A prospective investigation of cognitive-behavioural models of irritable bowel and chronic fatigue syndromes: Implications for theory, classification and treatment.

Meagan Jane Spence

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Abstract.

The purpose of this study was to prospectively evaluate the application of the cognitive-behavioural model to two common functional somatic syndromes: irritable bowel syndrome (IBS) and chronic fatigue syndrome (CFS). A range of predisposing, precipitating and perpetuating variables operationalised from this model were assessed in two acutely ill samples. The significance and relative importance of these variables with regard to the development of post-infectious IBS and CFS were then examined. At the same time, information was gathered to assess the appropriateness of an overall conceptualisation for the functional somatic syndromes. Similarities and differences between the two syndromes were investigated, and the impact of differing thresholds and disability criteria were compared to determine the utility of current diagnostic criteria.

Patients with a positive laboratory test result for *Campylobacter* gastroenteritis or glandular fever were recruited through general practitioners. A total of 1018 participants completed a baseline questionnaire at the time of infection which included measures of anxiety, depression, perfectionism, somatisation, perceived stress, acute illness perceptions and illness related behaviours. Those previously diagnosed with CFS or IBS were excluded, along with participants experiencing any medical condition known to impact on fatigue levels or bowel function (n=183). Participants completed follow-up questionnaires at three (93% response rate) and six months (90% response rate) post-infection. At each point, cases of IBS and CFS were identified using published diagnostic criteria.

Results indicated that a range of cognitive, behavioural, physiological and emotional variables were significantly related to the development of both IBS and CFS. Whilst there were some similarities between the two conditions, there were also some key differences. Depression and somatisation were significant predisposing variables in the development of CFS, but not IBS, for which anxiety was a key predictor. Perceived stress and the type of acute infection were more important as precipitants of IBS than CFS. *Campylobacter* was a significant predictor of IBS at both timepoints, whilst the presence of this illness type also strengthened the association between IBS and the psychological variables. In contrast, glandular fever was a significant predictor of CFS at three months only, and this

association was outweighed by the inclusion of the psychological variables. With regard to perpetuating factors, negative illness perceptions at the time of acute infection were significantly related to both conditions, and all-or-nothing behaviour was also associated with IBS. When CFS and IBS cases at six month follow-up were compared, CFS cases had higher levels of disability, but not health care utilisation. Finally, when subthreshold cases of IBS and CFS were compared to their diagnosed counterparts, on the whole they did not differ with regard to the psychological risk factors, disability or health care utilisation.

These results support the application of the cognitive-behavioural model to IBS and CFS as a useful explanatory tool and guide for treatment. The results provide a degree of empirical detail that has previously been lacking with regard to these models. Comparing the application of the model to two separate conditions has demonstrated subtle but important differences between the development of post-infectious IBS and CFS. These findings suggest that an overall conceptualisation for the functional somatic syndromes may not be capable of determining and addressing such differences for individual conditions. With regard to the diagnostic criteria for IBS and CFS, results suggest that the current criteria may be unnecessarily restrictive and complex. Simplification or the formalised addition of subthreshold conditions may result in more widespread usage and clinical applicability of these criteria.

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Table of Contents.

List of Tables.

List of figures.

List of abbreviations.

AGA	American Gastroenterological Association
ANCOVA	analysis of covariance
BRIQ	Behavioural Responses to Illness Questionnaire
CBT	cognitive-behavioural therapy
CDC	Centers for Disease Control and Prevention
CF	chronic fatigue
CF/CFS	chronic fatigue/ chronic fatigue syndrome
CFS	chronic fatigue syndrome
CG	*Campylobacter* gastroenteritis
CI	confidence interval
DBF	disturbed bowel function
DSM-III	Diagnostic and Statistical Manual of Mental Disorders – 3rd Edition
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders – 4th Edition
EBV	Epstein-Barr virus
FGID	functional gastrointestinal disorders
GF	glandular fever
GP	general practitioner
HADS	Hospital Anxiety and Depression Scale
IBS	irritable bowel syndrome
IBQ	Illness Behaviour Questionnaire
IPA	Independent Practitioners Association
IPQ	Illness Perceptions Questionnaire
IPQ-R	Illness Perceptions Questionnaire - Revised
ME	myalgic encephalomyelitis
MHI-5	Five Item Mental Health Inventory
PANPS	Positive and Negative Perfectionism Questionnaire
PSS	Perceived Stress Scale
RET	rational emotive therapy
SAIB	Scale for the Assessment of Illness Behaviour
SS	Support Seeking
UK	United Kingdom
USA	United States of America
VCA	Viral Capsid Antigen
WSAS	Work and Social Adjustment Scale

Chapter 1.

Introduction.

Headache, fatigue, digestive problems, backache, muscle and joint pain are all common symptoms that affect the daily lives of millions of people around the world. The ubiquitous nature of these symptoms makes them easy to disregard as an unavoidable feature of the human condition. No matter how unpleasant and irritating they may be, such symptoms are usually minor and only temporarily disruptive. They are often easily explained and treated by those suffering from them, or by the physicians investigating them. For some people, however, common symptoms such as these cannot be so easily dismissed (Kroenke & Mangelsdorff, 1989). For this group, the symptoms may be persistent and severe and, even after medical investigation, appear to have no identifiable cause. It is this lack of an adequate physiological explanation that provides the cardinal feature of the medically unexplained or functional somatic syndromes.

Functional somatic syndromes are defined as "related syndromes that are characterised more by symptoms, suffering and disability than by disease-specific, demonstrable abnormalities of structure or function" (Barsky & Borus, 1999, p.910). Well known functional somatic syndromes include fibromyalgia, chronic fatigue syndrome, multiple chemical sensitivity, chronic pain and irritable bowel syndrome. The theory, classification and treatment of syndromes like these have all been hampered by the medically unexplained nature of their associated symptoms. Throughout history there has been conceptual confusion regarding the aetiological basis of these syndromes and debates have often been characterised by conflict and opposing views (e.g. Gwee, 1996). A dearth of effective treatment options has also had an adverse impact on clinical interactions. Patient satisfaction has been poor, whilst increasing stigma has become associated with the functional somatic syndromes (Looper & Kirmayer, 2004).

Medically unexplained symptoms account for a significant proportion of general practice consultations and an even greater number of specialist consultations (Reid, Wessely, Crayford, & Hotopf, 2001). Surveys of primary and secondary care consistently identify that 20-50% of patients present with symptoms that remain medically unexplained following investigation (olde Hartman, Lucassen, van de Lisdonk, Bor, & van Weel,

2004). Despite the lack of causal explanations, functional somatic syndromes are consistently associated with high levels of disability (Bombardier & Buchwald, 1996), increased medical costs (Fink, 1992), decreased productivity (McCrone, Darbishire, Ridsdale, & Seed, 2003), and high levels of emotional distress (Haug, Mykletun, & Dahl, 2002). While the symptoms themselves are often viewed by the medical system as benign, it is difficult to ignore the pain, distress and disability associated with these conditions.

From Aristotle to Freud to the Gulf war, functional somatic syndromes have been categorised by those observing them. Over time, the names have changed reflecting the impact of societal influence, but the groupings of symptoms have remained largely consistent (Shorter, 1995). Another change in recent years has been the level of research interest devoted to the functional somatic syndromes. In the past twenty years, growing acceptance of the extent of the problems associated with these syndromes has been accompanied by an increasing number of related research articles. A brief MEDLINE search using the subject headings mapped from the term 'functional somatic syndrome' reveals that in the decade from 1965 only 177 articles were cited under these keywords. From 1975-1985 a further 422 were cited. In contrast, this number jumps considerably in the following decade to 3176 studies, before doubling in the most recent decade to 6330. Alongside this burgeoning research interest has been the evolution of an extensive array of clinical definitions and formal classification criteria (Feinstein, 2001).

In the absence of clear pathophysiology, diagnostic criteria have been developed based on each particular syndrome's prominent symptom profile. As a result, individual syndromes are numerous, with each medical specialty claiming its own particular syndrome, often without consideration of other related syndromes (Nimnuan, Rabe-Hesketh, Wessely, & Hotopf, 2001). There is considerable overlap in symptomatology and significant comorbidity, leading some to suggest that these conditions are better grouped together and that the similarities between the conditions outweigh the differences (Wessely, Nimnuan, & Sharpe, 1999). Set against this, is an increasingly complex body of knowledge associated with each individual syndrome and frequent calls to subcategorise (Guilera, Balboa, & Mearin, 2005). This debate is often tied to incomplete aetiological evidence, with those advocating core psychological factors favouring the 'one syndrome' approach, whereas those working on biological causes tending to argue for the 'many syndromes' conceptualisation (Moss-Morris & Wrapson, 2003). A central feature of this debate is the requirement for clear aetiological evidence in order to determine which approach is likely to be most useful.

Just as debate surrounding the classification of functional somatic syndromes has been characterised by polemic thinking, research concerning the aetiology of the functional somatic syndromes has also reflected a dualist approach. The focus has often been on psychological explanations at the expense of the physiological, or vice versa. For many years, functional somatic syndromes were considered the domain of psychiatry, viewed purely as the somatic presentation of an established psychiatric disorder such as depression (Hudson & Pope, 1994). Societal influence has also been considered as a cause for these syndromes with theorists postulating that vulnerable individuals, prone to general somatisation of psychological concerns, are susceptible to "diseases of fashion" that are popularised through cultural media (Shorter, 1994). From the biological perspective, many researchers have continued to pursue physiological causes of particular syndromes with varying degrees of success (Talley & Spiller, 2002).

More recently, integrative models have been proposed, with biological, psychological and social factors all finding a place in the explanatory models (Manu, 1998). It is now acknowledged that all of these factors play a part in the development of functional somatic syndromes, and that none can provide an adequate explanation of these conditions on their own (Sharpe, 2001). Biopsychosocial models are now considered by many to be the most promising means by which we can begin to understand the complex aetiological processes found in these syndromes (Ryff & Singer, 2000). One particular model that has found favour in the field of functional somatic syndromes is the cognitive-behavioural model which has its origins in the treatment of depression. Most extensively adapted to provide an explanatory framework for chronic fatigue syndrome, it has since been applied to many other functional somatic syndromes (Sharpe, Peveler, & Mayou, 1992).

Although emphasising cognition as a core concept in the explanatory process and mode of intervention, the cognitive-behavioural model recognises the reciprocal nature of the interactions between cognition, physiology, emotion, behaviour and the environment. Rather than following a direct causal approach, whereby one of these five factors may be the root cause of the problem, the model allows for reciprocal effects in any direction (Turk & Salovey, 1995). The model also distinguishes between predisposing, precipitating, and perpetuating factors that may be influential in each of these areas. By utilising these two explanatory concepts, the cognitive-behavioural approach has provided the basis for psychological treatments of the functional somatic syndromes, and has found some success where other approaches have failed (Hutton, 2005; Kroenke & Swindle, 2000; Lackner, Mesmer, Morley, Dowzer, & Hamilton, 2004; Rimes & Chalder, 2005).

This model goes some way toward addressing the complexities of the functional somatic syndromes. It has also provided a vehicle by which further communication and exploration of the interactions between these factors is possible (Novy, Nelson, Francis, & Turk, 1995).

Despite the controversies, significant advances have been made in the areas of classification, aetiology and treatment of the functional somatic syndromes over the last few decades. The current study aims to further this progress by focusing on the importance of psychological and biological factors in the development of two distinct functional somatic syndromes. It will begin with a review of the current classification systems for the functional somatic syndromes in the context of a historical review. The debate regarding whether they should be conceptualised as one common syndrome or whether each individual syndrome should retain its place as a distinct diagnostic entity will then be considered.

Controversies surrounding the aetiological origins of the functional somatic syndromes will then be briefly reviewed, before examining in more detail the influence and contribution of the cognitive-behavioural model as a means of understanding the development and maintenance of these conditions. Untested theoretical constructs and gaps in the empirical research base for the cognitive-behavioural model will be identified. Throughout this review, particular reference will be made to chronic fatigue syndrome (CFS) and irritable bowel syndrome (IBS), two of the most common functional somatic syndromes, and the specific conditions targeted in this study. Comparisons between the two will be made, with commonalities and differences highlighted. At the conclusion of the review, the literature will be summarised in the context of the rationale and hypotheses of the current study.

The remainder of the thesis will describe two studies designed to test these hypotheses. The first of these is a smaller preliminary study designed to construct and validate a measure of behavioural response to illness. The methodology and results of this study will be outlined before discussing its implications. The second study, the main study of this thesis, investigates the role of psychological factors in the development of post-infectious CFS and IBS. The methodology and results of this study are presented before the results are discussed according to the specific hypotheses outlined at the commencement of the study. Finally a general discussion will place these results within the context of their contribution to the understanding of these two conditions.

Chapter 2.

Classification of the functional somatic syndromes.

"When man does not understand, he seeks to classify"(Thomas Kuhn, 1970)

2.1. Historical overview

The purpose of classification.

Classification systems provide a convenient shorthand for communication in many fields of human interest and endeavour. They are capable of ordering complex information, making it possible to convey large amounts of information in a concise manner. They facilitate discussion within fields as diverse as botany, chemistry and musical composition. In the field of medicine, the classification of human ailment has its origins with Hippocrates who proposed the four bodily humours as the basis of disease. Modern medical classification provides a common language that allows comparison of aspects of an individual according to those shared with all humans, those shared with some humans, and those unique to the individual (Kendell, 1975). By considering their patients in such a way, clinicians are able to set limits on assessment, treatment and prognosis. Without commonly accepted classification systems, knowledge becomes fragmented and confined to lengthy clinical anecdote.

Classification is particularly important in medical research; the focus of which is the systematic accumulation of knowledge about the different manifestations of poor health. The advancement of scientific knowledge depends on a researcher's ability to ensure that the topic under consideration is easily identifiable and consistent with that of other studies. Without an understanding of the means by which a particular condition can be defined, a number of basic research tasks become complicated. It becomes difficult to conduct research that is meaningful to others, to compare relevant studies, or to integrate multiple strands of information gathered across diverse research settings. Apparently contrasting

research findings can be attributable to differing definitions, or to variations in the rigorousness by which the same definition is applied.

Diagnostic criteria in medicine are utilised by a wide range of professions and need to be intelligible to all. Diagnostic confusion can hamper scientific progress and aggravate interdisciplinary conflict. Numerous examples of this can be found in the field of the functional somatic syndromes. As one author has pointed out with regard to IBS, "those interested in the condition possess disparate viewpoints: epidemiologists, primary care physicians, consultants, researchers, psychologists, physiologists, third party payers, and of course, the patients themselves" (Thompson, 1999, p.81). Finding a classification system that meets the needs of such a wide range of users has presented considerable challenges.

Terminology.

Despite acknowledgement of the need for a classification system, there is very little agreement about the most appropriate terminology to apply to the functional somatic syndromes as a group. The term "medically unexplained symptoms" is used to describe all medically unexplained conditions, whereas the term "functional somatic syndrome" is limited to those conditions that comprise a group of symptoms recognised and defined as a distinct entity. Somatisation, somatoform disorder, hypochondriasis, and abnormal illness behaviour, are other general terms used to describe these problems (Mayou & Farmer, 2002). Some authors, dissatisfied with these descriptors, have put forward others such as "unexplained physical symptoms" (Engel, 2000), "subjective health complaints" (Eriksen & Ursin, 2004), "disability syndromes" (Ferrari & Kwan, 2001), and "unexplained clinical conditions" (Aaron & Buchwald, 2001). Still others have argued that more energy has gone into finding a perfect term than has gone into understanding the basis for classification (Rief & Sharpe, 2004).

In an introductory chapter of their book on the treatment of functional somatic syndromes, Sharpe and colleagues summarise the various terminology historically used to describe this group of conditions (Sharpe, Mayou, & Bass, 1995). After considering the origins and merits of the terms used throughout history, they conclude that none are entirely satisfactory, based as they are on an arbitrary division between the mind and body. They argue that even those terms that attempt to combine psychological and physiological influences implicitly endorse the distinction. Instead, these and other authors now

advocate for the position that physiological and psychological mechanisms in these conditions are inextricably linked, and interdependent in their influence.

For the purposes of this thesis, the term settled on by Sharpe and colleagues, that of 'functional somatic' symptoms and syndromes, will be used. As they point out, this term appears to provide the best overall descriptor at present, portraying as it does a genuine abnormality of function without making specific assumptions about aetiology. It has also been shown to be one of the most acceptable labels from the patient's perspective (Stone et al., 2002). The term functional somatic syndrome then is used to refer to those conditions in which functional somatic *symptoms* cluster together in a manner recognised by the research community.

The role of aetiology in classification.

Throughout history, the labels used to describe medical conditions have often been related to aetiology, whether or not that aetiology has been adequately investigated. With the advent of sophisticated diagnostic testing and research techniques, however, medicine has advanced considerably in its understanding of aetiological factors in disease. By association, aetiologically-based classification systems have proved valuable in their ability to assist in the prevention, prediction and treatment of disease. The success of such classifications has led to an assumption that aetiology provides the only legitimate pathway to a valid and useful diagnosis (Kendell, 1989). When there is a lack of clear aetiological evidence for a disorder, as is the case for the functional somatic syndromes, such a stance becomes problematic.

In those disciplines where aetiology is less certain and where non-organic factors play an important part in the presentation, classification presents considerable challenges. It does not, however, lessen the need for diagnostic labels, and in fact many argue that without adequate classification systems, aetiological influences are less likely to be revealed. After years of debate and conceptual confusion, psychiatry, for example, devised a classification system that eschewed aetiology. The result was a descriptive, symptom-based system that was published as the third edition of the *Diagnostic and Statistical Manual of Mental Disorders*, or the DSM-III (American Psychiatric Association, 1980). Despite a significant number of ongoing classification dilemmas and two further revisions, this system has provided the impetus with which to advance a wide range of research in psychiatry. As a measure of its success, there has been a recent acknowledgement that it may soon be

possible to move back to a more aetiologically-based classification system in psychiatry (Mayou, Levenson, & Sharpe, 2003).

A similar process has occurred in the classification of the functional somatic syndromes. Despite the absence of convincing evidence of clear aetiological pathways, causally linked diagnostic labels have been popular throughout history and many continue to be used today. In a commentary on what he calls the "Blame-X syndrome", one author has cautioned against the premature adoption of aetiologically-based criteria (Feinstein, 2001). Feinstein argued that where aetiologically-based nomenclature has been adopted without adequate investigation of that aetiology, the ability of researchers to find the true cause has been hampered. More importantly, he insists that patient recovery is impeded in this situation, due to the overemphasis on a causal factor for which no evidence, nor treatment, is available. Because of reasons such as these, symptom-based diagnoses have also been advocated for the functional somatic syndromes and as a result, explicit aetiological hypotheses have in most cases been removed from diagnostic criteria and labels.

The removal of aetiological influences is evident in the labels used in the two systems of classification for the functional somatic syndromes that exist today. Despite this lack of obvious aetiological influence, both systems are still subtly aligned to a dualist separation of the mind and body (Mayou & Farmer, 2002). The first method of classification is that found in the DSM-IV under the heading of somatoform disorders, which highlights commonalities between conditions by focusing on the number of symptoms and related psychological processes rather than the type of symptoms, thereby emphasising the 'mind'. The second method is medically based, and considers each disorder in isolation, resulting in a range of definitions that are specific to particular bodily systems. Research using these definitions is more often centred on establishing physiological abnormality; hence the 'body' is often the focus of this system.

Despite efforts to avoid the problems associated with aetiological uncertainty, subtle theoretical influences are still apparent in the classification of these disorders. The two parallel classification systems remain in common usage, each with their own difficulties, and the simultaneous use of both is seen as unacceptable and unhelpful in the clinical context. As a result, there have been calls for a major overhaul of the classification of the functional somatic syndromes, with the aim of integrating the two existing systems in a way that can provide a more holistic and dimensional approach to these disorders (Mayou, Kirmayer, Simon, Kroenke, & Sharpe, 2005; Mayou et al., 2003).

Cultural influences.

In the absence of clear aetiological evidence, classification systems are not only vulnerable to the distortion of theoretical bias, but can also be subject to wider societal influence. In their review of the functional somatic syndromes, Barsky and Borus (1999) point out that throughout history conditions have arisen, attracted intense medical attention and then declined in incidence; largely due to the failure to find a medical cause. Despite this, the same clusters of symptoms have evolved relatively intact, with a different presumed cause and a series of new labels. They illustrate this using writer's cramp, which has evolved with technology to become telegraphist's wrist, and more recently repetitive strain injury. This process is not, however, limited to the realms of history. A study examining the reporting of fatigue-related conditions in the period 1990-2001 concluded that differing levels in the reporting of distinct syndromes had more to do with fashion than with true changes in incidence (Gallagher, Thomas, Hamilton, & White, 2004).

Along with diagnostic labels, patients' response to the reassurance of negative medical findings has also changed over the course of history. In the past, patients tended to be relieved and reassured by their physicians; in the modern era this has more often been replaced by mistrust and frustration (Barsky & Borus, 1999). Barsky and Borus cite three reasons for this; the decline of the physicians' prestige and authority, the influence of mass media, and the increasing prominence of political, legal, economic and regulatory ramifications of the functional somatic syndromes. Each of these factors has impacted on the classificatory process over time, as the functional somatic syndromes are no longer the exclusive domain of the treating physician. Patient advocacy groups, insurance providers and drug companies all now exert pressure with regard to the labelling of functional somatic syndromes. Noting these influences, some authors have gone so far as to propose yet another re-labelling of these conditions as "culture-driven disorders" (Aceves-Avila, Ferrari, & Ramos-Remus, 2004).

With so many different factions expressing opinions about decision making, an unfortunate side effect has been at times hostile division between stake holders. Of all the functional somatic syndromes, CFS has experienced the brunt of such division. For example, CFS was once known as myalgic encephalitis (ME) in reference to an aetiological theory that is now widely accepted as being disproved. A vocal group of sufferers continue to believe in the label and its aetiological underpinnings, however, referring to those who use the term CFS as minimising the suffering associated with the condition. On occasion researchers

and clinicians have been vilified, abused and intimidated for speaking out against these groups. An unfortunate side effect of such polarised debate has been the association of CFS with negative stereotypes that have ultimately affected the treatment of patients. As Wessley has pointed out, the majority of patients do not subscribe to these viewpoints, yet "destructive ideological fault lines…continue to divide the field, to the benefit of no one" (Wessely, 2001a, p.1378).

