strongly Disagree (1) Disagree (2) Agree (3) Strongly Agree (4)

I'm afraid that I might injury myself if I exercise

If I were to try to overcome it, my pain would increase

My body is telling me I have something dangerously wrong

My pain would probably be relieved if I were to exercise

People aren't taking my medical condition seriously enough

My accident has put my body at risk for the rest of my life

Pain always means I have injured my body

Just because something aggravates my pain does not mean it is dangerous I am afraid that I might injure myself accidentally

Simply being careful that I do not make any unnecessary movements is the safest thing I can do to prevent my pain from worsening

I wouldn't have this much pain if there weren't something potentially dangerous on in my body

Although my condition is painful, I would be better off if I were physically active

Pain lets me know when to stop exercising so that I don't injure myself

It's really not safe for a person with a condition like mine to be physically active

I can't do all the things normal people do because it's too easy for me to get injured

Even though something is causing me a lot of pain, I don't think it's actually dangerous

No one should have to exercise when he/she is in pain

Appendix B: Questionnaires (Continued)

Patient Health Questionnarie – 15 (Kroenke et al., 2002)

During the past 4 weeks, how much have you been bothered by any of the following problems? Please indicates how much each statement applies to you.

Not bothered at all (1) Bothered a little (2) Bothered a lot (3)

Stomach pain

Back pain

Pain in your arms, legs or joints (hips, knees, etc.)

Menstrual cramps or other problem with your periods (women only)

Headache

Chest pain

Dizziness

Fainting spells

Feeling your heart pound or race

Shortness of breath

Pain or problems during sexual intercourse

Constipation, loose bowels, or diarrhea

Nausea, gas, or indigestion

Feeling tired or having low energy

Trouble sleeping

Appendix B: Questionnaires (Continued)

Short Form 12v2

Removed for copyright purposes

Appendix B: Questionnaires (Continued)

Gastrointestinal Symptom Rating Scale

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Appendix B: Continued

The Chronic Pain Grading Scale (Von Korff et al., 1992)

In the past 6 months, how has this pain changed your ability to work (including housework)?

0 1 2 3 4 5 6 7 8 9 10

How would you rate your pain on a 0-10 scale at the present time, this is right now, where 0 is 'no pain' and 10 is 'pain as bad as it could be'?

0 1 2 3 4 5 6 7 8 9 10

In the past 6 months, how intense was your worse pain rated on a 0-10 scale?

0 1 2 3 4 5 6 7 8 9 10

In the past 6 months, on average, how intense was your pain rated on a 0-10 scale? (That is your usual pain at times you were experiencing pain.)

0 1 2 3 4 5 6 7 8 9 10

In the past 6 months, how much has this pain interfered with your daily activities on a 0-10 scale where 0 is 'no interference' and 10 is 'extreme change'

0-6 days (1)

7-14 days (2)

15-30 days (3)

Greater or equal to 31 days (4)

About how many days in the last 6 months have you been kept from your usual activities (work, school, housework) because of this pain?

0 1 2 3 4 5 6 7 8 9 10

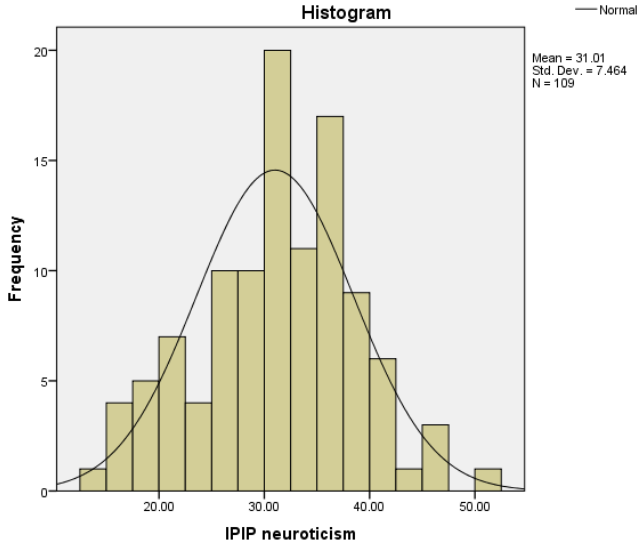
In the past 6 months, how much has this pain changed your ability to take part in recreational, social, and family activities?