Negative stereotypes such as these can attach themselves to diagnostic labels like glue, invoking stigma and often resulting in poor management (Dixon-Woods & Critchley, 2000). For example, a study of nurses' attitudes and understanding of IBS found that despite two-thirds of nurses acknowledging that they did not have a good understanding of the condition, the majority endorsed statements that IBS patients are unable to cope with life, are lazy, and waste doctors' time (Letson & Dancey, 1996). The authors noted that these attitudes were most likely the result of culturally driven processes as the majority of nurses in the study did not have first hand knowledge of IBS patients. Doctors are not immune to these processes either. A qualitative study comparing general practitioners' perceptions of CFS and IBS found that doctors' beliefs often led to negative stereotyping and suboptimal management strategies, and that this was particularly noticeable for CFS patients (Raine, Carter, Sensky, & Black, 2004).

In a more positive light, however, diagnostic labels can provide a sense of legitimacy and a pathway to understanding for patients (Salmon, Peters, & Stanley, 1999; White, Nielson, Harth, Ostbye, & Speechley, 2002). In one study, for example, 70 IBS patients referred to a gastroenterology clinic were given a standardised consultation emphasising a positive diagnosis, education and reassurance. Six month follow-up indicated that this limited intervention reduced both health care utilisation and pain associated with gastrointestinal complaints (Ilnyckyj, Graff, Blanchard, & Bernstein, 2003). A similar study using IBS patients recruited from the community also found significant relief from symptoms six months after a comparable structured consultation (Monsbakken, Vandvik, & Farup, 2005).

Diagnostic proliferation.

The lack of clear aetiological evidence and the existence of strong cultural influences have culminated in a proliferation of definitions relevant to the area of the functional somatic syndromes. Although these definitions have prompted a considerable increase in research

activity, there has also been a good deal of confusion generated by them. The process of definition has been complicated by the fact that these conditions are found across the spectrum of medical specialties and encompass a wide range of commonly encountered symptoms. As one author has pointed out, description is not equivalent to explanation (Deary, 2005). For many conditions such as CFS, multiple definitions exist, while others such as noncardiac chest pain, still have no operationally defined criteria (Nimnuan, Hotopf, & Wessely, 2001).

Table 1. Functional somatic syndromes; key symptoms and medical specialty.

Syndrome	Key symptoms	Medical specialty
Atypical facial pain	Pain in face/jaw/mouth, or burning sensation	Dentistry
Chronic fatigue syndrome	Persistent or relapsing fatigue	Neurology/infectious diseases
Chronic pelvic pain	Pelvic pain unrelated to menstrual cycle	Gynaecology
Functional dyspepsia	Abdominal pain above the navel	Gastroenterology
Fibromyalgia	Musculoskeletal aches/pain/stiffness	Rheumatology
Globus Hystericus	Throat discomfort/ swallowing problems	Gastroenterology
Hyperventilation	Overbreathing/ dizziness/ faintness	Respiratory
Irritable bowel syndrome	Lower abdominal pain/ disturbed bowel habit	Gastroenterology
Multiple chemical sensitivity	Reaction to 2 or more substances at a level commonly tolerated	Gastroenterology/ allergy
Noncardiac chest pain	Chest pain not due to exertion	Respiratory/ Cardiology
Premenstrual syndrome	Menstruation related disturbance in mood/ appetite, breast tenderness, abdominal bloating	Gynaecology
Tension headache	Headache or neck pain	Neurology/ Rheumatology
Temperomandibular joint dysfunction	Pain in face/jaw/mouth associated with movement	Dentistry

(Adapted from Moss-Morris & Wrapson, 2003; Nimnuan, Hotopf et al., 2001)

Table 1 lists the common syndromes along with their key symptoms and the medical specialty they are most commonly found in. Some of these conditions are well established, and have a long history of description within the medical literature. These syndromes tend to have widely accepted published criteria, and include conditions such as CFS, IBS and fibromyalgia. Other conditions such as multiple chemical sensitivity and atypical facial pain are newer, and tend to have been less extensively researched. For these conditions criteria are in their early stages of development and acceptance. Other conditions not included in the table, such as chronic whiplash or repetitive strain injury are still the subject of controversy regarding their independent existence and published criteria are yet

to be endorsed by the wider research community. Table 1 identifies the main symptoms that distinguish each condition, however, it is worth noting that in many of the published criteria there is significant overlap regarding symptomatology, with fatigue and pain listed in the criteria for a large number of conditions.

Not only has there been a proliferation of criteria for individual functional somatic syndromes across medical specialties; there has also been an eagerness to subclassify those syndromes that have existed for some time. For example, IBS sits within the overriding category of the functional gastrointestinal disorders, which now includes 20 other related conditions such as functional dyspepsia, rumination syndrome and functional abdominal pain, as well as a further four categories for use with children (Thompson et al., 1999). Subcategorisation is often based on symptom predominance, proposed aetiological influence or symptom site. As one reviewer points out, however, the choice of these distinctions may be contradictory with varying pathophysiologies producing similar symptom patterns or the same pathophysiology affecting different bodily symptoms (Holtman, 2004).

For example, IBS itself can now be subclassified into three categories according to symptom predominance (constipation, diarrhoea, and alternating). Whilst it may make intuitive sense to distinguish between constipation predominant and diarrhoea predominant IBS, in that symptomatic treatment of these conditions is likely to be different (Whitehead, 1999), the use of subtypes can also complicate comparisons between studies and create arbitrary distinctions that may obscure similarities. A recent review of the IBS subtypes found vastly different prevalence rates of each subtype according to research setting (Guilera et al., 2005). Whilst some studies found equal numbers of each of the three subtypes, an earlier community study found that the majority of the IBS sample fell into the alternating subtype (Hungin, Whorwell, Tack, & Mearin, 2003). It has been argued that such categorisation ignores the frequent overlap of symptoms and creates artificial waste basket diagnoses that are limited in their usefulness (Corazziari, 2004). Are functional abdominal pain and functional diarrhoea, for example, distinct from IBS or are they simply different thresholds for the same condition? A recent review found that there was good evidence to suggest that IBS and functional dyspepsia, the two most common functional gastrointestinal disorders, are different manifestations of a single condition (Cremonini & Talley, 2004).

Concerns regarding this sudden proliferation of categories and labels have led to one of the more contentious debates in the area of the functional somatic syndromes. The usefulness of the distinctions made between individual syndromes and the adoption of such a wide range of symptom-based diagnoses has been challenged. Existing criteria have been modified and new categories adopted with such frequency that some have questioned whether these developments have added to our understanding of these conditions or detracted from it. At the core of this debate is whether the functional somatic syndromes should be conceptualised as variations within a single syndrome, or whether they are indeed distinct and unrelated entities reflecting qualitatively different problems (Kirmayer & Robbins, 1991). Given the potential ramifications of such a major classification change, this debate is now considered in some detail.

2.2. Functional somatic syndromes: different manifestations of the same underlying condition?

In 1999, two important reviews of the functional somatic syndromes were published by leading researchers in the field (Barsky & Borus, 1999; Wessely et al., 1999). In these two articles, the authors highlighted the many similarities between individual functional somatic syndromes. Substantial evidence was presented regarding the high degree of overlap in case definitions, significant levels of comorbidity with other functional somatic syndromes, and common associations with non-symptom variables such as female gender, history of abuse, anxiety and depressive disorders. Similarities with regard to epidemiology and inferred causal mechanisms were also highlighted. Outcome was seen to be comparable across conditions and the few successful treatments in this area were seen to share common principles and techniques.

Based on this evidence, it was suggested that these conditions would be better conceptualised as 'one' overriding syndrome rather than 'many' unrelated individual ones (Wessely et al., 1999). Rather than criteria reflecting fundamental differences in the syndromes themselves, it was proposed that the individual syndromes were more alike than they were different, and could be better conceptualised within an overriding category. These authors suggested that individual diagnoses were potentially an artefact of the medical subspecialty that patients presented to and that specialists assessing patients have an inherent bias towards recognising conditions in their own disciplines, with little consideration for similar presentations in other specialties. Many were supportive of the

notion that new insights could be gleaned by considering the syndromes in this light (Deary, 1999; Read, 2001). As one group had earlier warned, when researchers and clinicians consider individual symptoms and syndromes in isolation, the size of the problem can be concealed, and the development of general treatment strategies can be hampered (Mayou, Bass, & Sharpe, 1995).

Letters in response to these review articles, however, were dominated by clinicians, sufferers and advocates offended that their particular syndrome had in some way been denigrated or trivialised (Clemenger, 2000; Colby, 1999; Goudsmit & Shepherd, 1999). Several cogent criticisms rebutting the conceptualisation of the functional somatic syndromes as one condition were put forward. Prominent among these were the impression that 'lumping' the conditions together had tacitly promoted the concept that these disorders were 'all in the mind'. In an article rebutting the 'lumping' idea, Peter White argued that an overarching concept fails to satisfactorily enhance the understanding of the functional somatic syndromes, their aetiology, treatment and outcome; and thereby failed Kendall's four tests of clinical validity for a classification system (Wessely & White, 2004). For example, he argued that subclassification or 'splitting' of illnesses has historically enhanced the understanding of aetiology rather than hampered it, and that by deconstructing the individual syndromes we are better able to detect differences in causation and target treatments accordingly.

Five years after the initial review article proposing an overriding conceptualisation, Simon Wessely was given the opportunity to clarify the core of the argument (Wessely & White, 2004). After reviewing the main points, he expressed that much of the controversy surrounding the initial exposition centred on two misperceptions; firstly, that there was an assumption that these conditions were solely psychiatric and by implication imaginary, and secondly, that the many differences that exist between the syndromes had been disregarded as trivial. Both charges were strenuously denied. He reiterated that it was the system of classification that was being challenged and not the veracity of the conditions themselves (Wessely & White, 2004). In the intervening time, a number of review articles and empirical studies had addressed the question of whether these diverse syndromes should in fact be incorporated into an overall conceptualisation. These studies will now be reviewed.

Statistical analysis of symptom clusters.

A number of studies addressing this question have utilised statistical techniques to analyse the occurrence of symptom clusters, in order to determine whether functional somatic symptoms cluster together in recognisable patterns. The first of these used confirmatory factor analysis to explore the relationships between the symptoms of depression, anxiety, fibromyalgia, IBS and CFS in a general practice setting (Robbins, Kirmayer, & Hemami, 1997). They tested three models and found that whilst an overall construct existed, it was unable to adequately account for covariation amongst the conditions. A two factor model of somatic distress was also inadequate. Instead, a five factor model provided the best fit with the data, providing tentative confirmation that the conditions can be distinguished from each other. A second study appeared to confirm this view by using hierarchical classes analysis to examine patient groupings of medically unexplained symptoms in primary care (Gara, Silver, Escobar, Holman, & Waitzkin, 1998). They found 11 distinct patterns of symptom groupings that varied with respect to a number of non-symptom factors such as psychiatric status, gender and disability. A limitation of each of these studies was the use of symptom lists that could not account for organic disease or the frequency or nature of the symptoms. As a result it is unclear whether the results can be said to apply to definitive functional somatic syndromes.

A subsequent study aimed to more closely approximate diagnostic criteria using a cross-sectional survey of functional somatic syndromes in patients attending seven medical specialty clinics (Nimnuan, Rabe-Hesketh et al., 2001). Results indicated that over half of new attendees had more than one functional somatic syndrome. In contrast to the two previous studies, exploratory factor analysis of reported symptoms in this study found that a large amount of the variance was related to a common underlying factor. The majority of syndromes tended to cluster together under the labels of 'fatigue/pain' and 'cardiorespiratory'. The authors concluded that not only were these syndromes common in tertiary care, they were often comorbid with other functional somatic syndromes and that the symptoms associated with the conditions do indeed cluster together. As further evidence of an overriding syndrome, a reanalysis of the statistical data from the Robbins study cited earlier concluded that the earlier analyses did not convey the complexity of the original data (Deary, 1999). Results from this analysis indicated that although there were coherent symptom families that were indeed separable, there was also a large amount of very general variance that disposed people to any of these diverse symptoms.

These contrasting findings may be due to a number of variables. The first two studies used symptom reports from primary care patients, and used theory driven statistical techniques. In contrast, the third approximated diagnostic definitions of the individual syndromes in tertiary care patients and used exploratory factor analysis rather than confirmatory techniques. Therefore it is possible that the conflicting results may represent methodological differences such as sample selection, symptom measurement and choice of statistical technique. The differences may reflect the impact of setting, with those in primary care displaying a wider range of less severe symptoms in comparison to secondary care patients. In his reanalysis of the Robbins data, Deary warned that psychometric studies run the risk of producing statistical artefacts (Deary, 1999). Wessely has also pointed out that statistical clustering techniques may have provided all the insight they are capable of, and more sophisticated examination of the underlying mechanisms common to the functional somatic syndromes is now required (Wessely & White, 2004).

The nature and extent of overlap between individual conditions.

Systematic reviewers have also aimed to clarify the extent and nature of the overlap between conditions. On the basis of an extensive review of the literature examining the case for conceptualising the functional somatic syndromes as one condition, it was concluded that "unexplained clinical conditions frequently co-occur and share key symptoms and selected objective abnormalities" (Aaron & Buchwald, 2001). The review found that formal criteria for individual conditions bore many similarities, however this alone was unable to account for the overlap amongst conditions. They also ascertained that a consistently high proportion of patients meet criteria for two or more conditions, regardless of the nature of the originally diagnosed condition. However, the same review also pointed out that as yet there is no aetiological evidence to link these conditions, thereby weakening explanatory models that favour the 'one' syndrome conceptualisation.

A number of studies have looked at the importance of comorbid conditions in an attempt to find answers to this question. Depression, somatisation and anxiety have all been explored as potential underlying common factors in the presentation of the functional somatic syndromes. In an early investigation of the links between a number of somatic syndromes, mood and anxiety, Hudson and Pope proposed the concept of affective spectrum disorder (Hudson & Pope, 1994). Based on research into comorbidity, response to treatment and family studies, they concluded that these conditions are likely to have a common underlying pathophysiology that may be best represented by an affective component.

Later research has indicated that such a concept may be an oversimplification of the relationship between the disorders. A meta-analytic review of the relationship between anxiety, depression and medically unexplained symptoms found that four functional somatic syndromes (IBS, CFS, non-ulcer dyspepsia and fibromyalgia) were related to, but not fully dependent on anxiety and depression (Henningsen, Zimmermann, & Sattel, 2003). In contrast, they were unable to find convincing evidence of a relationship with medically unexplained syndromes in general, and concluded that an overall conceptualisation was premature.

There has been some support for the concept of somatisation as an underlying common mechanism in the functional somatic syndromes. A study which compared a functional gastrointestinal symptoms group, a somatisation syndrome group, and a group with non-somatic mental disorders, found that differences on an array of measures disappeared when somatisation was taken into account (Hiller, Cuntz, Rief, & Fichter, 2001). Support for the impact of somatisation can also be found in a recent study that compared 182 primary care patients diagnosed with chronic functional symptoms, with demographically matched controls recruited from the same practices (olde Hartman et al., 2004). Although not measuring somatisation directly, results indicated that patients with chronic functional conditions presented with a higher number and greater diversity of symptoms than controls and were significantly more likely to have symptoms in two or more body systems. They also reported greater medication usage, psychiatric morbidity and referral rates to specialists than controls. These authors concluded that their results did not appear to support separate classification of these symptoms according to the medical subspecialty definitions.

Taken together, these studies provide tentative support for an overriding conceptualisation for the functional somatic syndromes. The striking overlap and sheer weight of commonalities identified amongst the syndromes make a common overriding concept a useful one, heuristically at least. A single common aetiological factor remains elusive, however, and it is likely that the underlying connections will be complex. Conditions like depression and somatisation are associated with many functional somatic syndromes, but this does not necessarily mean that they are underlying causal factors (Sharpe et al., 1995). As an earlier cited review indicated, many functional somatic syndromes have some degree of association with these concepts, but the nature and degree of that association varies considerably between conditions (Henningsen et al., 2003). The complexity of the debate

is also apparent in the conflicting results from statistical clustering analyses which at times appear to add to the confusion rather than provide definitive answers.

'One' or 'many' functional somatic syndromes; or both?

The 'one' or 'many' debate is essentially an argument that rests upon noting overriding similarities at the expense of individual differences and vice versa. It is a common difficulty encountered when developing a taxonomy of classification in any area of science. In clinical practice, however, both global and specific terminology are important and can be seen as complementary. Each is useful for determining different parts of the wider question particularly in a newly developing area of investigation. In their 'for' and 'against' debate regarding the 'one' conceptualisation, Wessely and White themselves offer suggestions for a common ground (Wessely & White, 2004). White refers to an overriding concept (that of somatisation) that he believes is useful in its application to a range of medical conditions both explained and unexplained, and Wessely admits that over time differences will almost certainly emerge based on an improved understanding of aetiology. At least two reviewers of the 'one or many' debate have also concluded that neither conceptualisation will be adequate on its own and that a more complex combination of these positions is required (Deary, 1999; Whitehead, Palsson, & Jones, 2002).

In his reanalysis of the earlier Robbins data, Deary proposed that the conflicting results indicated three levels of variance that need to be taken into account in any system of classification (Deary, 1999). The first level pertains to general factors that predispose an individual to medically unexplained symptoms; the second source of variance refers to why people tend to have one type of grouping than another; and the third relates to the variance within syndromes with regard to the pattern of symptom reporting. He concluded that these levels of analysis make it possible to explain the existence of evidence for both the 'one' and 'many' conceptualisations of the functional somatic syndromes. Whereas both aspects warrant investigation, he warned that the most useful information will be that gained collaboratively, rather than by concentrating on one aspect at the expense of the other.

Whitehead and colleagues echoed this perspective in their review of the comorbidity of IBS with other disorders, and offered a different explanation (Whitehead et al., 2002). After reviewing the evidence, they concluded that the individual disorders are likely to

have independent aetiological mechanisms; however, they overlap much more frequently than would be expected by chance. They proposed that this overlap is likely to be related to a common factor relevant to the expression of all the disorders and that this common factor is most likely to be psychological, such as stress reactivity or the selective attention and amplification of somatic sensations. By separating out aetiology from presentation, these authors offered a potential reason for the seemingly conflicting notion that an overriding classification can exist alongside a symptom specific one.

In summary, this chapter has provided a brief overview of some of the forces that have contributed to the classification systems currently utilised in the area of the functional somatic syndromes. Classification acts as a tool to advance knowledge, and to facilitate communication of that knowledge. In the absence of sound aetiological evidence, descriptive symptom-based criteria have been developed as the most appropriate and meaningful way to investigate the functional somatic syndromes further. As a result, however, strong cultural forces have become evident which have the potential to undermine the usefulness of this system. In addition, multiple systems have been developed simultaneously, each with a different perspective and each with evidence to support their method of classification. Competing ideologies and other cultural influences have in some cases created artificial boundaries that are unhelpful to patients and can distort research findings.

Which descriptive system should be used and why? Is an overriding definition capable of furthering our knowledge of these seemingly disparate conditions, or can we gain more by continuing to classify and subclassify? Is aetiologically-based classification a future possibility or must we accept a descriptive system indefinitely? In order to explore these issues further, two of the most common functional somatic syndromes, IBS and CFS, will now be considered in more detail. By focusing on these two conditions, it is possible to examine the process of diagnostic definition, and the associated methodological difficulties created by these definitions. Other difficulties that have plagued research into the functional somatic syndromes can also be illustrated.

IBS and CFS have been selected as the focus of this review and subsequent study as they have enough similarities to make comparison possible, whilst retaining enough differences to make those comparisons relevant. Because their symptom focus is very different, they are seen as independent conditions and have rarely been studied together. CFS research has largely been conducted in the field of psychiatry and psychosomatics, whereas IBS has

been studied mostly within gastroenterology. However, like many of the functional somatic syndromes they bear similarities with regard to non-symptom variables that make them comparable. In addition, both of these conditions have been extensively researched and have well established and recognised criteria to define them. By comparing these two conditions it may be possible to shed light on the 'one' or 'many' debate with regard to both classification and aetiology. Should the same issues arise with regard to the development of criteria, then an overriding conceptualisation may be more relevant. Similarly, if the same factors are implicated in the development of these two conditions, there will be more evidence for an overall conceptualisation of these disorders. Should these factors differ significantly, however, more symptoms specific criteria will be warranted.

The following chapter will outline the development of diagnostic criteria for CFS and IBS, followed by a discussion of some of the difficulties apparent in the application of these criteria. Attention will then turn to an examination of some of the methodological weaknesses that have complicated much of the research in the area of the functional somatic syndromes. Chapter 4 will then introduce an aetiological model that will enable us to compare the evidence pertaining to the development of these two individual conditions.

Chapter 3.

IBS and CFS: Development of diagnostic criteria and associated methodological issues.

The process of establishing recognised diagnostic criteria for individual conditions follows a similar pattern, regardless of the nature of the condition. The classification process begins with a new set of symptoms that does not fit any pre-existing problem definition. Over time, clinical knowledge is accumulated and reported on in the form of case reports and clinical anecdote until diagnostic criteria can be formulated. Historically, this process was conducted intuitively, using observation, clinical reporting and imaginative insight (Kendell, 1989). In the last century, however, the process has been more formalised with the increasing sophistication of interviewing and statistical techniques aimed at developing and testing new classifications.

As discussed in the previous chapter, for those syndromes without clear aetiology, the pathway from clusters of symptoms to symptom-based diagnoses and then onto disease status, often has more to do with sociocultural factors than biological or clinical ones (Aronowitz, 2001). Without clear biological markers, a process of legitimising symptom-based diagnoses is often undertaken using techniques such as factor analysis, response to treatment analysis, and expert consensus panels. Diagnostic criteria for both IBS and CFS have been developed in this way. For each, the final step in the adoption of a widely accepted case definition entailed the meeting of expert scientific committees to review the evidence and determine the best means of classifying the condition. The classification process can have a far-reaching impact on the research and clinical practice associated with these conditions. As a means to illustrate this process, the current criteria for CFS and IBS will now be outlined, followed by a review of some of the major methodological difficulties that have hampered our understanding of these conditions.

3.1. Development of diagnostic criteria for CFS and IBS.

Chronic fatigue syndrome

The condition that we now know as chronic fatigue syndrome has had a long and controversial history. Over the last two centuries, conditions with persistent fatigue as the main feature have been diagnosed as febricula, neurasthenia, DaCosta's syndrome, chronic brucellosis, myalgic encephalomyelitis and chronic Epstein-Barr virus (Demitrack & Abbey, 1996). As has been the case for the functional somatic syndromes as a group, many of these labels implied aetiological mechanisms that proved difficult to verify, and in many cases were subsequently disproved. The plethora of definitions associated with these labels led to disparate research findings with no-one sure whether they were discussing the same condition, let alone able to determine consistent research outcomes. Following years of controversy surrounding the labelling of this condition, the Centers for Disease Control and Prevention (CDC) in the United States of America developed the first consensus case definition which became known as chronic fatigue syndrome (Holmes et al., 1988).

This first attempt at consensus definition was greeted with enthusiasm by the research community, however problems soon became apparent. Parts of the definition proved to be ambiguous, the number of symptoms required to make the diagnosis did not seem to differentiate cases from non-cases particularly well, and the general medical community seemed slow to embrace the criteria (Schluederberg et al., 1992). Around the same time, a second set of criteria, referred to as the British criteria were established during a consensus meeting at Oxford (Sharpe et al., 1991). These criteria stipulated that fatigue must be the main symptom which has been present for at least six months, and for at least 50% of the time. The fatigue needed to be of definite onset, be severe, disabling, and affect both physical and mental functioning. Whilst listing other symptoms such as myalgia, mood and sleep disturbance, these were not considered necessary for diagnosis.

Meanwhile the original CDC definition was revised and published and subsequently became known as the Fukuda Criteria (Fukuda et al., 1994). These criteria stated that an individual must be suffering from clinically evaluated fatigue that is: unexplained, persistent or relapsing, of new or definite onset, and which is not the result of exertion or alleviated by rest. The fatigue must result in a substantial reduction in activity levels in a range of daily activities (occupational, educational, social and personal) and be accompanied by at least four of seven symptoms; including impaired short term memory or

concentration, sore throat, tender lymph nodes, muscle or joint pain, headaches, un-refreshing sleep and post-exertional malaise lasting for more than 24 hours. Multiple other definitions still exist for this condition, however it is these two consensus definitions, the British and the Fukuda criteria that are most commonly used and accepted (see Table 2 for a summary of these criteria).

Table 2. Commonly used diagnostic criteria for chronic fatigue syndrome.

British Criteria, 1991	Fukuda criteria, 1994
Fatigue as the main symptom that: Is of definite onset (not lifelong) Is severe and disabling Affects both mental and physical functioning Has been present 6 months or longer and for more than 50% of the time	Clinically evaluated, unexplained fatigue that: Is persistent or relapsing Is of new or definite onset (not lifelong) Is not the result of ongoing exertion Is not substantially alleviated by rest Results in a substantial reduction in previous activity levels. And is accompanied by four or more of the following symptoms which must have been persistent or recurrent during 6 months of the illness and not present prior to the development of the fatigue: impaired short term memory or concentration, sore throat, tender lymph nodes, muscle or joint pain, headaches, unrefreshing sleep, post-exertional malaise lasting >24 hours

(Adapted from Demitrack & Abbey, 1996)

Both definitions agree on the CFS nomenclature, despite reservations that a substantial number of patients and clinicians saw it as trivialising the condition. The balance of evidence, however, suggested that such a label was necessary until more appropriate subclassification could be made based on clear aetiological evidence (Fukuda et al., 1994). As a way of countering this perception, the severity of the condition was emphasised in both definitions, with agreement that the fatigue must be debilitating and chronic (six months or longer). Each definition also provided a careful list of exclusion criteria that included any medical or psychiatric condition known to cause chronic fatigue (such as untreated hypothyroidism, hepatitis, schizophrenia and severe obesity), thereby emphasising the medically unexplained aspect of this condition.

The two definitions differ with regard to the number and requirements of associated symptoms, the level of functional impairment required and the specific exclusions listed (Nisenbaum, Reyes, Unger, & Reeves, 2004). As a result, prevalence rates are generally

slightly higher using the British criteria (between 1% and 3%) than when using the Fukuda criteria where rates are generally less than 1% (Wessely, 1996). Regardless of definition, however, primary care and community sample prevalence rates of CFS are very low, ranging from 0.01% to 2.6% (Ranjith, 2005). With such low prevalence rates, comparative studies in community samples become difficult, needing very large samples to ensure meaningful comparisons. As a result, researchers have often been forced to lower their thresholds to include groups that do not meet the strict criteria associated with CFS. For example, one study of post-infectious fatigue included 64 cases; however, only 23 fulfilled strict British criteria for the condition (Cope, Mann, Pelosi, & David, 1996). Recognising this difficulty, the Fukuda criteria included provision for a subthreshold condition (labelled idiopathic chronic fatigue) to represent those experiencing persistent fatigue that does not meet the full criteria for CFS. Because of a lack of detail regarding the application of this category, however, it has been interpreted very broadly; with some researchers requiring only six months of persistent fatigue, whereas others require all criteria except the full number of associated symptoms.

Irritable bowel syndrome

IBS has experienced a similar diagnostic development process as CFS. The term irritable bowel was thought to have been first coined in 1944 (Talley & Spiller, 2002), however it remained a diagnosis of exclusion until a group of researchers were able to demonstrate that the presence of six major symptoms could differentiate between IBS and organic disease (Manning, Thompson, Heaton, & Morris, 1978). These symptoms became known as the Manning criteria and were the first set of diagnostic guidelines for IBS. Soon after, Kruis and colleagues developed a scoring system that included what are now known as "alarm indicators"; including symptoms, test results or demographic indicators that should alert the physician to the presence of organic disease (Thompson, 1999). Since that time, other definitions have been developed that represent modifications or extensions of these original criteria (Agreus, 2000; Mearin et al., 2001). Just as was the case for CFS, however, it has been the criteria developed through a consensus scientific panel, known as the Rome criteria, that have retained the most credibility and are the most widely used.

Whilst the CFS criteria have remained relatively stable over the past ten years, the IBS consensus criteria have continued to be reviewed and refigured. The Rome criteria for IBS (see Table 3 for a summary) have undergone several revisions since a consensus committee in the late 1980s developed the original case definition (Thompson, Dotevall,

Drossman, Heaton, & Kruis, 1989). This definition was later modified (Thompson, Creed, Drossman, Heaton, & Mazzacca, 1992) and then reviewed to become the Rome II criteria (Thompson et al., 1999). These criteria are currently under review again, with the next revision scheduled for publication as Rome III in 2006.

Table 3. Accepted diagnostic criteria for irritable bowel syndrome.

Rome I criteria, 1989	Rome modified, 1992	Rome II criteria, 1999
Continuous or recurrent symptoms of: 1. Abdominal pain that is: a. relieved with defecation, or b. associated with a change in frequency or consistency of stool AND/OR 2. Disturbed defecation as evidenced by two or more of: Altered stool frequency Altered stool form Altered stool passage Passage of mucus USUALLY WITH 3. Bloating or abdominal distension	Continuous or recurrent symptoms of: 1. Abdominal pain that is: a. relieved with defecation, or b. associated with a change in frequency or consistency of stool AND 2. Irregular pattern of defecation at least 25% of the time as evidenced by two or more of: Altered stool frequency Altered stool form Altered stool passage Passage of mucus Bloating or abdominal distension 3. Symptoms should be present for at least three months.	At least 12 weeks in the preceding 12 months (need not be consecutive) of abdominal pain or discomfort that is associated with two of the following features: 1. Relieved with defecation 2. Altered stool frequency 3. Altered stool form

(Adapted from Saito et al., 2000)

The original Rome criteria stated that patients must be experiencing continuous or recurrent abdominal pain that is relieved by defecation or associated with a change in frequency or consistency of stool. This pain-related criterion could be accompanied or replaced by two or more symptoms of disturbed defecation as defined by altered stool frequency, stool form, or stool passage, or by the passage of mucus. These symptoms could also be accompanied by abdominal bloating. After concerns abut the specificity of the original Rome criteria, they were subsequently modified to include a minimum three-month criteria and the requirement of both pain-related symptoms and two symptoms of disturbed defecation. Confusion surrounding the two versions of the Rome criteria and the relative complexity of the criteria led to a major revision by the same working party. The revised Rome II criteria made abdominal pain or discomfort the main feature, thereby dropping the need for additional evidence of disturbed defecation unrelated to pain. Pain was still required to be associated with two of three features related to defecation. That is,

the pain needed to be relieved with defecation, or associated with a change in frequency or form of stool. The Rome II criteria also stipulated that the abdominal pain should be present for at least 12 weeks in the preceding twelve months, although not necessarily consecutively.

One example of the subtle impact of these revisions can be found in the changing emphasis on the symptom of abdominal pain in the various Rome criteria. In the original definition, abdominal pain was not an essential symptom. In practical terms this meant that IBS was able to be diagnosed with other symptoms of disordered bowel function in the absence of pain. The 1992 modification, however, made abdominal pain a requirement for diagnosis, and Rome II elevated its importance to being the cardinal feature. At this time, it was generally accepted that abdominal pain was the prominent symptom in IBS. A subtle wording change in the Rome II definition, however, saw the addition of "abdominal discomfort" as an alternative to "abdominal pain"; a change that could be interpreted as a relaxing of the stringent pain-related criteria by the inclusion of those less severely affected. A study analysing the effect of this word change did indeed find that twice as many IBS patients labelled their abdominal symptoms as discomfort rather than pain. However, with the two groups similar in all other respects, the authors were forced to conclude that the distinction most likely reflected a cognitive selection bias rather than any difference in the severity of the abdominal symptoms (Sach et al., 2002).

Whilst the two definitions of CFS had limited impact on the overall prevalence rates for the condition, revisions of the IBS definition have had a significant impact on prevalence rates, which vary widely according to the definitions in current use (Mearin et al., 2001; Saito et al., 2000). The epidemiology of any condition clearly reflects the criteria used to classify it and as would be expected, the stricter the criteria, the lower the prevalence of the disease (Agreus, 2000). Prevalence rates from studies using the Manning criteria range from 13% to 22%, whereas studies using Rome I criteria report rates between 9% and 15% (Mearin et al., 2004). In contrast, studies using the Rome II criteria find prevalence rates around 3 - 5%, leading some to conclude that these criteria may be unnecessarily restrictive (Boyce, Koloski, & Talley, 2000). Despite recent studies finding slightly higher rates for the Rome II criteria, many still question whether this definition underestimates the true extent of IBS. For example, a recent community study of IBS using self-report Rome II criteria confirmed by a follow-up interview, found a prevalence rate of 11% (Wilson, Roberts, Roalfe, Bridge, & Singh, 2004). The authors noted, however, that a quarter of these patients were not initially identified by Rome II criteria due to their symptoms not

being present at the time of the survey or due to respondents using different terminology to that of Rome II.

Another large population study also suggested that current methods of defining IBS consistently underestimate the number of sufferers regardless of the definition used (Hahn, Saunders, & Maier, 1997). This study examined the overlap of those who met the Manning criteria, the Rome modified criteria and those who self-reported having IBS, and found that only 12% of the total were in all three groups, indicating little overlap. As would be expected, the largest group were those who met Manning criteria, whilst almost all those meeting the Rome criteria also met the Manning criteria, confirming the stricter threshold for the Rome criteria found in other studies. Of interest, however, were the 18% of participants who reported experiencing significant bowel disturbance that they labelled IBS, who did not meet either set of criteria. Because of this the authors proposed that future studies should be extended to include those with subthreshold symptoms so as not to exclude a substantial portion of potential IBS sufferers.

These studies would suggest that the different criteria reflect differences in severity of symptoms. Despite there being no explicit reference to disability in any of the IBS criteria, it has been confirmed that the smaller group of patients who meet the Rome II criteria represent a more severely affected group in comparison to those who meet Rome I and Manning criteria. These patients experience higher levels of health care utilisation and disability, and describe poorer health-related quality of life (Badia et al., 2002). There is some indication however, that these differences may not simply be a matter of quantitative disparity. Some studies have indicated that when strict criteria for IBS are used, qualitative differences in the experience of IBS appear also; for example, the well documented association with psychopathology disappears (Read, 2001) and gender differences become less apparent (Muller-Lissner et al., 2001). It is therefore important in the interpretation of any study of IBS to have clarity with regard to the criteria used.

In summary, the establishment of internationally recognised diagnostic criteria for CFS and IBS has enabled researchers to compare their work with others and to advance knowledge in their particular field. These criteria have simultaneously increased the quantity and improved the quality of research on these syndromes (Hammer & Talley, 1999). However, there is still considerable variation in the definitions being used and the rigorousness with which each of these definitions have been applied. As can be inferred from the various revisions of diagnostic criteria for CFS and IBS, the development of case definitions for

symptom-based classification can seem something of a moveable feast. The criteria for both IBS and CFS have undergone a series of revisions over time, and it is likely that they will continue to do so as knowledge regarding each condition accumulates. Whilst such an ongoing process is necessary to incorporate new research or to correct previous omissions, an obvious effect is that group membership can change in a variety of ways with each revision. These effects can be obvious, such as the impact of a change in definition with regard to prevalence rates; or more subtle, such as a change in reported associations with other conditions. These problems have been particularly evident in research on IBS, which has seen a large number of definitions utilised over a relatively short period of time.

The usefulness and relevance of these criteria may also fluctuate according to their application, recruitment methods, and research setting. In many cases this has prompted researchers to consider subthreshold categories. It has been demonstrated that case definitions are useful when researching these conditions, however, it is still far from clear which of the existing definitions are most likely to advance our understanding of these conditions; particularly in the case of IBS. In order to determine the relevance of the research, therefore, it is important to determine not only which definition was used, but how rigorously that definition was applied, the setting in which it was used and the recruitment procedures followed. Methodological issues such as these will now be considered with respect to IBS and CFS.

3.2. Methodological issues.

Consistency of application of criteria.

In the absence of definitive objective disease measures, the application of diagnostic criteria is crucial to the validity of symptom-based diagnoses. Many of the criteria for IBS and CFS, however, require subjective assessment on the part of the clinician and/or the patient. For example, the Rome II specification that symptoms must be experienced 25% of the time or more is an arbitrary cut-off that can be interpreted differently by patients and clinicians depending on how the question is asked (Hammer & Talley, 1999). For CFS, the term "substantial disability" can be open to a wide range of interpretations also. The exactness with which exclusion criteria are assessed can also impact on group membership from study to study. Self-report studies that rely on subjects to recall health information may be less reliable than studies which use clinical examination to determine exclusions.

In their review of the overlap between the functional somatic syndromes, Aaron and Buchwald (2001) point out that the degree of overlap often depends on the rigorousness of the approach used to determine their presence, with noticeably different results being obtained by varying the method of definition.

Practical application of these criteria must also be considered if the results of research are to be relevant to clinicians and their patients. Given that patients with IBS and CFS are common in both primary care and specialist settings, the diagnostic criteria for those conditions must be valid and useful in those settings. In one recent study assessing the relevance of the Manning, Rome I (modified), and Rome II criteria (Lea, Hopkins, Hastleton, Houghton, & Whorwell, 2004), approximately 80% of general practitioners (GPs) had no specific knowledge of any criteria for IBS, and only 4% reported using them. In contrast, all gastroenterologists surveyed in the study knew of at least one of these sets of criteria. Despite their greater knowledge, however, only two-thirds actually used the criteria in their clinical practice.

The same authors went on to assess 100 IBS patients diagnosed in secondary care, according to each of the three main IBS definitions (Lea et al., 2004). They found that the most recent Rome II criteria excluded almost a quarter of these patients. Rome I was able to identify 82%, whereas 94% fitted the Manning criteria. The authors concluded that the Rome II criteria are unnecessarily restrictive and unlikely to be clinically acceptable. A separate study in primary care compared the rates of IBS diagnosis using a self-report questionnaire based on the Rome II criteria, and diagnosis by a GP. Of 533 patients attending a GP for a gastrointestinal complaint, 209 were diagnosed with IBS using the questionnaire. Of these, only 107 were diagnosed with IBS by the GP (Vandvik, Aabakken, & Farup, 2004). These authors also concluded that the role of the Rome II criteria in the clinical arena remains uncertain and deserving of further study.

These two studies give some indication of the complexity of transferring diagnostic criteria from research into practice. Despite community and secondary care studies demonstrating that the Rome II criteria do not accurately reflect the true extent of the problem, these criteria still capture a wider population than is identified by primary care physicians. Clinicians argue that they simply do not have the time for detailed questionnaires and lengthy diagnostic criteria. The low rates of usage may reflect the complexity of the criteria, however some researchers point to the fact that because they are not often validated in general practice, they may not even be applicable (Agreus, 2000). They point

out that patients themselves do not always discriminate between consistency and frequency of stools; rather they describe these symptoms as "constipation" or "diarrhoea". One study indicated that many patients themselves were unable to decide if their gastrointestinal problems could be described as mostly constipation, mostly diarrhoea or whether their symptoms fitted an alternating pattern (Hungin et al., 2003). Difficulties such as these have led to attempts to modify the IBS criteria considerably, in a way that more closely approximates actual clinician behaviour. At least one study has indicated that it is possible to greatly simplify the criteria in a manner that is answerable in a self-report questionnaire (Agreus, Talley, Svardsudd, Tibblin, & Jones, 2000).

It is clear that the criteria for IBS are still evolving and that changes will continue to be made in the future. In the meantime, researchers and clinicians must be aware of the impact of differing diagnostic definitions on research outcomes and their applicability to clinical practice. It is likely that rigidly applying the most recent criteria, in the case of IBS at least, may not always be appropriate. A wider definition such as the Manning criteria may be more useful in a community sample, whereas a more restrictive definition may be more suitable when conducting a medication trial in secondary care. In other cases, aggregating definitions may provide more relevant subject groups. Whichever definition is used, the rationale for its use should be noted, the definition and the application of that definition clearly stated, and the potential impact of the chosen definition on results should be commented on.

Subthreshold conditions.

In those conditions that are relatively rare, such as somatisation and hypochondriasis, it has been demonstrated that there are much larger numbers of patients with clinically significant subthreshold variants of these syndromes (Looper & Kirmayer, 2002). Prevalence rates for CFS are also very low, but it is clear that there is a much larger group that suffers from clinically significant fatigue. In a study of fatigue in general practice, 50-75% of those presenting with persistent chronic fatigue did not meet full criteria for CFS (Chalder, Godfrey, Ridsdale, King, & Wessely, 2003). As was noted earlier, different thresholds can impact greatly on prevalence rates in symptom-based diagnoses. In a community sample of nearly 5,000 people, only 0.8% were classified according to the Fukuda criteria which requires clinical examination (Nisenbaum et al., 2004). A further 5.3% met self-report criteria, but did not meet CFS criteria during clinical examination. Significantly, almost 22% of the sample reported chronic fatigue lasting greater than six

months, whilst a further 13% were experiencing prolonged fatigue of 1-6 months duration. With regard to IBS, the Manning criteria, for example, can be seen to identify a subthreshold group of patients who do not meet the stricter Rome II criteria for IBS. Some studies suggest that there may also be a group who report significant bowel disturbance that does not meet the Manning criteria (Hahn et al., 1997).

Common sense would suggest that threshold and subthreshold groups differ from their diagnosed counterparts simply with regard to severity and related disability. One study confirming this view found that those with prolonged fatigue were less severely disabled, had less severe symptoms and experienced less anxiety and depression than those with CFS, although their fatigue was of a similar duration (Darbishire, Ridsdale, & Seed, 2003). However, not all functional somatic syndromes include disability-related criteria, making it difficult to compare disability levels across conditions. There is no reference to disability in any of the criteria for IBS, and yet studies have found that individuals diagnosed according to Rome II criteria are more disabled than those diagnosed according to Rome I criteria (Badia et al., 2002; Mearin et al., 2004). Based on these studies, it would appear that subthreshold conditions can be distinguished according to disability; however, it is unclear whether disability criteria per se artificially create this distinction or not. In other words, it is possible that these differences in definition impact on the number of cases meeting criteria for a condition, without necessarily reflecting the nature of relative disability.

As suggested earlier, however, subthreshold cases may not only be differentiated by the severity of their symptoms and related disability, but also by the quality of their symptom profile. For example, a large prospective study of fatigued employees found that different factors predicted the development of CFS as opposed to subthreshold fatigue (Huibers et al., 2004). This study reported that these two groups could be distinguished according to age, gender, education, baseline exhaustion and number of visits to their general practitioner. Both groups, however, differed from those who were not fatigued with regard to their self-perception of their own health, with both subthreshold cases and cases rating themselves more poorly than those who did not go on to experience fatigue.

The considerable size of these populations with significant symptomatology who do not meet criteria for CFS and IBS, indicates they warrant investigation in their own right. Some have argued that subthreshold fatigue cases, whilst highly heterogeneous, may also, with their greater numbers, provide insight in to the more severely disabled CFS group

(Sullivan, Kovalenko, York, Prescott, & Kendler, 2003). Future research may benefit from widening their definitions to include both groups in their analyses in order to further explain the importance of subthreshold conditions. However it is also possible that the inclusion of subthreshold conditions may obscure important qualitative differences, and hamper research attempts to elucidate aetiological mechanisms and treatment modalities. More research is required to clarify the utility of subthreshold conditions in both research and clinical practice.

Recruitment and study setting.

As well as issues of definition, research setting, the method of recruitment and design of a study can all have a significant impact on research outcomes. Individuals who meet criteria for IBS and CFS are found in community samples, primary care (general practice), and secondary care (hospital outpatient clinics such as gastroenterology, infectious diseases). In some countries, tertiary care is also available in the form of specialist clinics for each condition. In addition, researchers are able to recruit from a variety of sources including random community samples, patient support groups, physician referrals, and self-referrals through advertising. Finally, study designs can range from single case reports to large community-based epidemiological investigations.

Despite this wide range of methodological options, a significant amount of the research conducted on CFS and IBS has been cross-sectional or retrospective in its design, and recruitment has largely been concentrated on those patients from secondary or tertiary care. Shortcomings are apparent in the methodologies of a number of studies which inevitably weaken conclusions and limit comparability (Aaron & Buchwald, 2001). The impact of study design will be covered in some detail in later sections with regard to aetiological implications. For now, the influence of study setting and recruitment will be considered.

Just as the prevalence of CFS and IBS differ according to the definitions used, the proportion of sufferers also differs according to the setting in which they are measured. In general, prevalence estimates rise in an orderly fashion according to the level of health care involvement; with the lowest prevalence rates in the community, slightly higher rates in primary care, between 20-50% of referrals to secondary care and the majority of referrals to tertiary care (Jones, 1999; Ranjith, 2005). As is often the case with the functional somatic syndromes, however, this seemingly sensible guide can belie a multitude of complexities. For example, in a specialised tertiary care clinic, the majority of clients

would be expected to fulfil criteria for the condition. However, one study indicated that only half of those referred to a clinic specialising in CFS met criteria for the condition (Euba, Chalder, Deale, & Wessely, 1996). Many primary care physicians do not use the CFS and IBS criteria as demonstrated in the previous section, making research estimates of the extent of these problems in primary care something of a moot point.