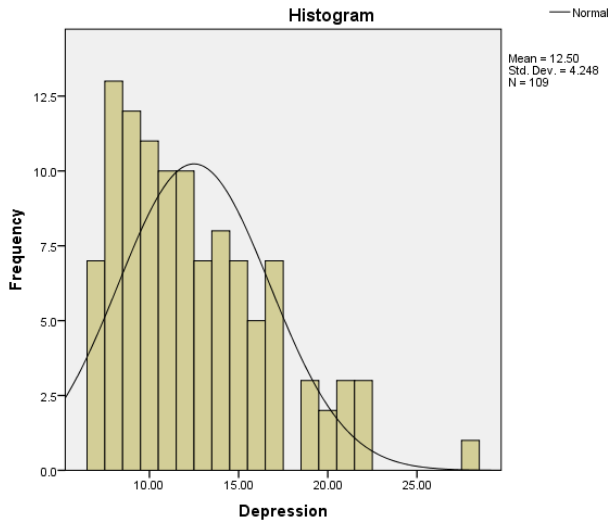
0 1 2 3 4 5 6 7 8 9 10

Appendix C

Normality of Measures

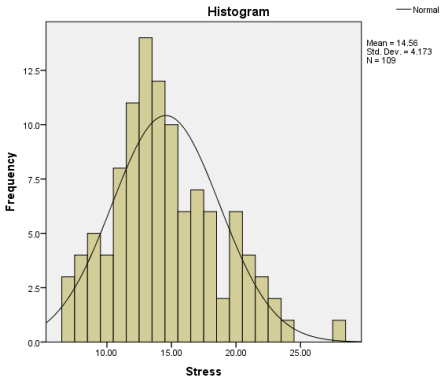
Measure	Statistic	Df	p-valuie
IPIP Neuroticism	.986	109	**.337**
DASS: Depression	.923	109	.000
DASS: Anxiety	.921	109	.000
DASS: Stress	.972	109	.020
DASS Total	.946	109	.000
PHQ	.976	109	.042
VSI	.95	109	.000
TSK	.974	109	.034
PCS	.934	109	.000
GSRS	.927	109	.000
CPGS Intensity	.979	109	**.080**
CPGS Disability	.873	109	.000
Chalder fatigue Scale	.976	109	**.080**