A number of studies have indicated that it is not only the expected differences in prevalence rates that are affected by the research setting. Qualitative differences have been found in groups of IBS and CFS patients according to the setting in which they are studied. For example, many reported epidemiological associations with CFS are thought to be attributable to study setting (Ranjith, 2005). CFS was initially viewed as a disorder affecting young, white, professional females and was thought to be a purely western phenomenon (Wessely, 1996). However, much of this research came from tertiary referral settings, and the results often reflected selection bias, and differences in health care access and utilisation. One study that directly compared CFS patients in primary and tertiary care, found that those in the latter setting had a higher level of socioeconomic status, were more likely to hold beliefs that their symptoms were physical, and had higher levels of fatigue, somatic symptoms and functional impairment, but lower levels of psychological symptoms such as depression and anxiety (Euba et al., 1996). Systematic reviews have since confirmed that CFS is found across all social classes and cultures (Afari & Buchwald, 2003).

The dangers of indiscriminately applying research results from studies using different settings and different recruitment methods are clear. In the UK, many of the controversies surrounding diagnostic labelling and appropriate treatment for CFS have been heavily influenced by patient advocacy groups arguing their cause in the wider media. A common methodology for investigators of the psychological effects of ill-health is to recruit through patient support groups. However, involvement in such groups formed for CFS patients has been associated with greater chronicity, greater severity of symptoms and a tendency to be less likely to accept a psychological cause for their illness. Being a member of such a group has also been linked to poor treatment outcome (Bentall, Powell, Nye, & Edwards, 2002). Such relationships cannot be transferred to all CFS patients uncritically, and the majority do not hold such strong viewpoints (Wessely & Hotopf, 1998). For example, in a study of CFS patients in primary care, 50% attributed their fatigue to psychological or mainly psychological causes, in contrast to other studies in secondary care settings where such attributions are uncommon (Darbishire et al., 2003).

The IBS literature is also littered with debates regarding the impact of research setting. In a recent editorial discussing the merits of the various IBS criteria, studies were cited that point to differences between primary care and tertiary care patients with regard to a number of variables. These included the number and severity of symptoms, history of treatment failure, symptom attributions, and the number of non-gastrointestinal complaints (Corsetti & Tack, 2004). One review compared the gender ratio in IBS patients according to setting and also found important differences. In tertiary care, females outnumbered males 3-4:1 in contrast to primary care where the ratio was around 2.6:1 and in community samples where the ratio was 2:1 (Muller-Lissner et al., 2001).

Given the qualitative differences between these setting-based groups, it is essential then that great care be taken when extrapolating findings from tertiary care studies to those individuals with IBS and CFS found in other settings. It makes intuitive sense that tertiary care patients will represent a more chronic and severely affected sample from those identified in other settings, and most research bears this out. But can the same be said for those in secondary care as opposed to those in primary care settings, and those identified in the community who have not sought medical care? Approximately half of those identified with IBS symptoms in the community have never been diagnosed and approximately a quarter have never consulted about their symptoms (Chang, 2004; Hungin et al., 2003; Wilson et al., 2004). With regard to CFS, a recent population study found that only 16% of identified cases had been previously diagnosed, indicating that the majority were probably unrecognised by the medical community (Solomon & Reeves, 2004).

Despite these considerable numbers, little is known about what causes patients to present in one health care setting over another, and why some choose not to consult at all (Jones, 1999). Symptom severity, extent of disability, comorbidity with psychiatric conditions and psychological distress have all been considered as potential reasons for differences in patients' utilisation of health care (Phillips, 1999). Earlier studies argued that health care seeking for IBS was related more to psychosocial factors than to the extent of IBS symptoms (Drossman et al., 1988; Whitehead, Bosmajin, Zonderman, Costa, & Schuster, 1988). Later studies, however, indicated that neither of these factors could account for the difference between the two groups (Heaton et al., 1992; Talley, Boyce, & Jones, 1997).

A number of recent studies have directly compared consulters with non-consulters and found that symptom severity is unrelated to health care utilisation. In one study socioeconomic status, sudden onset of symptoms, and the reporting of specific

physiological symptoms was related to CFS diagnosis, whereas the number and duration of fatigue symptoms was not (Solomon & Reeves, 2004). A postal survey of IBS patients found that the most reliable predictors of consultation were reduced quality of life and previous diagnosis of a stomach ulcer (Wilson et al., 2004). A Japanese study found that only 22% of those who met criteria for IBS had consulted for these symptoms, and that non-consulters had similar levels of symptom severity, psychological distress, parental history of bowel problems, history of acute gastroenteritis and gender as that of a comparison group of IBS patients in secondary care (Kanazawa et al., 2004). A comparison of IBS patients in primary and secondary care, found that they also had little to distinguish them with regard to symptom severity and health-related quality of life, although they did find differences in chronicity, gender, and related disability (Smith et al., 2004).

These studies suggest that the association between research setting and CFS and IBS symptomatology is not limited simply to symptom severity and that help-seeking behaviour is a complex and multifactorial process. One author has suggested that the lack of difference with regard to severity between patients in secondary care and those in primary and community samples, may be due to better diagnosis and treatment causing an overall reduction in severity ratings in this setting (Jones, 2004). A recent review has also indicated that the proportion of those seeking help for IBS differed considerably from country to country, indicating that differences in access to health care may be implicated (Talley & Spiller, 2002). More research is required, however, before these associations can be completely understood. In the meantime, research conducted in one setting can not be seen to automatically apply to patients identified in another. Most importantly, because of the dominance of secondary and tertiary care studies, there needs to be wider investigation of the relevance of these results to patients in primary care and to those non-presenters in the community with IBS and CFS.

In summary, acknowledgement of methodological issues such as the use and application of various criteria and the setting in which they are applied, are crucial in the study of the functional somatic syndromes. This section has provided an overview of these issues as they have applied to CFS and IBS. With both conditions, similar classification problems have been identified, lending weight to those who advocate the 'one' functional somatic syndrome conceptualisation. The case definition and classification of these conditions provides us with a tool with which to investigate further. However these criteria are operational and no more; they allow research to be conducted, but as some have pointed

out this does not reify the diagnosis in clinical practice (Wessely, 2001b). This review of the classification of the functional somatic syndromes has revealed the complex, and in many cases, fragmented nature of the literature surrounding these conditions. Keeping in mind these issues, the next section examines explanatory models of the functional somatic syndromes, once again concentrating on CFS and IBS.

Chapter 4.

Functional somatic syndromes: The cognitive-behavioural model.

"In the medicine of the future the interdependence of mind and body will be more fully recognised, and the influence of one over the other may be exerted in a manner which is now not thought possible." Osler, 1928 (cited in Kirmayer, 1988).

4.1. Historical overview.

'Mind over matter' in the functional somatic syndromes.

Much of the variation in terminology relating to the functional somatic syndromes is related to the shifting popularity of physiological and psychological models that was outlined in Chapter 2. This mind/body split has it origins with Descartes' 17th century model that separated the functions of the mind from that of the body, and indeed the rest of the material world (Deary, 2005). This distinction has throughout history led to polarised debate in a wide range of medical research, with each perspective competing to prove dominance. Mind/body dualism has often led to restrictive definitions and models at the expense of more integrative approaches. Theoretical models formulated to explain chronic pain, for example, have traditionally focused on physiology at the expense of psychology or vice versa, whereas comprehensive models that attempt to incorporate both, have been a relatively recent phenomenon (Novy et al., 1995).

Over the course of the 20th century, progress in areas such as anatomy, biology, physiology and pharmacology all reinforced bodily explanations of disease. The widespread success of this approach to the assessment and treatment of patients resulted in the biomedical model becoming the dominant force throughout much of the 20th century. The biomedical model relied on three fundamental assumptions: 1. for each illness there is a single cause, 2. that each cause of illness is disease, and 3. that the removal of disease will return the individual to health (Wade & Halligan, 2004). What did not fit within the strict confines of this model, however, was relegated to exclusively mind-oriented conceptualisations. As a result, the fledgling field of psychiatry was passed responsibility for all those conditions

seen to have their origins with the mind. The perceived separation of psychiatry from other fields of medicine and the rapid success of the biomedical approach culminated in an overall decline in the perceived importance of non-physiological aspects of medicine.

As the biomedical model thrived, global communication and increased literacy became commonplace. Prior to the 20th century, doctors and patients alike had been more comfortable with uncertainty. Treatments had reflected this, with reassurance from a trusted physician and placebo prescription commonplace (Aronowitz, 2001). Approaches such as these had been the mainstay of treatment for the functional somatic syndromes prior to the biomedical revolution. Dualist conceptualisations combined with a reductionist approach, however, meant that general physicians no longer felt equipped to deal with medically unexplained symptoms. The concept of somatisation had become tainted with implications of imaginary disease and fraud, and effective treatments remained elusive (Sharpe, 2001). For those suffering from these conditions, the prestige that doctors had enjoyed in the past was replaced with mistrust and dissatisfaction (Shorter, 1995). All these influences led to a widespread assumption by patients that doctors viewed their conditions as being "all in the mind" and somehow less legitimate than those with a clear physiological explanation. In the backlash that followed, many patients joined the dualist debate by strongly resisting any suggestion that their symptoms were not physiological, or that psychological treatments may be helpful (Sharpe, 2005; Wessely & Hotopf, 1998).

The need for more comprehensive models.

In the latter part of the 20th century it was becoming clear that dualist assumptions were getting in the way of fully explaining many forms of illness. The biomedical and psychiatric models had each failed to find a clear cause for the medically unexplained syndromes, both individually and as a group (Lask, 1996). But there was also recognition that this approach had failed to account for individual differences in the course and treatment response of other medically explained illnesses (Deary, 2005), and that even in patients with active disease processes such as psoriasis, non-physiological aspects were influential (Main, Richards, & Fortune, 2000). Single minded pursuits based on the mind/body distinction had produced inconsistent and contradictory findings due to their failure to consider the impact of interactions between these two functions (Editorial, 1995; Novy et al., 1995).

Dissatisfaction with the explanatory ability of restrictive models led to the introduction of more comprehensive models, capable of integrating evidence from both biological and psychological perspectives. In one of the first papers to advocate the adoption of the biopsychosocial model, Engel proposed in 1977 that the biomedical model was no longer a satisfactory guide for medicine. He put forward the argument that by minimising the impact of psychological, social and behavioural influences, the biomedical model had failed to recognise the myriad of individual influences that may alter the presentation and course of disease (Engel, 1977). He argued that the inclusion of these factors in models of illness would allow for the investigation of interactions between them, and potentially explain many of the individual differences that the biomedical model had struggled to account for. Since that time, the biopsychosocial model has become popular as a means of clarifying the aetiological mechanisms relevant to the functional somatic syndromes (Sharpe, 1991). It is now clear that restrictive conceptualisations that rely on one particular process or aetiological influence will be unable to explain the huge variation found not only in the group as a whole, but also within each individual condition (Moss-Morris & Wrapson, 2003; Palsson & Drossman, 2005; Wessely, 2001b).

It is also acknowledged, however, that biopsychosocial models are still at a fledgling stage, and that there is much work yet to be done to make these models clinically viable (Ryff & Singer, 2000). At present, the hypotheses generated draw on work done in isolation in the dualist climate, combined with accumulated clinical experience. Research has only just begun to investigate the myriad of interactions proposed by such models. Whilst intuitively appealing, the reciprocal interactions proposed are complex and do not easily lend themselves to investigation. As a result, studies have often been limited to exploring a small number of related variables rather than testing comprehensive chains of interactions. Many of the hypothesised interactions remain untested, and there is still only limited understanding of the mechanisms that bridge the various domains.

4.2. The cognitive-behavioural model.

A number of comprehensive biopsychosocial models have been proposed across varying disciplines and a wide range of illnesses. This thesis will now turn its attention to one particular biopsychosocial model in order to further discuss the aetiology of the functional somatic syndromes. The cognitive-behavioural model, which has its origins in the discipline of clinical psychology, has been chosen for a number of reasons. First, it

exemplifies the biopsychosocial approach, allowing for the integration of psychological, social, and biological influences in an inclusive and reciprocally interactive manner. Second, it uses concepts that have been operationally defined and as a result it has accumulated a large body of supporting research since first being proposed in the 1960's. Third, the comprehensive nature of the explanatory model has seen its adaptation to a wide range of illnesses, including the functional somatic syndromes. Finally, the approach has proven successful in its adaptation to treatment in the form of cognitive-behavioural therapy (CBT). This section will briefly outline the origins of the cognitive-behavioural model, highlight key features of the model and describe its adaptation to the functional somatic syndromes in general. Chapters five and six will then review existing evidence for the model with regard to CFS and IBS in particular.

Historical origins.

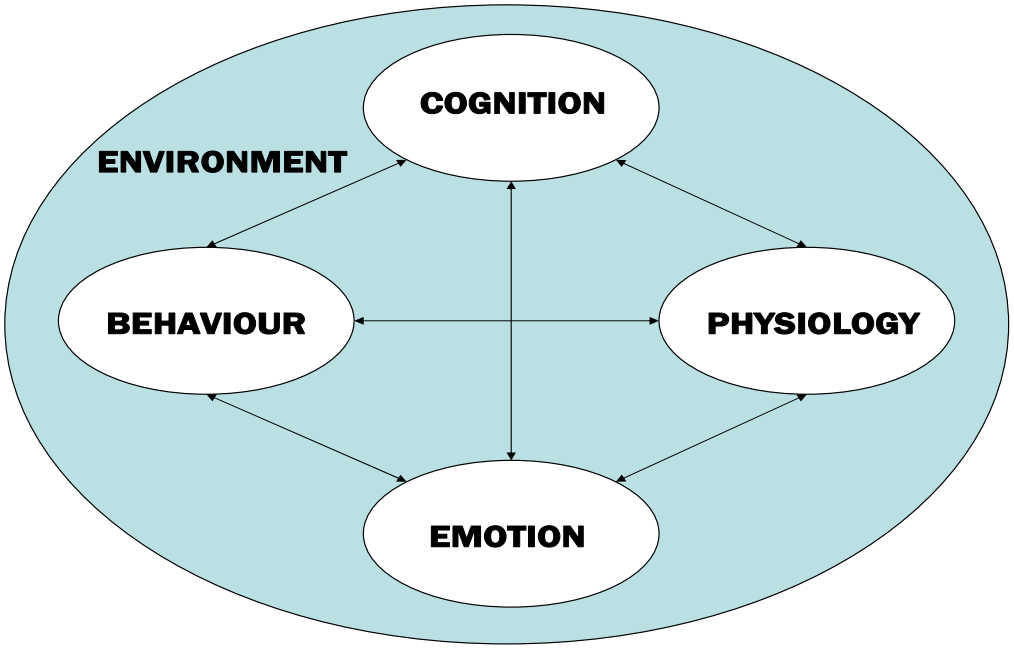
Cognitive-behavioural theory and the therapeutic application of that theory have their origins in the 1960s and 1970s. At this time there was growing dissatisfaction with psychoanalysis and behaviourism which disregarded the influence of cognition or the effect of the conscious mind (Dobson & Dozois, 2001). New approaches that incorporated the role of cognition were first developed for the treatment of depression. These interventions quickly became popular as it was demonstrated that incorporating the patient's cognitions into the psychotherapeutic process could significantly improve the efficacy of that treatment. All approaches had a common emphasis on targeting symptoms and problems in a manner that leant itself to the experimental method, something the psychoanalytic method had always resisted (McGinn & Sanderson, 2001).

Based on their success in the treatment of depression, cognitive-behavioural theory and techniques were then adapted to the conceptualisation and treatment of a wide range of disorders including anxiety, eating disorders, and substance abuse. More recently, treatments for disorders previously thought not to be amenable to the cognitive-behavioural approaches, such as the personality and psychotic disorders have also been developed (Hollon & Beck, 1994). As Aaron Beck (1991) highlighted in his 30 year retrospective on the development of cognitive therapy, one of the strengths of the cognitive-behavioural model is that the general principles can be applied across such a wide range of conditions. However, he reminds us that part of the success of the approach has been due to the specificity of the cognitive conceptualisations for each disorder or problem area.

Core concepts.

The cognitive-behavioural model is built around three core concepts that help to define the development and maintenance of a particular problem or illness. The first of these concepts incorporates the biopsychosocial proposal that physiological, psychological and social influences are equally important components in the understanding of illness. The cognitive-behavioural model expands the psychological component for investigation by separating out cognitive, behavioural and emotional domains. The social component is relabelled as environmental influences and incorporates the individual's interpersonal, physical and cultural environment. These core domains have been conceptualised by Padesky and colleagues as the five part model; incorporating cognition, emotion, behaviour, physiology and environment (Padesky & Mooney, 1990). The relationships between these domains are seen to be reciprocal in manner, with each one capable of eliciting or modulating changes in the others (see Figure 1). In this sense causal priority is seen to be less important than the interactions between them. Given that the cognitive-behavioural model originated in the field of psychology it necessarily emphasises the role of psychological factors, however modern theorists are quick to point out that it does not do so at the expense of other components (Turk & Salovey, 1995).

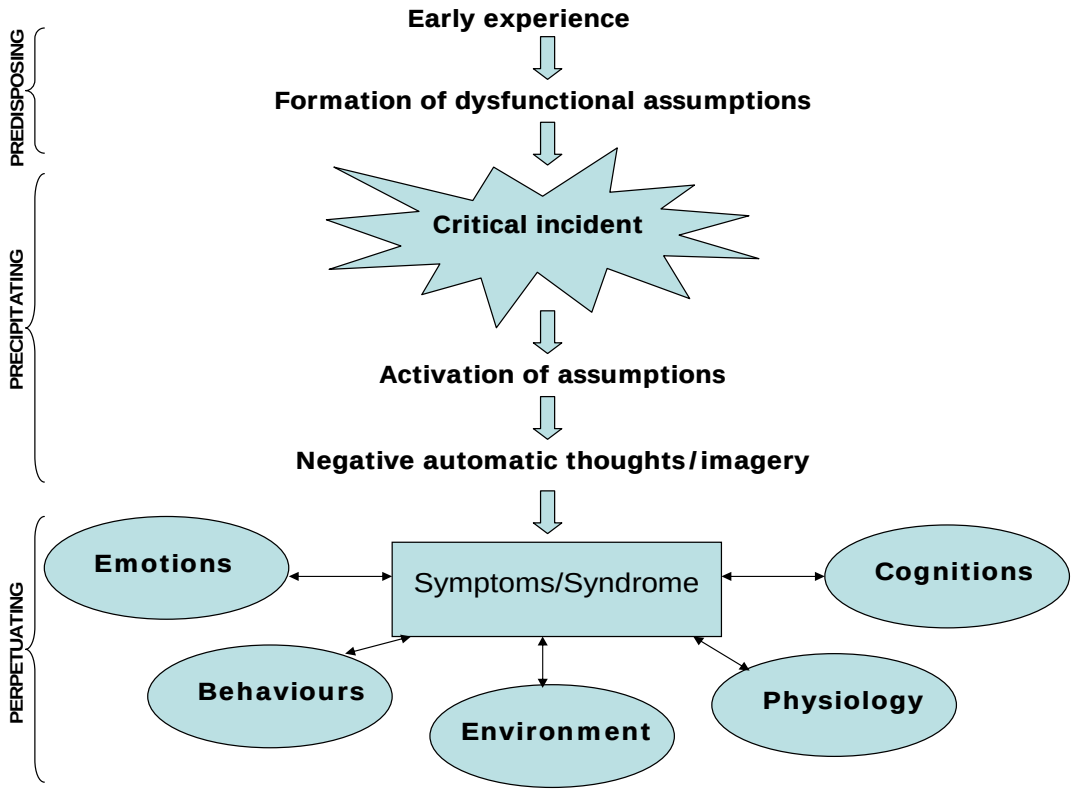
Figure 1. Five part cognitive-behavioural model.



(Adapted from Padesky & Mooney, 1990)

The second concept applies to how the evolution of a disorder is conceptualised in this model (see Figure 2). The model highlights the importance of viewing predisposing, precipitating and perpetuating factors in the aetiology of an illness as varied and potentially independent. This contrasts with the more straightforward biomedical model which focuses on a linear model of physiological changes at the expense of other potential influences. In this way, the cognitive-behavioural model differentiates between factors that have made the individual vulnerable to the development of an illness, those factors that have triggered the illness, and those that maintain or perpetuate it. Once again, although there is an emphasis on the role of psychological variables at each of these phases, the influence of variables from the other domains is considered equally important. For example, significant early experience is considered an important psychological predisposing factor in the development of a disorder, in the sense that it prompts the formation of general beliefs and assumptions about the world that may precipitate or maintain dysfunction. However, a range of other predisposing factors such as genetic vulnerability can also be considered within this model.

Figure 2. Cognitive-behavioural model of the development and maintenance of symptoms and illness.



(Adapted from Warwick & Salkovskis, 1990)

An example of this process could be as follows. An individual who grows up with high parental expectations to succeed may form the inaccurate assumption that in order to be accepted and liked by others they need to be successful in all areas of their lives. This provides them with a sense of self-esteem that may be functional for the individual until they experience a critical incident which leaves them unable to maintain their high standards. This may take the form of a major life stressor or a serious illness, and is viewed as the precipitant or trigger for the development of symptoms that interfere with daily activities. The situation of being unable to maintain previous standards because of these symptoms is in direct conflict with their prior assumptions, leaving the individual vulnerable to negative thoughts about themselves such as, "if I do not go back to work my boss will sack me". These thoughts may lead the individual to overly focus on symptoms, prompting a range of cognitive, behavioural, emotional, environmental and physiological responses to them. These responses can in turn intensify existing symptoms or create new ones that ultimately perpetuate the problem.

The third core concept of the cognitive-behavioural model is the assumption that individuals are active processors of information about themselves and the world around them. The client is viewed as the most important instrument of change, allowing them to take control of the effect their illness has on their life. Because the cognitive-behavioural model implies that changes in cognition and behaviour can affect physiology and emotion, and vice versa, targets for change are more likely to be viewed as achievable by the client themselves. In addition, the therapist-client relationship is a collaborative and empowering one, such that the client is equipped to become their own therapist once treatment ends. It is this concept that has been credited with treatment trial results that indicate gains made in cognitive-behavioural treatment are maintained at follow-up, something that has proved more difficult for pharmacological and other psychotherapeutic treatments (Blackburn & Davidson, 1990).

The cognitive-behavioural model provided an approach to treatment known as cognitive behaviour therapy (CBT), which is based around these three core concepts. The success of CBT has been largely responsible for the widespread popularity of this approach. Although clinicians may vary the order of the different aspects of therapy according to the condition and individual treatment priorities, the standard components are the same across all approaches (Sharpe, 1993). Treatment begins with a thorough assessment to elicit cognitions, behaviours, and emotions, in addition to physiological and environmental factors relevant to the presenting problem. This is followed by education regarding the

multifactorial model including the importance of perpetuating factors, and presentation of the treatment rationale. As mentioned above, an important focus during this stage is engagement in the treatment process. Similarly, an emphasis on the role of cognitions and behaviours in the predisposition and perpetuation of problems highlights their importance as useful targets for intervention that remain in the control of the individual. The main part of treatment involves the challenging of symptom-related cognitions, facilitation of behaviour change, problem solving and a graduated increase in adaptive behaviours (such as increasing activity levels) and corresponding decrease in maladaptive behaviours (such as avoidance). Finally, preparation for the future involves specific planning for relapse prevention.

Adaptation of the cognitive-behavioural model to the functional somatic syndromes:

The adaptation of the cognitive-behavioural approach in general medicine began in the 1970's, when Lang put forward the view that subjective (i.e. cognitive/affective), behavioural and physiological response systems could all be influenced by a change in the other (Salkovskis, 1989). This perspective provided the foundation for interventions such as biofeedback, where individuals learned to voluntarily control physiological responses. On its own, however, patients found the skills learned during biofeedback difficult to generalise to everyday life. In contrast, cognitive-behavioural principles were seen to be more adaptable to everyday settings and began to be applied to a range of health problems such as stress management to reduce the risk of heart disease, smoking cessation, and helping patients deal with painful medical procedures.

In the 1980s cognitive-behavioural approaches were beginning to be applied to the field of psychosomatic medicine. For many years prior, treatment of the functional somatic syndromes had been seen as something of an oxymoron. Review articles would frequently conclude that there were no established treatments that could be considered efficacious for these conditions (Mayou & Sharpe, 1997). Patients with these conditions often provoked a nihilistic response in doctors frustrated by the lack of treatment options available, placing an even greater strain on the therapeutic relationship. The lack of effective treatments was a clear contributor to the stigma surrounding these disorders. Where conventional medical and psychiatric treatment had been found wanting, it was hoped that cognitive-behavioural methods could be effective, as they had been for depression and anxiety. Some of the first models to adapt the cognitive-behavioural approach to the functional somatic syndromes

were formulated for chronic pain (Turk, Meichenbaum, & Genest, 1983), and for health anxiety in its more severe form of hypochondriasis (Salkovskis & Warwick, 1986). Both these models drew on the accumulated knowledge from cognitive models of depression and anxiety in search of new treatment approaches for these conditions.

In an early description of the cognitive-behavioural approach to somatic problems, Salkovskis emphasised that patients' beliefs about their symptoms impact upon their mood, behaviour and physiology (Salkovskis, 1989). Most importantly, he put forward the idea that psychological factors can have a major role in the maintenance of somatic problems, whether or not these problems originally had a physical cause. These psychological factors included increased bodily focus, avoidant behaviours, and the misinterpretation of symptoms and medical information. He applied this model to a wide range of somatic problems such as hypochondriasis, irritable bowel, hypertension, insomnia, and chronic pain. Sharpe and colleagues then developed a general cognitive-behavioural model of the functional somatic syndromes, placing central emphasis on cognitions, and once again with a treatment focus (Sharpe et al., 1992).

Much of the early work in the area was carried out with patients whose previous physical interventions had failed, and who generally had more severe and chronic symptoms. As these patients were often particularly sensitised to any suggestion that their symptoms may be purely psychological in nature (i.e. "all in the head"), they would often view psychological treatment with some scepticism, if not outright hostility. Because of this, the early assessment process and engagement with the patient was seen as a crucial to ensure treatment success (Salkovskis, 1989). The collaborative approach emphasised by the cognitive-behavioural method provided a supportive and unconditional relationship within which an acceptable and easily understood model could be presented. Significantly, the cognitive-behavioural model did not require patients to accept a psychological explanation of their symptoms; instead, it gave them an opportunity to consider the impact of all variables in the development and maintenance of their symptoms (Taerk, 1988; Wessely, Butler, Chalder, & David, 1991). For many patients, the advent of cognitive-behavioural therapies provided the first opportunity in which an explanation of *why* they were experiencing symptoms was presented, as opposed to what their symptoms were *not*.

Following these early applications, the cognitive-behavioural model has since been applied to other functional somatic syndromes as well as several explained illnesses in which psychological factors have been found to be influential (Magnusson, Nias, & White, 1996;

Moss-Morris & Wrapson, 2003; Rief & Nanke, 1999; Sharpe, 1997; Williams, 1997). Developed in clinical practice, each cognitive-behavioural model of an individual syndrome has helped to develop an understanding of the syndromes in general. Reviews of treatment efficacy consistently demonstrate CBT to be effective in alleviating distress and disability associated with many of the disorders conceptualised by the cognitive-behavioural models (Hollon & Beck, 1994; Sharpe, 1995b). Randomised controlled trials have demonstrated the effectiveness of this approach in a wide range of functional somatic syndromes (Kroenke & Swindle, 2000; Looper & Kirmayer, 2002), including CFS (Prins et al., 2001; Rimes & Chalder, 2005; Whiting et al., 2001) and IBS (Drossman et al., 2003; Hutton, 2005; Kennedy et al., 2005; Tkachuk, Graff, Martin, & Bernstein, 2003). As a result, CBT has become one of the most promising treatments capable of being adapted to many if not all of the functional somatic syndromes.

Despite the success of cognitive-behavioural treatments for the functional somatic syndromes, not all are convinced of its merits. Some question the enthusiasm for the approach, arguing that it promotes a 'one size fits all' approach to psychotherapy that may not be suitable for a large number of individuals (Holmes, 2002). Others believe that the model tends to over-simplify what are undoubtedly complex processes (Sharpe et al., 1995). In addition, it is rarely commented on that many of the theoretical underpinnings of these models remain untested. At the time of these models first being presented, many of the hypotheses were based on clinical experience with patients from tertiary care settings, and had the stated aim of exploring potential treatment options. The comprehensiveness of the cognitive-behavioural model was an early strength, allowing evidence to be incorporated from research in other fields. However, much of this evidence was taken from studies not designed to specifically test the cognitive-behavioural model. The urgent need for effective treatments for the functional somatic syndromes and an emphasis on proving the efficacy of CBT resulted in treatment based on assumptions that in many cases are still to be empirically tested.

Attention has now turned to the investigation of more specific hypotheses regarding the influence of cognition, behaviour, emotion, physiology and the environment in the development and maintenance of the functional somatic syndromes. Recently, there has been a substantial amount of research carried out across a variety of settings and for a variety of particular disorders providing additional support for the cognitive-behavioural model. The following chapters will once again turn to a more specific examination of CFS and IBS. After a brief description of the cognitive-behavioural model as it applies to each

condition, the evidence will be reviewed according to the developmental approach described earlier; that is, according to the relevant predisposing, precipitating and perpetuating factors associated with CFS and IBS.

The comprehensive nature of the cognitive-behavioural model means that research from almost every scientific discipline would be required to fully review each of the five domains. In order to limit the scope of this review, and in keeping with the psychological foundations of the cognitive-behavioural model, the focus in these chapters will be on the most important cognitions and behaviours highlighted by the cognitive-behavioural models of these two conditions. Reviewing the myriad of physiological variables thought to be associated with these conditions is beyond the scope of this thesis, so discussion will be limited to the impact of acute illnesses in the development of these conditions. Similarly, the consideration of emotional variables will be limited to the impact of anxiety and depression. Societal factors have already been considered in Chapter 2 in the context of classification and will not be dealt with further here. By limiting the review in this way, it is hoped to give the reader an overall understanding of the literature most relevant to the cognitive-behavioural model of these two conditions and an indication of what is required for future research.

Chapter 5.

The cognitive-behavioural model of chronic fatigue syndrome.

One of the first conceptualisations of CFS to use a biopsychosocial approach was presented in 1991. Drawing on a wide range of research, Wessely and colleagues rejected the prevailing view that a single causal factor would be found for CFS, which at the time was referred to as post-viral fatigue syndrome. Instead, they proposed that a number of biological, social and psychological factors interact to effect the development and maintenance of this condition (Wessely et al., 1991). Without explicitly labelling their model as such, they effectively proposed the formative cognitive-behavioural conceptualisation of CFS. Their model hypothesised that a viral precipitant leads to symptoms such as fatigue and myalgia, which can in turn prompt a number of responses including inactivity or depression. Any of these factors may then instigate a perpetuating cycle of fatigue and ongoing disability.

Specific cognitions and behaviours were seen to be essential components in this process. A viral illness may prompt a period of inactivity; however, the individual's response to the effects of that inactivity was seen to determine whether they will return to full health or continue to experience symptoms. For example, a premature or sudden return to previous levels of activity following a viral illness could provoke further symptoms. The cognitive appraisal of these symptoms may include a belief that the symptoms represent ongoing illness or that exercise is harmful, leading to further avoidance of activity. The subsequent failure to return to previous levels of functioning may then activate negative cognitions that result in feelings of low mood, which can exacerbate existing symptoms or produce additional ones. In this way, cognitive variables such as physical illness attributions, excessive symptom focus and dysfunctional assumptions about the illness are seen to contribute to the perpetuation of symptoms. Behavioural factors such as excessive bed-rest and avoidance of activity were also seen to be central to the perpetuation of fatigue. One of the strengths of the cognitive-behavioural model was its ability to integrate a wide variety of influences. Although any one of these factors on its own was unlikely to result in ongoing fatigue, the model explained how each was capable of prompting a chain of interactions that could do so.

Michael Sharpe and colleagues have also written extensively on the cognitive-behavioural model of CFS (Sharpe, 1995a; Sharpe, 1997; Sharpe et al., 1992). This group also placed a clear emphasis on the central role of cognitions in the development of CFS, pointing out that bodily sensations can be caused by innocent physiological changes, physical disease or emotional arousal. They too emphasised that it is the cognitive interpretation of those sensations that may be more important in determining whether a functional somatic syndrome like CFS develops, rather than the sensations themselves (Sharpe et al., 1992). Sharpe and colleagues added to the original model, however, by suggesting that a range of variables may also predispose individuals to the development of CFS. They hypothesised that factors such as perfectionism, a tendency to "bottle-up feelings", and a hectic lifestyle combined with high personal expectations, can contribute to the development of CFS (Surawy, Hackmann, Hawton, & Sharpe, 1995). These predisposing variables were seen to be important in initiating the dysfunctional cognitions and behaviours highlighted by the earlier model. In endeavouring to explain the complex nature of CFS and promote useful treatment options, the cognitive-behavioural model provided a framework by which researchers could empirically test a number of hypotheses. The following sections will examine the accumulated evidence for the main predisposing variables, precipitants and perpetuators of CFS identified by the cognitive-behavioural model of CFS.

5.1. Predisposing factors

An understanding of what factors predispose an individual to illness can provide important information to guide not only treatment, but also prevention. Prior knowledge of identifiable markers of vulnerability makes it possible to reduce disability and suffering through the use of interventions aimed at minimising risk. Knowledge of predisposing variables can also provide insight into the development of perpetuating factors in the maintenance of syndromes such as CFS. Despite the clear benefits of identifying and understanding what predisposes an individual to illness, the investigation of these variables is not without difficulty. In order to determine what makes an individual vulnerable to a particular illness, it is first necessary to investigate the histories of those who already have the illness. Without detailed objective evidence, however, much of this information is subject to the recall bias of retrospective reporting.

Prospective investigations provide a more objective method of examining predisposing variables. However, they require very large populations and often extensive time periods

in order to identify enough people with the targeted illness. Even then, researchers are limited by the type of information previously gathered. To complicate matters further, it is rare to find variables that consistently indicate the certain development of an illness. It is more often the case that many variables are implicated at varying points and with varying degrees of importance. Because of these methodological difficulties and others discussed in Chapter 3, the empirical investigation of predisposing factors in the development of CFS has been difficult and empirical evidence is limited as a result. Variables relevant to the cognitive-behavioural model that have been investigated include; biological influences, previous psychiatric disorder, early experience, personality and premorbid behaviour.

Biology

There has been strong research interest in the investigation of physiological causes of CFS over the last few decades. Several reviewers have outlined this evidence in some detail, and the reader is referred to these articles for a more in depth discussion of these variables (Afari & Buchwald, 2003; Komaroff & Buchwald, 1998; Moss-Morris & Petrie, 2000a). Over time, various hypotheses have risen to prominence as possible causal mechanisms for CFS. These theories have been extensively investigated only to fall from favour in the absence of definitive evidence to support them. Earlier theories focused on the role of viral illnesses, whereas later research has considered immunological deficiencies, central nervous system abnormalities and genetic markers associated with the condition. Despite this lack of conclusive evidence, most researchers agree that subtle and complex physiological mechanisms are implicated in the development and particularly the maintenance of this disorder.

With regard to physiological factors that may predispose an individual to CFS, it is likely that there is more than one aetiological pathway to the development of chronic fatigue syndrome. Of the many pathophysiological mechanisms linked to CFS, however, none has proven to be consistent across the total subject group, leading one reviewer to conclude that, "it seems likely that CFS is a heterogeneous disease with different pathophysiological disturbances that manifest with similar symptoms" (Afari & Buchwald, 2003, p.221). It is also clear that a number of risk factors can be present in an individual without them succumbing to the condition. Because of these inconsistencies, treatments based on physiological links have been variable in their effects, and as a result none have been able to be recommended universally.

There are several possible reasons for these inconsistencies. The distinctions between factors that predispose an individual to CFS and those that perpetuate it have not always been made clear in the study of physiological mechanisms. Much of the research in this area has been prompted by findings of abnormalities in patients who already have CFS. As a result it has been difficult to establish whether these abnormalities have predated the onset of CFS or have arisen as a result of it. Alternatively, individuals may differ with regard to particular biological markers due to their complex interactions with other factors. It is also possible that post-infectious biological changes may only occur in the presence of a genetic vulnerability, for example. In a similar way, particular physiological factors such as neuroendocrine dysfunction may only be important in the presence of psychosocial distress. Reflecting this complexity, it is now accepted by the majority of researchers that whilst individual physiological influences will continue to offer important information about the development of CFS, it is unlikely to be able to provide a comprehensive answer to the question of vulnerability to this condition.

Premorbid psychiatric disorder and psychological distress

A similar situation exists regarding the influence of premorbid psychiatric conditions with evidence to support a link, but little to confirm a causal pathway. Studies have consistently found substantial overlap between CFS and the disorders of somatisation, anxiety and depression. A recent review of the literature highlighted the greatly increased prevalence of these disorders in individuals with CFS compared to healthy controls (Afari & Buchwald, 2003). Prevalence rates of mood disorder in CFS are reported to be around 25%, with lifetime prevalence as high as 50-75%. Similarly, rates of somatisation disorder are high; around 28% compared to only 0.03% in the community. Lifetime prevalence of panic disorder in individuals with CFS also ranges from 17% to 25% compared to 3.5% in the community.

Some of this overlap can be contributed to classification problems of the type reviewed earlier. Just as the operational definitions of several of the functional somatic syndromes ensure a degree of overlap between them, so too do the criteria for CFS and psychiatric disorders, making the relationship between disorders such as these difficult to unravel. Some authors suggest that the comorbid diagnoses of CFS and psychiatric disorder reflect fundamental flaws in our diagnostic systems, and that the differential diagnosis may have more to do with the perspective of the clinician than the symptoms of the patient (Sharpe, 2005). As was the case with comorbid functional somatic syndromes, however, symptom

overlap alone is unlikely to be able to explain the strength of the relationship between CFS and psychiatric conditions.

Taking depression as an example, the overlap with CFS could reflect one of the following options; CFS is a form of depression, depression causes CFS, CFS causes depression, or that the two conditions reflect different manifestations of a separate disorder (Moss-Morris & Petrie, 2000b). It is the first two hypotheses that are relevant to examining variables that may predispose an individual to CFS. The first considers CFS to be simply a somatic manifestation of psychological distress, with some researchers proposing that it and several other functional somatic syndromes can be regarded in the context of a spectrum of affective disorders (Hudson & Pope, 1994). If CFS is depression in disguise, then the same vulnerabilities that apply to that disorder will also lead to CFS. Despite the attraction of this concept, there is now substantial evidence to suggest that depression and CFS are distinct, regardless of their striking overlap. Differences in the type and presentation of core symptoms in the two conditions, physiological differences between them, the ineffectiveness of antidepressants in CFS, and the fact that not all patients with chronic disabling symptoms can be given a psychiatric diagnosis, all point to considerable differences between the two conditions (Afari & Buchwald, 2003).

The second hypothesis suggests that depression causes CFS. The same evidence that supports a distinction between the two conditions also argues against causality, however. For example, if depression were to be the primary cause of CFS, it would be expected that all CFS patients would report a history of depression, that there would be physiological similarities between the two conditions, and that the core symptoms would be the same. None of these assumptions have been proven empirically. Once again, however, the lack of evidence for direct causality does not mean that depression and other psychiatric illnesses are not risk factors for the development of CFS. For example, it is possible that depression increases the likelihood of other risk factors for CFS such as the physical de-conditioning associated with prolonged inactivity.

It is only possible to determine vulnerability using a prospective design however, and a small number of studies using subjects who have experienced a viral illness have done so. These studies provide some evidence that psychological distress and psychiatric disorder at the time of the initial virus is a better predictor of the development of fatigue than is the virus itself (Cope, David, Pelosi, & Mann, 1994; Hotopf, Noah, & Wessely, 1996; Wessely et al., 1995). A follow-up study to one of these used a nested case control design to more

accurately define the role of psychiatric disorder in the development of both fatigue and psychiatric disorder post-infection (Cope et al., 1996). They found that although past psychiatric history was the only predictor of a post-viral psychiatric diagnosis, it was not able to predict the development of post-viral fatigue, despite fatigue cases having higher levels of current and past psychiatric disorders than non-fatigued controls. Instead, fatigue caseness was significantly associated with other variables such as fatigue at the time of illness, time off work and attributional style. A similar study found no association between anxiety or depression and failure to recover at 2 or 6 months post glandular fever, however there was a significantly higher level of somatisation in the non-recovered group (Buchwald, Rea, Katon, Russo, & Ashley, 2000). A further study did find a significant association between fatigue post glandular fever and psychological distress at 3 and 6 months post illness, but this association was not robust in comparison to other psychological variables such as illness perceptions (Candy et al., 2003).

In summary, there are mixed findings with regard to the role of psychiatric disorders and psychological distress in the development of CFS and methodological difficulties prevent firm conclusions. The diagnosis of fatigue in these studies has been variable, ranging from self-reported fatigue states to clinician diagnosed CFS. Although some studies have verified self-reported history of psychiatric disorders with medical records most have relied on retrospective reporting. In addition, those studies that have measured psychiatric disorders at the time of viral illnesses have not always accounted for the effect of physical illness on depressive symptoms. Similarly, some studies have used measures of psychological distress whilst others have used categorical diagnoses (Buchwald et al., 2000; Candy et al., 2003). The stronger associations are with the former rather than the latter, indicating that diagnosable psychiatric illness may be less important than subthreshold levels of anxiety and depression.

An example of the subtle nature of the differences between CFS patients and those with mood disorders is evident in the pattern of responses on the Beck Depression Inventory (BDI). Whilst endorsement of somatic and vegetative items on the BDI appears to be similar, the two groups can be distinguished according to their responses to the mood and self-reproach items, with depressed patients having higher levels than CFS patients on these items (Johnson, DeLuca, & Natelson, 1996; Solomon & Reeves, 2004). These results suggest that there may be qualitative as well as quantitative differences between the type of depression experienced by those with CFS and those with a depressive disorder. Using instruments to measure depression (such as the Hospital Anxiety and Depression

Inventory) that deliberately exclude questions known to be affected by poor physical health may be more useful. Clearly, more research is required before the importance of this predisposing factor can be determined.

Personality and premorbid behaviours

The cognitive-behavioural model includes several hypotheses about personality and behavioural styles in the predisposition to CFS. Some of these factors included a constant striving to achieve high standards in individuals and/or their families, a high degree of perfectionism, a refusal to admit to weakness and a tendency to place the needs of others before their own (Surawy et al., 1995). Very few of these variables have been empirically examined, however, due to considerable methodological difficulties associated with the examination of premorbid personality.

The characteristics described above were hypothesised to result in a hectic lifestyle prior to the development of CFS and there is some empirical evidence to support this link. Retrospective research has indicated that patients with CFS often describe themselves as more 'action-prone' prior to their illness, as compared to patients with a chronic medical condition or those with primarily depressive or anxious symptoms (Van Houdenhove, Neerinckx, Onghena, Lysens, & Vertommen, 2001; Van Houdenhove, Onghena, Neerinckx, & Hellin, 1995). This tendency to be oriented toward direct action and achievement was often expressed in conjunction with a description of themselves as being very self-sufficient before they got ill, and more likely to look after others' needs than their own (Lewis, Cooper, & Bennett, 1994). Based on this research and that examining physiological responses to stress, some have concluded that a premorbid tendency to overactivity may reflect a stress regulatory device that is the result of complex biopsychosocial influences (Van Houdenhove, 2005). According to this theory, when this mechanism of dealing with stress is unable to be accessed (due to protracted illness or injury) a series of disruptions can occur that lead to fatigue.

The related concept of perfectionism has also been linked to the development of CFS, however the evidence regarding this link has been conflicting. A cross-sectional study of female nurses found that negative perfectionism (for example, doubts about actions and concerns about mistakes) was strongly associated with fatigue, whereas positive perfectionism (for example, organisation and personal standards) appeared to have a protective effect (Magnusson et al., 1996). The authors concluded that whilst negative

perfectionism may be sustainable under normal circumstances, when faced with additional stressors it is no longer productive and may trigger the perpetuating cycle of fatigue described by the cognitive-behavioural model. A later study compared CFS patients to those with rheumatoid arthritis and found no difference in personality measures or self-reported perfectionism, concluding that these differences may be the result of stereotyped reporting of CFS patients' personalities rather than actual differences (Wood & Wessely, 1999).

Confounding variables in these studies include the inherent bias found in retrospective reporting and the inability of cross-sectional research to account for the notion that behavioural responses undoubtedly change over time. For example, the contrasting results in the two studies regarding perfectionism can be accounted for by the hypothesis that levels of perfectionism may decline when faced with the reality of being unable to live up to those expectations. Conclusions regarding personality and behavioural variables in the predisposition to CFS are therefore limited by the cross-sectional and retrospective methodologies used in these studies. Once again, it is important that these hypotheses are examined prospectively before we can be certain of their importance.

Early experience and the development of dysfunctional cognitions and behaviours

The cognitive-behavioural model views personality variables and behavioural styles as being closely linked to core beliefs and assumptions about the world. The model suggests that cognitions such as these have their origins in an individual's early experience of the world. A perception of high parental expectations, the experience of significant childhood illness, and levels of childhood physical activity have all been proposed as formative environments for dysfunctional assumptions that may contribute to the development of CFS.