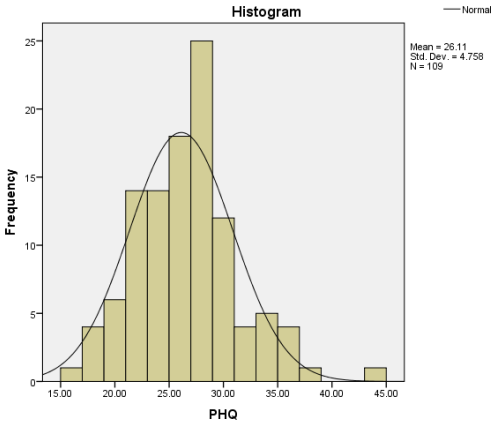


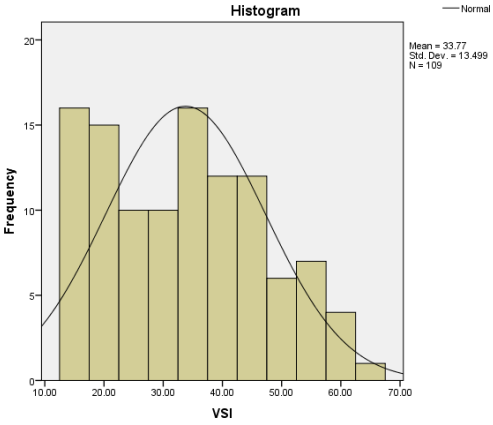


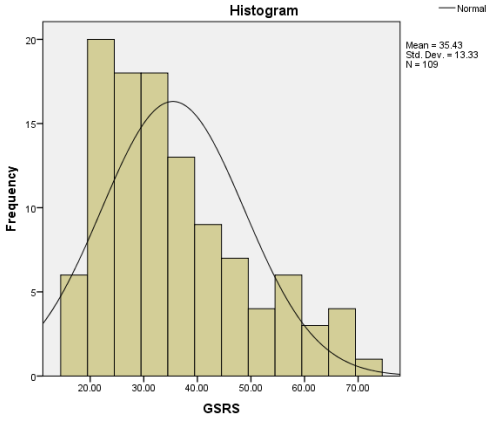
Appendix C: Continued

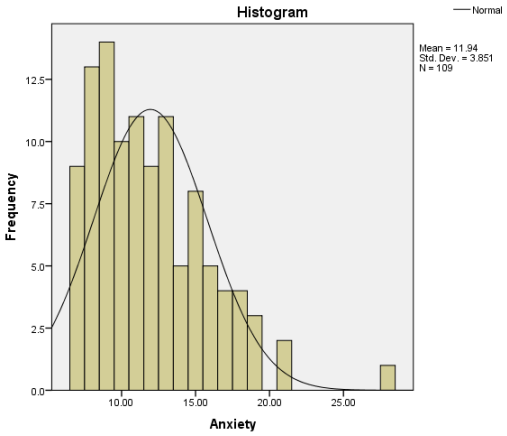
Normality of Measures

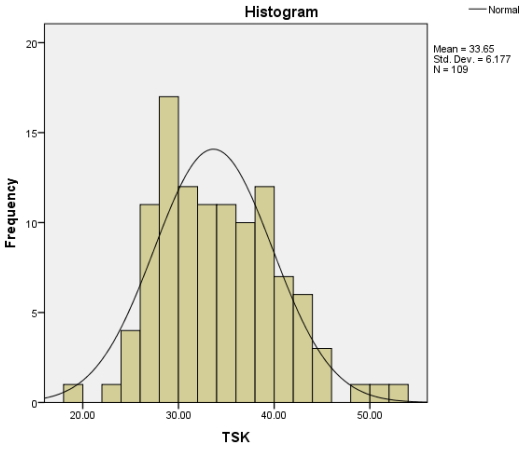






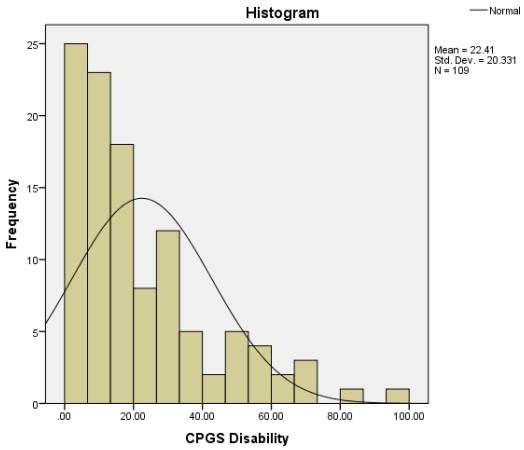


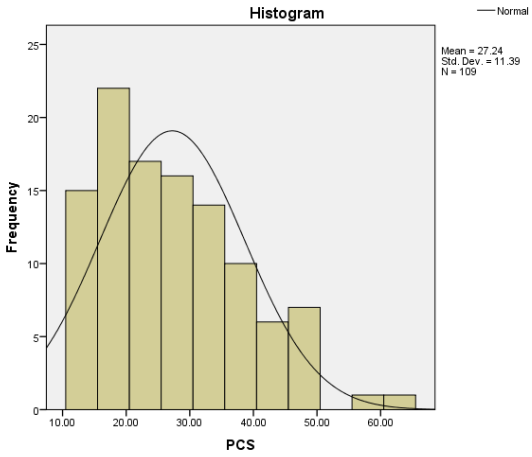


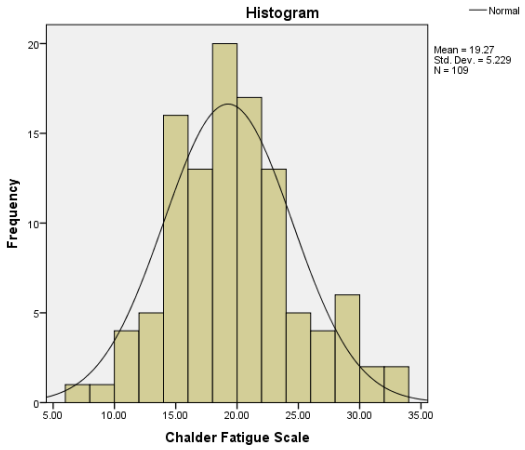


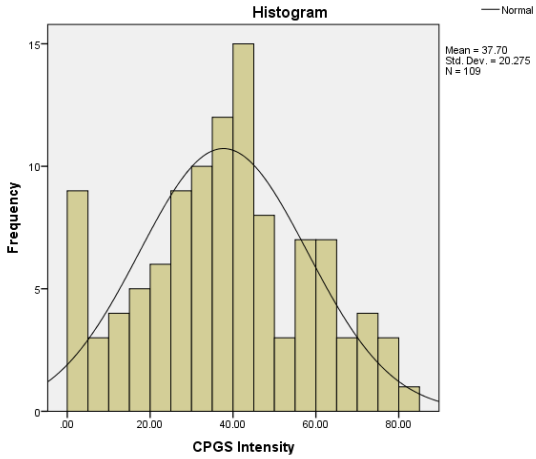
Appendix C: Continued

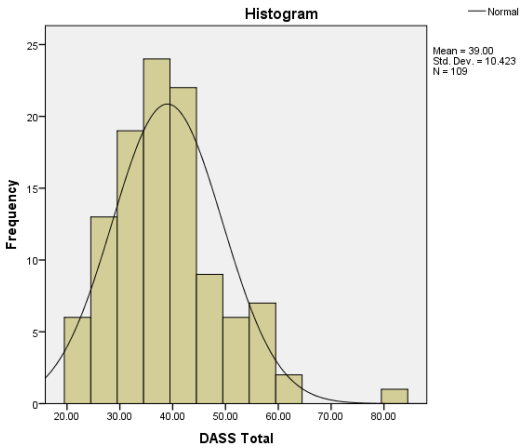
Normality of Measures











Appendix D: Path Model

FGID Population Path Model

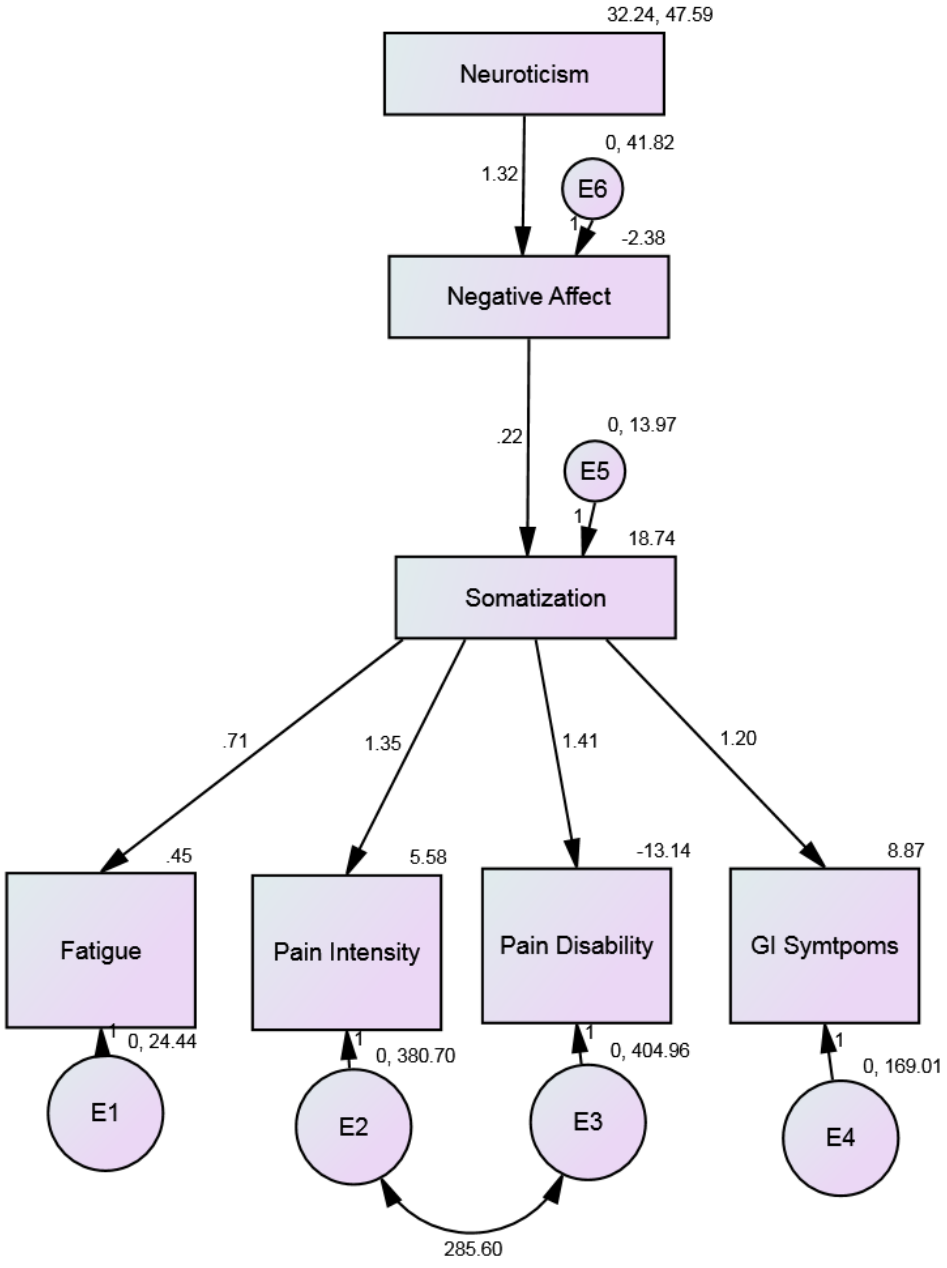