Perceived high parental expectations are often cited by patients with CFS as a defining feature of their childhood (Surawy et al., 1995). It is likely that an individual that has grown up in a family where there is a clear expectation to succeed, may believe that success is the only means by which they will be accepted by others. Some evidence for the impact of such expectations was found in an early prospective study which examined risk factors for the development of glandular fever, itself a risk factor for chronic fatigue (Kasl, Evans, & Niederman, 1979). Epstein-Barr virus is one infective agent known to cause the clinical signs and symptoms of glandular fever, however not all individuals experience the

clinical illness following infection with this virus. This study compared those who developed glandular fever with those who did not, and found several psychosocial factors that were significantly associated with the development of glandular fever. These included having a father who was an "overachiever", and having a high level of motivation to succeed in the context of relatively poor academic performance. These results suggested that the development of clinical signs following infection is dependent in part on psychological factors.

Other early experiences mooted as important in the development of CFS are prolonged childhood illness and inactivity as a child. A large prospective cohort study found that those participants who had experienced a limiting long-standing illness in childhood were at higher risk of self-reported chronic fatigue as an adult, whilst the rate of school absence and level of academic ability were not risk factors (Viner & Hotopf, 2004). The same study found that higher social class in childhood and lower levels of exercise during childhood were also associated with higher risk. In particular, children who were sedentary at the age of 10 years had twice the risk of developing chronic fatigue in their lifetime. These results suggest that behavioural responses to illness as a child may influence later coping strategies, and may be linked to the avoidant behaviour suggested by the cognitive-behavioural model to be a key feature in the perpetuation of this condition.

Related evidence for this hypothesis comes from a cross-sectional study that found parental encouragement of illness behaviour to be higher in families with a teenager with CFS, than it was in families of healthy controls or teens experiencing juvenile rheumatoid arthritis (Brace, Scott Smith, McCauley, & Sherry, 2000). This encouragement took the form of allowing the child to stay home from school, giving gifts when ill, and telling other family members to be kind to the child. Although this study was conducted with teenagers who were already diagnosed with CFS, the same reactions were not found in the arthritis families, suggesting a pattern of behaviour that may be particular to this group, rather than a reaction to the experience of having a child with chronic illness. Taken together the evidence suggests that early experiences such as these may lead to the development of dysfunctional cognitions and behaviours that are influential in the predisposition to CFS.

5.2. Precipitating factors

In the traditional biomedical model, the precipitant for an illness is purely physiological, taking the form of an infectious agent, disequilibrium in bodily function, or an organic insult. The cognitive-behavioural model widens the potential scope for such triggers to include critical incidents whose impact is psychological rather than purely physiological. As a result, the cognitive-behavioural model of CFS generally refers to two main precipitants in the development of this condition; infection and stress.

Infection

Retrospective studies of patients with CFS indicate that many report experiencing a flu-like illness prior to the onset of their fatigue symptoms (Komaroff & Buchwald, 1998). This led many to believe that an infectious agent could prove to be the cause of CFS. Prospective studies designed to assess the role of infection in the onset of CFS, however, have found mixed results. Whilst the presence of a common infection, such as an upper respiratory tract infection, has not been shown to predict ongoing fatigue, more severe infections do appear to be risk factors for the development of CFS (Cope et al., 1994; Wessely et al., 1995; White et al., 1998). Glandular fever (also known as infectious mononucleosis), acute hepatitis and viral meningitis have all been found to place individuals at greater risk of prolonged fatigue (Berelowitz, Burgess, Thanabalasingham, Murray-Lyon, & Wright, 1995; Hotopf et al., 1996; White et al., 1998; White et al., 1995).

The most widely studied of these infectious precipitants is glandular fever, largely due to the fact that there is a commonly available screening test, and because it usually affects younger populations, thereby reducing the likelihood of confounding pre-existing conditions (Rea, Russo, Katon, Ashley, & Buchwald, 1999). These studies have consistently demonstrated a significantly higher rate of fatigue six months post-infection compared to control groups and rates found in the general population (see Candy et al., 2002; Moss-Morris & Spence, in press, for reviews). Prevalence rates vary depending on the definition of fatigue used, and few studies have utilised standardised criteria to define CFS. For example, one prospective study of glandular fever patients found the rates of fatigue at six months to be 40% based on a cut-off of >3 on the Chalder fatigue scale (Candy et al., 2003). In contrast, another study found that 7% of glandular fever patients fulfilled CDC criteria for chronic fatigue syndrome six months following infection, whilst 15% met either the British criteria or idiopathic criteria for chronic fatigue (White et al.,

1998). An indication of the importance of clearly stating how fatigue is defined comes from an earlier prospective study of fatigue following viral illness. This study identified 64 subjects (13%) with chronic severe fatigue (Cope et al., 1994). However a follow-up of these patients with more detailed interviewing indicated that only 23 (3.7% of original sample) of these participants clearly met the British criteria for CFS (Cope et al., 1996).

Despite the robustness of the link between specific infections such as glandular fever and the development of fatigue, the causal nature of this link has been unable to be proven. A cross-sectional study comparing CFS patients with and without a self-identified infectious onset could not distinguish between the two groups on a range of objective measures (Buchwald et al., 1996). Other studies have demonstrated a state of immune activation in CFS suggesting a chronic infection, but no evidence has been found that infectious agents remain present in those individuals who go on to develop CFS (Komaroff & Buchwald, 1998). Even in the prospective studies, when the effect of the virus was compared against other factors such as prolonged convalescence and psychiatric history, the viral effect was weakened. These factors often outweighed the viral risk, indicating that complex interactions may be responsible for the development of fatigue even in post-viral populations. It is also significant that whilst these acute illness groups have a greater risk of developing CFS than controls, the majority of patients will return to full health.

These factors have led researchers to conclude that whilst specific infections may be an important risk factor in the development of CFS, they are unlikely to be involved in the ongoing symptomatology that represents CFS (Hotopf & Wessely, 1994; White, 1997). As a confirmed biological risk factor for the development of CFS, however, acute illnesses like glandular fever provide ideal prospective populations within which to investigate the role of additional factors in the development of this disorder.

Life events and stress

One such factor that has been examined prospectively with the use of acute illness samples is the impact of stressful life events in the 6-12 months prior to the onset of acute illness. The cognitive-behavioural model assumes that stress can be a trigger for the onset of CFS. One of the first studies to test this hypothesis compared the development of psychiatric disorder and CFS in a group of patients experiencing either glandular fever or an upper respiratory tract infection (Bruce-Jones, White, Thomas, & Clare, 1994). Six months following the acute illness, they asked participants to recall events six months prior to their

illness and in the six months since, using the Life Events and Difficulties Schedule. They found that although these events were associated with the development of a depressive disorder, they were unrelated to the development of fatigue. The authors noted that this result was in contrast to studies measuring social adversity in more long standing CFS cases, and in concordance with the cognitive-behavioural model, concluded that life events and difficulties may be more important in the maintenance of fatigue rather than as a precipitant.

Similar results have been found in other studies investigating this link. A retrospective study found that the number and severity of stressful life events experienced in the two years prior to the onset of CFS was not significantly different from that of IBS patients or healthy controls (Lewis et al., 1994). A more recent prospective study of glandular fever patients also failed to find a significant relationship between the number of life events reported at baseline and fatigue caseness at 3, 6, and 12 months following acute illness, although these authors did not specify the time frame in which the life events were measured (Candy et al., 2003).

The only prospective study thus far to demonstrate a link between ongoing fatigue and stress is a prospective study of glandular fever patients that used self-reported failure to recover as its outcome measure (Buchwald et al., 2000). They found that a greater number of life events more than six months before glandular fever was significantly associated with non-recovery at six months post-infection. Interestingly this effect was not significant two months post-infection, indicating that this difference was most likely due a change in the importance of predictors over time. Biological factors appeared to be more important in the sub-acute phase of an illness, whereas a more complex mix of psychological and social factors took precedence in the later stages.

The absence of a clear relationship between stress and CFS at first glance would indicate that this variable is perhaps less relevant than the cognitive-behavioural model would suggest. However, there are two key issues worth considering with regard to why this relationship has not been confirmed. The first relates to study design. Each of the prospective studies asked subjects to recall events over a period of 6-12 months prior to filling in their questionnaires, introducing a potential bias associated with this retrospective approach. The second issue relates to measurement. Each of the studies reported here used a measure of life events to indicate levels of stress. Although these measures have a degree of objectivity associated with them, there is an implicit assumption in this kind of

measurement that it is the events themselves that impact on an individual and their health. Such measures do not allow exploration of the potential variation in individuals' perception of the impact of those events, however.

A limitation of this approach is that an individual's perception of their own stress levels may not necessarily be correlated with the number or type of life events experienced (Moss-Morris & Petrie, 2000b). There is ongoing debate regarding the definition of stress and there are a myriad of methods for measuring this construct (Harris, 1997). It is possible that what may be important as a trigger for CFS is not so much the retrospective recall of events experienced in an extended period of time before the acute illness, but the individual's own interpretation of their current levels of perceived stress. The Perceived Stress Scale (PSS) was developed as a means of measuring subjective aspects of stress like this, unrelated to any particular event (Cohen, Kamarck, & Mermelstein, 1983). The authors aimed to measure "the degree to which respondents found their lives unpredictable, uncontrollable, and overloading" (p.387). Use of measures such as the PSS may provide more relevant information regarding the role of stress in the cognitive-behavioural model of CFS.

5.3. Perpetuating factors

The proposal that specific factors may perpetuate functional somatic syndromes such as CFS, regardless of the initial precipitants, was one of the most significant additions of the cognitive-behavioural model to this area of research. This hypothesis was eagerly embraced by researchers and clinicians alike, due to its potential to help generate new treatment options and its ability to explain how patients with different precipitants could go on to experience similar symptom patterns. Because of this enthusiasm, a large proportion of the studies investigating the cognitive-behavioural model in this area have focused on the investigation of perpetuating factors in the maintenance of CFS, and as a result, patient populations with well established conditions have been most extensively researched. In addition, the perpetuating variables investigated have often been assumed to be chronic and stable over time. One of the fundamental principles of CBT, however, is that the patient and their problems are constantly evolving (Beck, 1995). Therefore, what may perpetuate symptoms early on in the development of an illness, may not necessarily be the same as what maintains that illness as time passes.

In order to be diagnosed with CFS, patients must have been experiencing debilitating fatigue for at least six months. In many cases, symptoms have been present for much longer than this before diagnosis by a health professional. During the time from onset to diagnosis, the individual will most likely have experienced a number of responses to their symptoms, and those responses present at diagnosis, may not necessarily reflect those experienced earlier. In other words, the individual's behavioural coping strategies, their level of understanding of and beliefs about their symptoms, their physiological reactions and emotional responses may change over time. Some initial responses may have disappeared, some may have been retained in their original state, and others may have been modified. One of the few studies to address this issue found that the usefulness of various coping strategies (such as ignoring symptoms or planning to accommodate fatigue) differed according to the stage of fatigue (acute, sub-acute, or chronic). These researchers also found evidence that the subacute phase may be most important in terms of the adjustment of coping strategies (De Ridder, Leseman, & De Rijk, 2004). Awareness of what perpetuates symptoms early on in an illness has major implications for prevention and early intervention, and yet much less research attention has been paid to this period, as the following section will indicate.

Cognition

Several cognitive variables are identified by the cognitive-behavioural model as being important in the perpetuation of CFS, including causal attributions, symptom focus, fear avoidance and catastrophising, and negative illness beliefs. A recent review of the literature relevant to the cognitive-behavioural model of CFS concluded that there was good evidence for the role of cognitions such as these in the development of CFS (Moss-Morris, 2005). Cross-sectional studies have consistently shown that an individual's negative beliefs about their condition and their symptoms are associated with increased levels of disability and distress (Moss-Morris & Wrapson, 2003). Recent prospective studies also provide some evidence for the role of cognition in the early stages of the development of CFS. For example, negative illness beliefs at the time of acute infection, have been shown to predict chronic fatigue following glandular fever (Candy et al., 2003).

One of the most widely studied cognitive variables in the perpetuation of CFS is that of causal attributions. These beliefs represent an individual's cognitive interpretations of their illness in an attempt to make sense of that illness, or to explain its cause. A consistent finding across many studies is that CFS patients appear to view their illness and related

symptoms as physical or mostly physical (Butler, Chalder, & Wessely, 2001). A physical attributional style has been associated with a greater number of symptoms and level of impairment, and has been found to have a negative effect on prognosis (Chalder et al., 2003; Vercoulen et al., 1998). The importance of causal attributions may not be as clear cut as these studies suggest, however, with one study finding that causal beliefs had little impact on prognosis in treatment, and that CBT did not appear to effect any change in these beliefs (Deale, Chalder, & Wessely, 1998). Instead this study found that beliefs regarding the avoidance of activity were more strongly related to outcome and also more amenable to change. Another study found that illness specific attributions and general attributional style are highly correlated, suggesting that illness attributions themselves may be less important with regard to prognosis than the individual's general view of the world (Creswell & Chalder, 2003).

Some authors have suggested that other specific beliefs about an illness may be more important in the maintenance of CFS than causal attributions, and that these beliefs may indeed underlie such attributions (Deale, Chalder, Marks, & Wessely, 1997). The cognitive-behavioural model suggests that a physical attributional style combined with a tendency to focus on symptoms, can increase subjective awareness of those symptoms. Indeed, an excessive focus on symptoms has been found to be correlated with greater levels of fatigue and impairment in those with CFS (Ray, Jefferies, & Weir, 1997). Objective evidence for such impairment, however, has proved difficult to demonstrate, leading some to suggest that individuals with CFS may misinterpret the extent of their symptoms (Moss-Morris, 2005). In some cases this misinterpretation takes the form of extreme catastrophising, with one study demonstrating that a third of their CFS patients believed they would totally collapse or die if they pushed themselves too hard, and that these beliefs were correlated with fatigue and disability levels (Petrie, Moss-Morris, & Weinman, 1995).

Studies using the Illness Perceptions Questionnaire (IPQ:Weinman, Petrie, Moss-Morris, & Horne, 1996) with CFS patients have found that they have consistently high scores on the identity, consequences and timeline scales indicating that they believe a wide variety of symptoms are explained by their illness, that their illness has a considerable impact on their lives and that it will last a long time (Moss-Morris, 1997). Beliefs such as these have been shown to be stable over time and cannot be explained as the consequence of having a chronic disabling condition per se (Moss-Morris & Wrapson, 2003). They have also been associated with more maladaptive coping strategies (Moss-Morris, 1997), greater disability

and poorer psychological wellbeing (Moss-Morris, 2005), and are capable of predicting treatment outcome (Darbishire, Seed, & Ridsdale, 2005).

It is less clear whether these beliefs represent long standing assumptions about the nature of illness in general, or whether they are formed as a consequence of the experience of CFS. Results from the area of chronic pain provide some evidence that cognitions do indeed change according to the stage of chronicity. In one study, researchers used a cross-sectional design with patients who had been experiencing musculoskeletal pain for less than 1 year, 1-3 years, and longer than three years. They found that fear of movement was significantly related to function only in the two chronic groups, in contrast to depression which was relevant at all three stages (Boersma & Linton, 2005). A similar study, found that catastrophising only became a significant predictor of function after 2 years (Sullivan, Sullivan, & Adams, 2002). One prospective study that has investigated illness beliefs at the time of acute glandular fever suggests that beliefs formed early in an illness may also be important. These investigators found that negative beliefs about timeline and the consequences of an acute illness were significantly associated with the later development of CFS (Candy et al., 2003). This study indicates that negative illness beliefs may not only perpetuate CFS but may also play an important part in its onset. More studies of this nature are required to confirm this finding.

Behaviour

Behavioural perpetuators of CFS have most often been considered in the context of coping styles, and are seen as closely related to the cognitions discussed in the previous section. These cognitive mechanisms have been linked to a number of behaviours that can in turn help to mitigate or perpetuate symptoms in CFS (Butler et al., 2001; Ray, Jefferies, & Weir, 1995; Williams, 1997). According to the cognitive-behavioural model, behaviour can be viewed as functional if it is helpful in resolving problems or dysfunctional if it tends to perpetuate them (Taerk, 1988). The adaptiveness of a specific behaviour, however, clearly differs according to the phase of illness. For example, an individual who experiences acute back pain in response to lifting a heavy object is likely to put it down. Should that pain become chronic, the initial behavioural response may generalise to other activities leading to physical deconditioning, which in turn may produce further discomfort in response to behaviours that were previously of no significance. In this way, the cognitive-behavioural model recognises how the adaptiveness of certain behaviours can change over time.

A good example of this is bed rest, a commonly prescribed treatment for a wide range of medical conditions. As such, it is viewed by many as a functional behaviour in the early stages of an acute illness or injury. Historically, the "rest cure" was a mainstay of Victorian treatment for patients with chronic fatigue and versions of this approach are still popular with patients and their doctors today. However a recent review put forward strong evidence that bed rest does not significantly improve acute illness outcomes, and can in many cases worsen outcome for a wide range of conditions (Allen, Glasziou, & Del Mar, 1999). There is also now good evidence to suggest that bed rest and avoidance of activity can perpetuate the symptoms of CFS (Sharpe & Wessely, 1998). Bed rest is a component of one of the most extensively researched behavioural perpetuators of CFS; that is, the limiting style of coping, in which patients cope with their symptoms in an avoidant or passive manner that results in a gradual decrease in activity levels (Ray et al., 1995).

Prolonged physical inactivity inevitably leads to decreased tolerance and increased sensitivity to exercise. This process is known as deconditioning and is linked to a range of physiological changes that are thought to perpetuate the symptoms of CFS (see Clark & White, 2005; White, 2000 for reviews). The majority of cross-sectional studies that have investigated this process indicate that CFS patients are at least as deconditioned, if not more so, than sedentary but otherwise healthy controls (Clark & White, 2005). There is evidence to suggest that inactivity may be an important perpetuator of symptoms in the early stages of the illness also. A recent systematic review found that the strongest predictor of chronic fatigue following glandular fever was prolonged bed rest (Candy et al., 2002). A number of studies have found that cognitive variables may mediate this process through variables such as a fear of exacerbating symptoms, or abnormal perception of effort (Bazelmans, Bleijenberg, Van Der Meer, & Folgering, 2001; Gallagher, Coldrick, Hedge, Weir, & White, 2005).

Avoidance of activity is not the only behaviour that has been associated with CFS, however. Other patients describe an oscillating pattern of behaviour, where the avoidance of activity in response to symptoms is punctuated by extreme bursts of activity when symptoms ease (Surawy et al., 1995). Studies looking to confirm the existence of this behaviour have been limited, however. One such study measured activity patterns subjectively and objectively in CFS patients and healthy controls, and found that two groups of CFS patients could be identified; those who were pervasively passive and those who had an activity pattern similar to those of healthy controls (van der Werf, Prins, Vercoulen, van der Meer, & Bleijenberg, 2000). They found that although the peak

activity periods of this second group of CFS patients were less intense and shorter than controls, they were followed by longer subsequent rest periods; perhaps indicating that the perceived effort and subsequent fatigue was greater for these CFS patients. This study was conducted using patients with well established CFS, however, it is possible that it is this tendency to engage in an all-or-nothing oscillating pattern that is important in the early development of CFS, than a purely avoidant or limiting pattern of behaviour.

The effect of these limiting and oscillating patterns of behaviour early on in the development of CFS has not yet been investigated prospectively. One reason for this may be a result of existing measures focusing on the concept of "abnormal illness behaviour". This term is used to describe a range of cognitions and behaviours that are seen to be inappropriate or maladaptive in response to illness (Zonderman, Heft, & Costa, 1985). The difficulty with this concept, and instruments that try to measure it, is the failure to distinguish cognitions from behaviours. The most well known measure of abnormal illness behaviour is Pilowsky's Illness Behaviour Questionnaire (IBQ), which has been used to assess the impact of hypochondriasis, disease conviction, psychological versus somatic focus, affective inhibition, affective disturbance, denial and irritability on a wide range of medical conditions and processes (Pilowsky, 1993). As these subscale labels suggest, despite its name, the IBQ largely focuses on cognitive variables rather than actual behaviours.

In an attempt to address this imbalance, Rief and colleagues have created a scale that includes items which focus more specifically on behaviours rather than cognitions (Rief, Ihle, & Pilger, 2003). Their Scale for the Assessment of Illness Behaviour (SAIB) includes items that measure the behavioural expression of the following: verification of diagnosis, expression of symptoms, medication, consequences of illness, and scanning. The authors of the SAIB failed to find an avoidance of activity factor in their sample of patients with depression and somatisation, and concluded that this reflected an overemphasis in the theoretical models.

Both the IBQ and the SAIB were developed using cross-sectional designs, however, with samples in which somatisation behaviours were already established. In addition, neither scale is concerned specifically with the behavioural patterns described by CFS patients as being of particular importance in the development of their illness, or the avoidance pattern identified as a perpetuator of CFS. It is possible that these behaviours may be most relevant early in the development of syndromes such as CFS, rather than in the chronic

phase where behaviours may have adapted over time. This may be especially important for those functional somatic syndromes with an infectious precipitant, as the response to symptoms of an acute illness may also be relevant. At present there is no clearly defined measure of behavioural response to acute illness that can determine what people actually do when they become unwell. In order to verify the importance of behaviours in the early stages of the perpetuating cycle, a measure is required that is relevant to acute illness episodes. One of the first aims of this thesis therefore was to develop such a measure. The development of this measure is described in the preliminary study of this thesis and is the subject of a recent peer reviewed publication (Spence, Moss-Morris, & Chalder, 2005).

Emotion

According to the cognitive-behavioural model, many of the cognitive and behavioural processes already described in previous sections are also hypothesised to impact on the emotional experience of the individual. For example, previously high achieving individuals with a physical attributional style may become frustrated and depressed as they fail to maintain their expectations. As noted earlier, the evidence for the role of diagnosable psychiatric disorder in the predisposition to CFS remains unclear. Once CFS is established, however, the link between these disorders becomes less equivocal, indicating that it may be more relevant to consider them as perpetuating variables. Furthermore, emotional distress and arousal lead to bodily sensations that can be interpreted as evidence of disease; for example, anxiety increases the activity of the sympathetic nervous system whereas depression decreases energy (Sharpe et al., 1992).

Despite the common sense appeal of such a process, few studies have empirically investigated the connection between mood and the perpetuation of CFS. Cross-sectional designs have confirmed the association, but cannot prove causality. In contrast, longitudinal studies have provided conflicting evidence for the causal effect of these variables. One study followed 98 patients with chronic fatigue for 2.5 years and found that those who reported an improvement in psychological functioning were more likely to return to work (Russo et al., 1998). However, another treatment study found no significant difference between participants with or without a psychiatric diagnosis with regard to fatigue severity and impairment following CBT treatment for CFS (Prins, Bleijenberg, Rouweler, & Van Der Meer, 2005).

There are several possibilities that need to be explored further with regard to this association. The presence of mood or anxiety disorders may simply be an amplifying effect in the perpetuation of CFS (Gallagher et al., 2005). Should this be the case, all of the previously described variables may be more likely to be present if mood or anxiety is also present. A second possibility is that, once again, psychological distress and subthreshold emotional disorders may be more important in the perpetuation of CFS than psychiatric diagnosis per se. The final possibility is similar to that discussed earlier with regard to the impact of stress; the impact of emotional variables may change according to the stage of illness. These hypotheses need to be investigated further with the use of carefully designed prospective studies of early onset CFS.

In summary there is now a substantial amount of support for the cognitive-behavioural model of CFS. As highlighted in this review, however, a number of gaps in the literature leave a range of areas still to be investigated. In particular, the reliance on cross-sectional and retrospective designs for the majority of this work has meant that causal associations are not well studied. There is little understanding of how changes in these variables may occur over time, and there are only a few studies that investigate the relevance of cognitive-behavioural variables in the early stages of illness development. Whilst there is some evidence for the role of specific cognitions in the development of CFS, specific behaviours identified by the model have not benefited from the same level of attention. Finally, few studies have considered the potential interactions hypothesised to be an important part of this model.

Chapter 6.

The cognitive-behavioural model of irritable bowel syndrome.

Around the same time as the cognitive-behavioural approach was gaining momentum in the area of CFS, the field of gastroenterology was also beginning to recognise the benefits of a wider biopsychosocial conceptualisation of the functional bowel disorders. For IBS in particular, it had long been accepted that psychosocial factors played an important part in the development and presentation of this disorder. As with many other functional somatic syndromes, however, debate regarding aetiology had been somewhat polarised according to the dualist framework described earlier (Creed, 1994; Farthing, 1995; Mayer, 1996; Spiller, 1994). In addition, the objectively physical nature of the symptoms of IBS such as constipation and diarrhoea, and the localisation of complaints to a specific bodily system, had meant that the majority of research and reporting in this area had taken place within the gastroenterological community. As a result, there had been less integration of the psychosomatic literature and relevant psychological theory with regard to IBS.

Treatments for IBS based on the cognitive-behavioural approach had begun to be developed in the late 1980's, but had mostly been reported in psychological and psychosomatic journals to this point (Hutton, 2005). Drawing on the general functional somatic syndrome model of Sharpe and colleagues outlined earlier, researchers adapted the model for IBS, identifying a range of cognitions and behaviours thought to be important in the predisposition, precipitation and perpetuation of this condition (see Toner, Segal et al., 1998 for an example). Factors similar to that described in relation to CFS were proposed such as casual attributions, increased attention to bodily symptoms and heightened sensitivity to pain. Illness beliefs were believed to act to maintain and amplify symptoms, whereas stress and distress, interpersonal conflict and iatrogenic factors could also contribute at each stage of the development of IBS.

Over time, discussion of psychological variables with regard to IBS moved toward a broader biopsychosocial approach in the wider gastroenterological community. Douglas Drossman was a leading proponent of this approach since first adapting it to the functional gastrointestinal disorders in the 1990's (Drossman, 1996, 1998). Coming from a psychosomatic background, he proposed that early life factors such as genetics and

environmental influences can predispose an individual to certain patterns of psychological, social and physiological functioning, any of which may produce symptoms in later life. In his model, psychosocial factors such as mood, coping, social support and life stress were seen to impact on an individual's physiological responses, and vice versa. These interactions, in turn were hypothesised to impact on the individual's experience of symptoms and their behavioural response to them; both of which he proposed could serve to perpetuate symptoms.

Like cognitive-behavioural theorists in the area of CFS, Drossman attempted to integrate the array of psychosocial and physiological variables that were thought to contribute to IBS into a conceptual model that was capable of accommodating the considerable heterogeneity found within this population. He argued that physiological influences could outweigh psychosocial influences in some individuals, whereas in others the opposite could be true. For example, he proposed that differences between IBS presenters and non-presenters could be explained by contrasting emphases on particular components of the model (Palsson & Drossman, 2005). As he stated, "it is no longer rational to try to discriminate whether physiological or psychological factors cause pain or other bowel symptoms. Both are operative, and the task is to determine the degree to which each contributes and is remediable" (Drossman et al., 1999, p.25).

Emeran Mayer has also highlighted the importance of the interactions between cognitive, emotional, behavioural and physiological factors in his multicomponent model of IBS (Mayer, 1999). Coming from a more traditional background in medicine and gastroenterology, he emphasised the importance of the interactions between physiological and psychological factors with regard to alterations in pathways associated with the emotional motor system. Whilst Drossman and Mayer's models emphasise different aspects for primary consideration, each is consistent with the cognitive-behavioural model described earlier, and effectively paved the way for more widespread interest in cognitive-behavioural treatments.

Studies assessing the effectiveness of CBT in the treatment of IBS offer promising results compared to non-treatment controls (Hutton, 2005); however, they have failed to conclusively prove superior effectiveness in comparison to other psychological treatments such as psychotherapy, hypnosis and skills training (Lackner, Mesmer et al., 2004). There are a number of possibilities as to why CBT has not been found superior to other psychological treatments for IBS. The first is that the trials conducted so far may have

suffered from methodological difficulties common in the early stages of treatment trials, such as small sample sizes, high drop-out rates and inadequate control groups; a view that is given credence by a recent review of this literature (Lackner, Mesmer et al., 2004). The second is that IBS may be less susceptible to the cognitive emphasis that is inherent in the cognitive-behavioural approach, and that behavioural or other less specific methods may be adequate for the treatment of this condition.

A final possibility is that these treatment trials simply reflect that the process of adapting the cognitive-behavioural model to IBS is still in its fledgling stages. For example, many of the early treatments based their approach on models of anxiety rather than specifically adapting the approach to IBS symptomatology (Toner, Segal et al., 1998). Empirical evidence that aims to determine specific influences on IBS from a cognitive-behavioural perspective is at this point limited. That which exists, like the CFS literature, tends to be focused on those with more chronic conditions presenting in tertiary care. It is likely that a more thorough empirical investigation of the underlying concepts for this model is required before the treatment can be successfully applied to IBS. Only time and further well designed studies will determine whether CBT has something additional to offer in the treatment of IBS.

Another confounding factor in the investigation of variables relevant to the cognitive-behavioural model in IBS is the debate surrounding the importance of health care seeking behaviour. Early studies had demonstrated differences between IBS patients and healthy controls on a range of psychosocial measures; however, these differences came to be seen as an artefact of study design (Drossman et al., 1988). Without the inclusion of IBS non-consulters, these differences could not be seen to be representative of the IBS population. Studies comparing IBS presenters and non-presenters appeared to confirm this, with the psychological differences confined to IBS presenters, whilst non-presenters were more like the control populations (see Koloski, Talley, & Boyce, 2001 for a review). On the strength of results such as these it was assumed that psychological factors did not have a pivotal role in the development of IBS; rather that they impacted on the expression of the condition or consulting behaviour. More recent studies, however, indicate another turn in the tide, with several studies failing to find differences on psychological variables in presenters and non-presenters (Koloski, Boyce, & Talley, 2005; Talley et al., 1997; Weinryb et al., 2003). These studies suggest that the psychological factors associated with IBS may be relevant in the development of this condition after all. It is important to keep this study design issue in mind when reviewing the evidence.

This chapter will cover some of the main themes that have been addressed in the literature regarding cognitive-behavioural variables in the development of IBS. The same subheadings used to structure the evidence for CFS will be used again to provide continuity for the reader. The emphasis does differ, however, and the demarcations between predisposing, precipitating and perpetuating variables are often less distinct, reflecting the less advanced stage of theory development in this area.

6.1. Predisposing factors

Biology

As was the case for CFS, the investigation of pathophysiological mechanisms associated with IBS has undergone several phases across recent history, with popular theories waxing and waning in their importance. Once again, to review the detailed nature and extent of this literature is beyond the scope of this thesis and the reader is directed to several review articles that outline the evidence for each of these factors (Drossman, 2005; Lacy & De Lee, 2005; Mulak & Bonaz, 2004; Wood, Alpers, & Andrews, 1999). As one reviewer has pointed out, however, over the past half century, emphasis has shifted away from largely psychological and stress related research to the investigation of mechanisms such as motility disturbance, autonomic system imbalance and visceral hypersensitivity (Ringel, Sperber, & Drossman, 2001). In recent times, there has been a shift in emphasis onto hypotheses that propose the dysregulation of brain-gut interactions can be triggered by a range of psychological or physiological events. There is growing enthusiasm that these latter approaches have the possibility of integrating the old research with the new (Camilleri, 2005).

In 2002 the American Gastroenterological Association (AGA) put forward a position statement regarding IBS (American Gastroenterological Association, 2002). They summarised the physiological evidence into three interrelated categories of variables that can differentially affect individuals with IBS as follows: 1. altered gut reactivity in response to environmental stimuli, 2. gut hypersensitivity with enhanced visceral perception and pain, and 3. dysregulation of the brain-gut axis. The development of sophisticated technologies with which to investigate many of these mechanisms has led to an explosion of research in a number of specific areas, including genetics. As was found for CFS, however, the distinctions between predisposing, precipitating and perpetuating

variables in biological research into IBS mechanisms have been difficult to tease out. Each of these mechanisms may be the result of predisposing vulnerabilities, or could develop in response to other stimuli.

As the AGA pointed out in their position statement, "the symptoms of IBS have a physiological basis…although no specific physiological mechanism is unique to, or characterises IBS" (American Gastroenterological Association, 2002, p.2105). Therefore, whilst many biological factors have proved to be important mechanisms in IBS, none is consistent, mirroring the experience of CFS and many other functional somatic syndromes. What is different from the CFS literature, however, is the relative ease of acceptance of the interactions between biology and psychology in the development of IBS, and the notion that multiple pathways exist. Even the most biotechnical of descriptions in this area acknowledge the importance of the impact of psychosocial factors on the physiology of this disorder and that no single pathophysiological factor will prove to be the answer to the complex question of IBS (Gershon, 2005).

Premorbid psychiatric disorder and psychological distress

Rates of comorbid psychiatric disorder in individuals with IBS are similar to that found in CFS. A recent review indicated that anywhere between 40% and 94% of IBS patients meet criteria for at least one psychiatric diagnosis, with depression, anxiety and somatisation most common (Palsson & Drossman, 2005). The same methodological problems that existed in the CFS literature with regard to the role of psychiatric disorders in the development of that condition also apply here. Many of the studies have had small sample sizes, have been conducted on tertiary care patients and have lacked adequate comparison groups. Although high rates for comorbid psychiatric disorders in IBS have also been found in primary care, community samples generally find a much lower rate of psychiatric problems, with one New Zealand community study finding no significant difference in rates of psychiatric disorders in individuals with IBS, compared to those without (Talley, Howell, & Poulton, 2001).

As alluded to earlier, these findings have led researchers to view psychiatric disorder as a risk factor for health care utilisation rather than as a predisposing variable for IBS itself (Creed, 1999; Drossman, Camilleri, Mayer, & Whitehead, 2002). More recently, however, larger community studies have shown that the association between psychiatric disorders and IBS may indeed be more complex than this. Three large community samples have

indicated that levels of anxiety and depression are strongly associated with IBS, regardless of help-seeking. The first, a population study conducted in Norway, examined the relationship between gastrointestinal complaints and levels of anxiety and depression in 62,651 participants, and found a strong association particularly with anxiety (Haug et al., 2002). The second, a nested case control study conducted in Minnesota, U.S.A found participants with IBS had higher levels on a range of psychosocial factors including depression and anxiety than controls (Locke, Weaver, Melton, & Talley, 2004). Another study using stratified random sampling looked at the prevalence of anxiety disorders in 4,000 Japanese. They found higher rates of comorbid anxiety disorders in those with IBS compared to those without, and that within the IBS group there was no difference in anxiety levels between consulters and non-consulters (Kumano et al., 2004). Based on these studies it would appear that the association of psychiatric disorders and IBS is not merely an artefact of seeking help for symptoms.

The studies reported here are cross-sectional and therefore unable to determine causality, however there is other evidence to suggest that some psychiatric disorders are indeed risk factors for IBS rather than a consequence of it and that the relative importance of those factors may change over time. One study of 188 IBS patients seeking treatment found that of those who had experienced a psychiatric diagnosis at some point in their lifetime, that disorder was significantly more likely to have developed before the onset of IBS symptoms than after it (Sykes, Blanchard, Lackner, Keefer, & Krasner, 2003). Closer examination of the results indicates that this was primarily due to anxiety disorders, whereas there was only a trend towards the same result for depression. Other studies have indicated that levels of anxiety and depression change according to the setting from which IBS patients are recruited, with anxiety being more prominent in primary settings and depression more prominent in tertiary settings (Creed, 1999). Whether the results from these two studies reflect an association with severity or chronicity of IBS, however, is difficult to establish.

One prospective study that examined the influence of both physiological and psychological mechanisms in the development of post-infectious IBS concluded that whilst biological mechanisms contribute toward the expression of symptoms, psychological factors such as anxiety, neuroticism and somatisation more clearly predicted the development of IBS (Gwee et al., 1999). A later study also assessed the relative importance of anxiety, depression and physiological measures of mucosal change three months following gastroenteritis (Dunlop, Jenkins, Neal, & Spiller, 2003). Despite all these measures being significantly raised in patients with IBS in comparison to non-cases, the strongest

predictors of IBS were depression and increased enterochromaffin cells. Taken together these results indicate that emotional factors are at least as important as physiological ones in the early development of IBS.

Taken together these results suggest that anxiety and depression are associated with the development of IBS, however, their relative importance in relation to each other as well as to other variables is yet to be clarified. Again, as proposed for CFS, it is possible that subthreshold levels or tendencies toward these conditions may also place an individual at risk of IBS. A dimensional approach to the investigation of psychological distress may therefore, provide richer information than the categorical diagnoses provided by most studies to this point. A review of studies using dimensional measures of psychological distress in IBS suggests that this may be the case (Blanchard, 2001). As a group, IBS patients consistently report more psychological distress than patients with other gastrointestinal diseases or healthy controls, but these differences are not always statistically significant. The reviewers concluded that on average IBS patients have noticeable but generally mild levels of psychological distress and that a distinct proportion of IBS patients have scores in the normal range.

It is possible that the use of cross-sectional designs and categorical diagnoses may have overstated the relationship between anxiety and depressive disorders and IBS. Some evidence to support this view comes from a prospective study which found that higher levels of anxiety and depression at the time of acute gastroenteritis have been associated with the development of IBS six months later, but that these levels were not in the range for diagnosable disorder (Gwee et al., 1996). Further prospective studies using dimensional measures of psychological distress may help to unravel what is clearly a more complex relationship than was once assumed.

Personality and premorbid behaviours

Knowledge regarding the influence of personality and premorbid behaviours in the development of IBS has suffered from the same problems found in the CFS literature. Once again the majority of studies have been cross-sectional and conducted on those patients at the more severe end of the spectrum. In a review of personality variables associated with IBS, it was noted that IBS patients consistently report higher levels of neuroticism and state anxiety than general medical patients and the general population, and that they also tend to be more introverted than the general population (Langeluddecke,

1985). A recent study explored interpersonal problems in severely affected IBS patients and found that they had difficulties with assertiveness and had higher levels of social inhibition in comparison to controls, suggesting a submissive interpersonal style (Lackner & Gurtman, 2005). Given the cross-sectional nature of most studies, however, it is impossible to say whether these results represent long-standing personality traits that leave an individual vulnerable to the development of IBS or whether they have developed as a response to the illness. More research in this area is required before assumptions can be made regarding the relationship between personality and IBS.

Early experience and the development of dysfunctional cognitions and behaviours

There is some evidence to suggest that the patterns of childhood social learning that were found in CFS patients are also relevant in IBS. Several studies have determined a familial association in first degree relatives with IBS, however, these studies are unable to determine if the association represents genetic influences or that associated with social learning as a result of heightened awareness of gastrointestinal symptoms (Kalantar, Locke, Zinsmeister, Beighley, & Talley, 2003; Locke, Zinsmeister, Talley, Fett, & Melton, 2000). A series of studies conducted by one research group suggest that social learning is also an important factor, however. They found that special parental treatment during childhood illness is associated with the development of IBS, that parental reinforcement of symptoms as a child affected adult disability days and symptom reporting, and that the specificity of complaints as an adult is related to those symptoms receiving parental reinforcement as a child (Whitehead, 1997). The experience of childhood abdominal pain has also been associated with later IBS in a New Zealand longitudinal birth cohort study (Howell, Poulton, & Talley, 2005). Whilst providing important clues as to the development of cognitions and behaviours relevant to IBS, these studies cannot differentiate between the roles of genetic and environmental factors.

A large twin study set out to clarify the influence of genetics and the environment by studying IBS in 6060 twin pairs (Levy et al., 2001). They found that despite monozygotic twin pairs being more likely to both have IBS than dizygotic twins (indicating a genetic contribution to IBS), this contribution was outweighed by having a mother or a father with IBS. These parental factors were stronger predictors than having a twin with IBS, and the authors concluded that whilst heredity contributes to the development of IBS, what an individual learns from those in his or her environment has an equal or greater influence.

These findings were supported by a similar recent study of 1008 twin pairs, although in this case the genetic influence was somewhat weaker (Mohammed, Cherkas, Riley, Spector, & Trudgill, 2005).

Further evidence for the impact of social learning comes from two studies that assessed the behaviour of mothers with IBS. The first study found that mothers with IBS were more likely to seek treatment for a greater number of conditions for their infants than mothers with stomach ulcers, despite no greater incidence of symptoms (Crane & Martin, 2004). Because the children were only aged between 0-18 months, it was clear that this behaviour was mediated by the mother rather than the child. A second study looked at the impact on older children by comparing the children of 208 mothers with IBS, and the children of 241 mothers with no IBS. Results indicated that the children of IBS mothers had a significantly higher number of gastrointestinal symptoms, non-gastrointestinal symptoms, school absences, and physician visits for both gastrointestinal and other complaints (Levy et al., 2004). They also measured the mother's response to illness complaints from their children and concluded that parental modelling and reinforcement of childhood illness are important risk factors for the development of this condition.

An important aspect of both of these studies, that has implications for the cognitive-behavioural model, is that the effects were not specific to gastrointestinal symptom-related reporting. In addition, the study by Levy and colleagues indicated that social learning influences were not limited to gastrointestinal-related help-seeking and disability, but rather increased these variables for all symptoms. Finally, the effects of modelling (parental IBS status) and reinforcement of gastrointestinal complaints were found to be independent, with modelling impacting on the frequency of complaints, but not perceived severity of symptoms, and the opposite being true for reinforcement. In summary, it is likely that a number of social learning experiences impact on the development of illness specific cognitions and related behaviours relevant to IBS.

The importance of severe stressors early in life has also been a focus of the IBS literature, particularly with regard to abuse. There is a high prevalence of both physical and sexual abuse in IBS patients across all settings, and although the rates are lower in community surveys they are still much higher than healthy controls (Whitehead, 1997). Results like this have indicated the potential role of early trauma in establishing a predisposition to IBS, and the potential for later life stress to precipitate the condition. The experience of significant stress in early life is thought to be a predisposing factor for the development of

IBS, and many believe this vulnerability to be physiologically mediated (Mulak & Bonaz, 2004). IBS patients with an abuse history are more likely to be depressed, anxious, have more severe IBS symptoms, more pain, more psychological distress, poorer daily function, more frequent health care visits, and more lifetime surgery than non-abused IBS patients (Creed, 1999).

A recent study has shed some light on the complex pathway from childhood abuse to IBS, by focusing attention on parental behaviours that may increase stress reactivity in a child, thereby making them vulnerable to IBS as an adult (Lackner, Gudleski, & Blanchard, 2004). They found that whilst a history of abuse was associated with negative parenting styles, only the latter was associated with increased somatisation. They argued that the literature has focused too narrowly on severe stressors as a risk factor for IBS rather than the more chronic effect of living in a dysfunctional family environment. Further evidence to support this hypothesis comes from another study indicating that separation from one or both parents as a child is significantly more likely in IBS patients than controls (Whitehead, 1997). However, the same or similar prevalence of abuse is also found in other gastrointestinal disorders, chronic pain conditions and psychiatric disorders, and not all IBS patients have a history of abuse and vice versa. Taken together, this area of research indicates that childhood abuse is more likely to be a non-specific risk factor for the development of IBS rather than a causal pathway.

6.2. Precipitating factors

Infection

In some of the earliest clinical descriptions of IBS, infectious diarrhoea had been retrospectively identified as a precipitant for a proportion of patients (Chaudhury & Truelove, 1962), however it was not until 1994 when this relationship was first investigated prospectively. Following a *Salmonella* outbreak, 38 affected individuals were assessed 12 months following infection; of these 12 (32%) were diagnosed with IBS (McKendrick & Read, 1994). Risk factors for the development of post-infectious IBS in this study included female gender, longer duration of acute illness, vomiting and weight loss. A five year follow-up of these 12 patients indicated that the majority were still affected by bowel symptoms, although formal diagnosis of IBS was not assessed at this point. Two years later another study investigated 75 patients hospitalised with

gastroenteritis and found 25% with new onset IBS six months following infection (Gwee et al., 1996). Once again, female gender and duration of initial illness were significant risk factors for the development of IBS. Although these studies were small and limited to hospitalised patients, they provided the first clear link of a role for gastroenteritis in the development of IBS.

The initial findings from these two studies have since been confirmed in several larger studies of community patients with microbiologically confirmed gastroenteritis (Neal, Hebden, & Spiller, 1997; Rees et al., 2004; Thornley et al., 2001). Each of these studies used a postal questionnaire to determine the incidence of gastrointestinal problems following gastroenteritis. The first two studies obtained very similar results with 6% and 9% reporting IBS six months post-infection, and 23% and 25% experiencing persistent bowel dysfunction (Neal et al., 1997; Thornley et al., 2001). Female gender and duration of illness were once again significant risk factors. A third study only followed patients for three months post-infection and found that 9% were experiencing altered bowel habit at this point (Rees et al., 2004).

Whilst the reported rates of bowel dysfunction in these samples were still high, the incidence rates for IBS were lower than that found in the original two studies, indicating a potential influence of setting. The initial studies were conducted with hospital inpatients as opposed to the community samples that were used in the later studies. Given that severity of illness was a risk factor for IBS in these studies, it seems likely that severity of initial illness in the community would be less than that of inpatients, and therefore have resulted in lower numbers in the community-based studies. However, the lack of control groups in these studies made it difficult to determine the relative risk of developing IBS following gastroenteritis as opposed to that for healthy controls.