Figure 5. Path Model: FGID Population χ^2_{14}=20.64, *p*=.111, *CMIN/df*=1.474. *CFI*=.955, *RMSEA*=.096.

Appendix D: Continued

Extra-GI Population Path Model

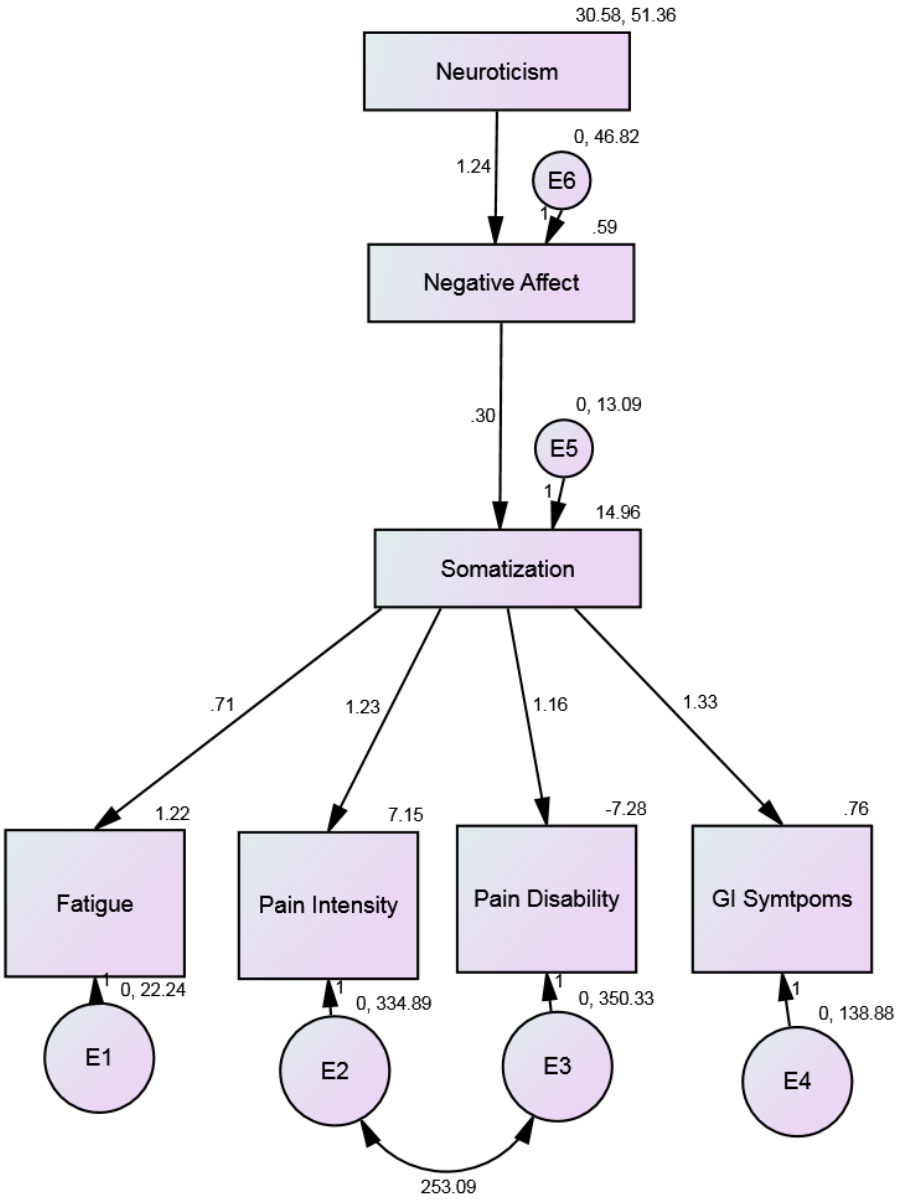


Figure 6. Path Model: Extra – GI Population χ^2_{14}=23.279, *p*=.056, *CMIN/df*=1.663. *CFI*=.955, *RMSEA*=.103.