The first case control cohort study used a large computerised database of general practice patients and found the risk of developing IBS following gastroenteritis to be ten times that of a control group (Rodriguez & Ruigomez, 1999). A number of other case-control studies from a variety of countries have since confirmed this association. The first, conducted in the United Kingdom, compared 128 gastroenteritis patients and 219 age and sex matched non-gastroenteritis controls, and also found IBS to be ten times more likely six months following gastroenteritis, with 17% of gastroenteritis patients developing IBS as opposed to 2% of control subjects (Parry, Stansfield et al., 2003). Another study of 467 patients infected during a *Salmonella* outbreak in Spain, found the risk of developing IBS 12

months following infection to be eight times that found for the 561 control subjects without infection, with incidences of 10% and 1% respectively (Mearin et al., 2005). A further case-control study in China found the incidence of IBS to be 8% in gastroenteritis patients compared to 0.8% in the control group although odds ratios were not reported (Wang, Fang, & Pan, 2004).

The most recent study of 101 *Shigella* patients and 102 control subjects in Korea found a much lower relative risk of developing IBS, however the gastroenteritis patients were still almost three times more likely to develop IBS than the control group, with prevalence rates of 15% and 6% (Ji et al., 2005). The lower relative risk in this study was due to a higher rate of IBS in the control group than was found in the other studies. The authors suggested several reasons for this, including the potential confounding effects of stress, age, gender and illness duration in this study. In particular, participants were all hospital employees and therefore in a high stress occupation, whereas 50% of the control group were female and younger than 41. Because previous studies had identified stress, female gender and younger age as additional risk factors, the authors concluded that these variables may explain the higher rate of IBS in the control group. In addition, the gastroenteritis group in this sample experienced on average a shorter duration of illness in comparison to that found in previous studies, which may have resulted in a lower prevalence of IBS in the gastroenteritis group also.

In summary, based on these studies there is now clear evidence that gastroenteritis is a significant risk factor for the development of IBS. The results are surprisingly consistent given the wide range of countries in which these studies were conducted and the variety of enteric infections included. Prevalence rates range from 6-32%, however the majority of studies are relatively consistent within the 9-17% range. With regard to the relative risk associated with gastroenteritis three of the four studies reporting this have found an 8-10 fold risk. A recent review of this literature highlighted the significance of these findings, estimating that given the high annual rate of gastroenteritis in the UK population, as many as two million people could potentially develop IBS-like symptoms in any one year (Parry & Forgacs, 2005). With even higher rates of food-borne gastroenteritis in New Zealand (Eberhart-Philips et al., 1997), the situation is likely to be similar here.

Life events and stress

As was reported in the previous section, early life stress has been associated as a non-specific predisposing factor in the development of IBS. There is also evidence to suggest that stress is associated with the onset and exacerbation of gastrointestinal symptoms, indicating that it may be an important precipitant for IBS (Mayer, 1999). Acute emotional responses are known to affect gastrointestinal dysfunction, and represent one of the clearest indications of brain-gut interaction (Kamm, 1998; Posserud et al., 2004). Self-awareness of this connection is reported by approximately half of the healthy population and almost three-quarters of IBS patients (Drossman, Sandler, McKee, & Lovitz, 1982). According to the results of one study, more than 90% of the variance in IBS symptoms over time can be accounted for by prolonged stressors such as divorce, serious illness and forced redundancy (Bennett, Tennant, Piesse, Badcock, & Kellow, 1998).

Retrospective and cross-sectional studies investigating the association between stress and IBS have been inconsistent, however. In a review of this literature, Blanchard (2001) noted that the wide range of measures used to identify stress in IBS patients and the variety of control groups used, has made it difficult to ascertain the impact of major life events and minor life stresses in IBS. Causal relationships have been difficult to establish and the role of psychological distress in the form of anxiety and depression have often been confounding factors, as has the assertion that increased stress determines help-seeking rather than IBS outcome (Mayer, 1999). However, a recent study investigating this relationship used a population-based case-control design and a well validated inventory, and found that a higher level of total life stress was one of the strongest indicators of IBS caseness in comparison to controls (Locke et al., 2004).

The only prospective study of post-infectious IBS to investigate the connection between life events and the onset of IBS also goes some way towards clarifying these issues. At the time of acute illness researchers measured the total number of life events experienced in the 12 months prior to an episode of gastroenteritis, and then again three months following. They found that higher levels of life events were a significant risk factor in the development of IBS. Not only did this result remain significant after controlling for the effects of anxiety, somatisation and neuroticism, it also outweighed the impact of the physiological measures studied (Gwee et al., 1999). Results also indicated that those who developed IBS following gastroenteritis had higher levels of stressful life events in the three months following their acute illness in comparison to those who did not develop IBS,

leading some to conclude that this represents a greater susceptibility to environmental stressors than that found in non-cases (Mayer, 1999). An alternative explanation proposed by another author is that IBS patients may exaggerate the importance of stress in an effort to assign meaning to their symptoms (Whitehead, 1997).

In summary, the weight of evidence suggests that stress is an important factor in the predisposition to IBS and is a likely precipitant. The difficulties in defining this relationship may be similar to those found in CFS, that is, it may not be the nature or number of life events that is important, but the individual's perception of those events that determines the relationship. Once again, prospective studies of levels of perceived stress at the time of acute infection may help to determine more precisely the role of stress in the development of IBS.

6.3. Perpetuating factors

The investigation of factors associated with the perpetuation of IBS is not as extensive or as focused as that for CFS. The distinctions between predisposing factors, precipitants and perpetuators in the IBS literature are less obvious, and many of the variables mentioned in previous sections are also relevant here. This blurring of the boundaries between these stages of development is largely due to the influence of the biopsychosocial model in models of IBS, which does not emphasise these distinctions as strongly as the cognitive-behavioural model does. As was found in CFS, the distinction between what may perpetuate IBS in its early stages and what maintains it in a more chronic phase has rarely been commented on. This possibility becomes even more relevant to IBS than was the case with CFS for one important reason. What little is known of the natural history of CFS and IBS indicates that the experience of symptoms over time differ for each condition. IBS is known to have a fluctuating course with symptom free periods interspersed between bowel symptom episodes, as opposed to a more chronic symptom course found in CFS. The argument that the investigation of perpetuators of CFS needs to be considered in the context of the course of illness is even more relevant with regard to the symptoms of IBS which may be present only episodically. With this in mind the limited literature regarding perpetuators of IBS will be briefly reviewed.

Cognition

A small number of studies have investigated the role of cognition in IBS, giving some support to the hypothesis that cognitions help to maintain the condition. Causal attributions, symptom focus and anxiety about health have all been proposed to influence the course of IBS. Crane and colleagues (2002) showed that individuals with IBS believe that they have a greater vulnerability to illnesses in general compared with controls. They also have higher levels of anxiety specifically associated with stomach and bowel sensations, than control subjects do, indicating a greater symptom focus in those with IBS (Hazlett-Stevens, Craske, Mayer, Chang, & Naliboff, 2003). Bodily preoccupation has also been found to be a risk factor in the development of post-infectious IBS (Gwee et al., 1999). Those seeking health care for IBS are more likely to make somatic attributions regarding their gastrointestinal symptoms than are non-treatment seekers and are more likely to attribute the physiological symptoms of anxiety and depression to their IBS diagnosis, despite similar levels of symptom severity in each group (Martin & Crane, 2003).

Two small experimental studies have also provided evidence for the role of selective attention to gastrointestinal symptoms in the perpetuation of symptoms. The first compared IBS patients with asthma patients and healthy controls on their attention to a range of words, including gastrointestinal sensation words, respiratory-related words and neutral words (Gibbs-Gallagher et al., 2001). They found that both patient groups selectively recalled the words associated with their own symptoms in comparison to the controls, and concluded that this provided evidence of selective attention to gastrointestinal sensations in IBS. The second study of IBS patients found that the presentation of illness specific cues were associated with the reporting of an increased range and severity of IBS symptoms as compared to control conditions, whereas neutral cues were associated with less anxiety and less severity of IBS symptoms than under control conditions. The authors of this study concluded that the cognitive appraisal of symptoms can be manipulated according to the context within which symptoms are interpreted, implying that the challenging of negative illness beliefs and rumination is likely to be beneficial for IBS patients (Crane & Martin, 2003).

The Illness Perceptions Questionnaire (Weinman et al., 1996) has also been used to investigate the role of negative illness beliefs in IBS, with similar results to that found for CFS patients. A cross-sectional study of members of an IBS support group found that

beliefs regarding the consequences of IBS and extent of control over their symptoms were associated with lower quality of life, lower satisfaction with health, and higher scores for anxiety and depression (Rutter & Rutter, 2002). A prospective investigation of functional gastrointestinal disorders (FGID) following gastroenteritis also found that negative illness beliefs at the time of acute infection can predict new onset FGID six months later (Parry, Corbett, James, Barton, & Welfare, 2003). Results indicated that those who developed a FGID were more likely at the time of their acute illness to attribute more of their symptoms to that illness, believe it would last a long time and that it would have more severe consequences for them. Interestingly, they found similar beliefs in those patients excluded from follow-up due to a prior FGID, indicating that these beliefs may also be associated with an underlying vulnerability for FGID.

At least two measures of illness-related cognitions specific to IBS have been designed. The first examined common misconceptions regarding IBS and found that whilst IBS patients were better informed than tertiary students, there was still a high level of inaccuracy in their answers, particularly with regard to the relation of IBS to other serious diseases (Dancey, Fox, & Devins, 1999). A second scale was designed using thought diaries of IBS patients in order to specify common automatic thoughts that may be useful targets in cognitive-behavioural treatment. They found themes including bowel performance anxiety, lack of control over bowel symptoms, pain, perfectionism, anger/frustration, self-efficacy, social approval, embarrassment, heightened sensitivity to social rules and norms, and self-nurturance although only one factor was found using principal components analysis (Toner, Stuckless et al., 1998). Both these measures demonstrated good reliability and validity, and both sets of authors identified the potential uses of these measures in further research, however, neither has been widely used or examined with regard to their association with outcome or influence on treatment. Despite these studies demonstrating that it is possible to identify IBS specific cognitions, more research is required before their role in the perpetuation of IBS can be determined.

Behaviour

As mentioned in the introduction to this chapter, the investigation of behavioural factors in the development of IBS has been dominated by the controversy surrounding the impact of health care utilisation. Despite the large number of studies addressing the role of psychological factors on consulting behaviour, however, there has been very little investigation of the impact of help-seeking behaviour itself. The cognitive-behavioural

model views help-seeking behaviour as a potential perpetuator of the symptoms of many functional somatic syndromes, in a manner similar to the checking behaviour of some anxiety disorders. Clinical accounts emphasise the importance of minimising unnecessary investigations and interventions in IBS (Cash, Schoenfeld, & Chey, 2002), yet the impact of high health care utilisation on the course of this condition has yet to be investigated.

Other behavioural factors implicated in the perpetuation of IBS have also had limited empirical investigation. Several studies have used the Illness Behaviour Questionnaire (IBQ) to investigate the relationship between abnormal illness behaviour and IBS. One study found that IBS patients displayed significantly higher levels of abnormal illness behaviour in the form of hypochondriasis and disease conviction than non-patient controls, but did not differ from a group of Crohn's disease patients on these measures (Hobbis, Turpin, & Read, 2003). A second study found that the only subscale of the IBS to differentiate IBS consulters with non-consulters was the disease conviction scale, indicating that consulters were more likely to believe they were experiencing symptoms representing serious pathology (Koloski et al., 2005).

As indicated in the section on CFS, the IBQ focuses largely on cognitive variables at the expense of actual behaviour, and the results from these studies are in keeping with this. Although providing further evidence for the importance of cognitive variables in IBS, they do not adequately define specific behaviours that may be important in the development of IBS. Clinical treatment trials have emphasised the importance of minimising avoidance behaviour and excessive checking in response to symptoms (Corney, Stanton, Newell, Clare, & Fairclough, 1991), however empirical evidence regarding the impact of such behaviours is sparse. As was found for CFS, the potential for changes in behavioural responses to IBS symptoms over time is not well understood. It is possible that similar behavioural mechanisms proposed as influential in the development of CFS may also be relevant to IBS. For example, excessively limiting behaviours or engaging in an oscillating pattern of behaviour at the time of gastroenteritis may impede recovery in such a way as to increase the risk of IBS also. It is clear that whilst behavioural factors have been considered theoretically in the perpetuation of IBS more investigation is needed before this aspect of the cognitive-behavioural model can be confirmed.

Emotion

Similar problems are apparent when considering the impact of emotional variables in the perpetuation of IBS. Much of the research regarding the impact of emotional variables in IBS centres once again on its effect on help-seeking behaviour, rather than IBS symptoms (Drossman et al., 1988; Heaton et al., 1992; Whitehead et al., 1988). Studies have often been cross-sectional and unable to comment on the causal role of these factors in ongoing IBS symptomatology. Measurement issues of the type encountered with CFS are also problematic here. Emotional variables can be measured in a range of ways, and the type of measurement can often give what seem to be conflicting results. For example, a study investigating gender differences in levels of psychological distress in IBS patients found that despite females having higher levels of anxiety and depression on dimensional measures than males, there was no difference in the percentage who met criteria for one or more psychiatric disorders (Blanchard, Keefer, Galovski, Taylor, & Turner, 2001). This study also provided evidence that subthreshold levels of anxiety and depression may be more important than categorical diagnoses in determining risk.

Depression and anxiety have been found to contribute to poor outcome in IBS patients receiving psychological treatments, indicating that the emotional variables do have some impact on the maintenance of this condition (Blanchard et al., 1992; Creed et al., 2005). One prospective study providing evidence of this association looked at the impact of psychological distress, anxiety and depression on gastrointestinal symptoms over a twelve month period (Koloski, Talley, & Boyce, 2003). Distress levels were associated with persistent symptoms and increased levels of health care seeking; however, changes in distress levels were not reliably associated with symptom change over time. Although this study used a community sample of individuals with unexplained gastrointestinal symptoms rather than IBS, the results indicate a similar pattern to that found in earlier studies. These results suggest that anxiety and depression, despite promoting vulnerability to IBS, may not necessarily have a direct impact on the perpetuation of symptoms. The complex nature of this relationship is evidenced by the results from an earlier longitudinal study of IBS patients. This study found that at five year follow-up, levels of anxiety were more important in the ongoing maintenance of IBS, whilst depression appeared to affect fluctuations in perceived distress and illness behaviour in response to adverse life events (Fowlie, Eastwood, & Ford, 1992). Clearly, the relationship between emotional variables and the perpetuation of IBS deserves further investigation.

In summary, evidence for the cognitive-behavioural model of IBS is slowly emerging, although the gaps are wider than that seen in CFS. The model itself has not been as clearly articulated as it has for CFS, and as a result, research efforts have been somewhat piecemeal and lack integration. Most of the evidence, like that for CFS, is cross-sectional or retrospective, making causal hypotheses and those regarding interactions between variables difficult to verify. Although there are a significant number of post-infectious IBS studies, the majority of these studies have been designed to determine prevalence rather than examine the impact of psychological risk factors. Very few studies have considered cognitive, behavioural and emotional variables specific to IBS, instead focusing on general concepts such as psychological distress and life events. Despite this, there is more widespread acceptance of models such as the cognitive-behavioural one in regard to IBS, and a greater acknowledgement of the integration of psychological and biological factors than has been the case for CFS. There are promising results from studies examining the role of stress and early experiences; however, more detailed examination of these variables is required before the cognitive-behavioural conceptualisation of IBS can be confirmed.

Chapter 7.
Rationale for the current study.

7.1. Overview of the literature

This thesis aims to expand the current body of knowledge regarding psychological factors important in the classification and aetiology of the functional somatic syndromes. Multiple classification systems have been developed for these syndromes along with complex levels of subclassification for single conditions; resulting in symptom-based definitions that are in some cases arbitrary. These case definitions often attempt to incorporate a wide range of perspectives (physiological, psychiatric, and psychological) into what purport to be non-aetiologically biased nomenclature. In a similar way, the cognitive-behavioural model for the functional somatic syndromes has proven capable of generating hypotheses about the aetiology of these conditions from a psychological perspective. At the same time, this model has been flexible enough to incorporate research from other disciplines. Despite this, many of the basic tenets of the cognitive-behavioural model of functional somatic syndromes remain untested, and are often based on cross-sectional research, theoretical assumptions and clinical anecdote. For both the cognitive-behavioural model and the current systems of classification of these syndromes, it is important that they continue to be shaped by sound empirical investigation, in order to maintain their long term clinical effectiveness and integrity.

The purpose of this study is to evaluate psychological and biological risk factors in the development of IBS and CFS, and to do so in a more detailed way than has been previously attempted. It aims to critically examine untested assumptions about the origins of these two conditions by using a prospective design to clarify the relative importance of proposed psychological and biological precipitants. In doing so, it is intended to gather evidence that will further enhance the cognitive-behavioural model, and provide some of the detail that has thus far remained hypothetical. At the same time it will be possible to determine whether the similarities between these two syndromes outweigh the differences with respect to this model. By comparing the development of these two conditions the study also intends to shed light on the one-or-many debate regarding the functional somatic syndromes. Finally, the usefulness of distinctions across and within these syndromes will

be explored by comparing the two conditions and their subthreshold counterparts in order to ensure that current criteria are meaningful to both clinicians and their patients.

Taxonomic debates.

As discussed in Chapter two, the usefulness of the plethora of individual diagnoses within the overriding category of functional somatic syndromes is subject to ongoing debate (Nimnuan, Rabe-Hesketh et al., 2001; Wessely & White, 2004). In the absence of physiological markers and clear aetiological information, consensus committees have been forced to consider a wide range of information in order to delineate one disorder from another. In summary, those who argue that these syndromes should be conceptualised as one group point to the overlap between different functional somatic syndromes with regard to symptoms, disability levels and patient characteristics such as gender (Aaron & Buchwald, 2001). Should this be the case, we would expect that the type and relative importance of biological and psychological predictors of post-infectious functional somatic syndromes would be largely consistent for CFS and IBS. From the other side of the debate, researchers point to the gains to be made by subclassifying conditions, arguing that important distinctions are lost when overriding definitions are too heterogeneous (Jason, Corradi, Torres-Harding, Taylor, & King, 2005). By comparing psychological predictors and infectious precipitants of two distinct functional somatic syndromes in relation to each other and to their subthreshold conditions, it will be possible to determine if this is indeed the case.

Despite calls for an overriding category, the development of independent criteria and their subsequent revision continues with a proliferation of classification systems and subcategorisation. The thresholds for defining individual functional somatic syndromes are constantly being revised. In such a climate it is important to examine the heuristic value of the different definitions offered up to practitioners. If the use of a different threshold results in wildly different prevalence rates, severity rates, or relevance of etiological factors, then it is important for practitioners to understand these distinctions and to incorporate them into their practice. If, however, the thresholds make very little difference to the above-mentioned factors, then we can simplify the definition process considerably.

These issues are more than theoretically interesting – they are relevant to everyday clinical practice. Can the current classification systems help define useful groups of patients for

whom more thorough assessment is indicated? Can they help determine effective early intervention or targeted treatment options for certain groups? If our classification systems are to be complex, it is important that our assessment and treatment processes are usefully guided by this complexity rather than confused by it. By comparing actual cases of CFS and IBS diagnosed by current criteria with regard to prevalence, predisposing variables, disability levels and patient characteristics we can determine the nature of their similarities. Similarly, by comparing these cases with those identified using a lower threshold, the usefulness of subclassification at this point in time can also be determined.

Utility of the cognitive-behavioural model.

Cognitive-behavioural theory has made great advances over the past two decades in our understanding and treatment of a wide range of conditions for which traditional biomedical approaches have been found deficient (Mayou & Sharpe, 1997). Its application to the functional somatic syndromes has revealed an array of theoretical and clinical options to explore. Cognitive-behavioural approaches have been seized upon with great enthusiasm particularly in the area of treatment, since first showing success in alleviating the suffering associated with these conditions (Kroenke & Swindle, 2000). Its greatest strength is its ability to accept the complex interplay of multiple causes, rather than hold to a single causality model that has proved problematic in the area of the functional somatic syndromes.

However, the theoretical basis for these treatments comes largely from cross-sectional and retrospective research, anecdotal evidence, or has been adapted from those developed for other conditions. Gaps remain in the empirical literature to support several important assumptions of the cognitive-behavioural model in the area of the functional somatic syndromes. The fundamental structure of the cognitive-behavioural model of functional somatic syndromes appears sound; however much of the detail that makes up the subtle process of the development of these conditions remains sketchy. In order to maintain its current standing and relevance to the functional somatic syndromes, to enable us to further refine the theory, and to provide researchers and clinicians with specific guidance regarding areas to target, empirical clarification of this detail is required.

When examining the existing evidence for the cognitive-behavioural models of IBS and CFS, the similarities are striking. Each body of literature has taken a different path, with emphasis on differing aspects of the overall model. The cognitive-behavioural model of

CFS appears to be at a more advanced stage of development than its IBS counterpart; however, consistent themes still emerge. By using the same variables to prospectively investigate the development of two distinct functional somatic syndromes, it is possible to take variables hypothesised as important in one syndrome and to determine their relevance to the other. For example, limiting behaviour has been found to be predictive of post-infectious CFS; it may also be important in post-infectious IBS. This study aimed to provide more of the detail required to confirm the utility of the cognitive-behavioural models for these separate conditions, but also to learn more about the underlying similarities and differences that relate to them. In doing so, it will be possible to determine the utility of an overarching model for the functional somatic syndromes as compared to individual models for each condition. In this way, arguments for the "one or many" debate can be considered from a theoretical perspective as well as a taxonomic one.

Finally, those studies that have used the theoretical framework of the cognitive-behavioural model to select variables under consideration have tended to look at specific aspects of the model rather than the interactions it proposes. This may be the result of the traditional influence of mind-body dualism, but it is more likely to reflect the complexity of empirically testing such a multifaceted model (Novy et al., 1995). Whatever the reason, more integrative work is now required that is capable of examining the relative influence of biological, psychological, and social factors in the development of these conditions. As one editorial pointed out, these influences can best be explored using prospective cohort studies of conditions which are known to be associated with later functional somatic syndromes, such as stressful life events, viral infection or post-operative states (Hotopf & Wessely, 1999). By using such a population, the current study will attempt to operationalise the key psychological components of cognitive-behavioural model in order to determine their specific impact alongside that of a known infectious precipitant.

The prospective investigation of post-infectious populations.

Post-infectious functional somatic syndromes provide us with intriguing populations within which we can compare the relative influence of biological and psychological factors. It has been established that particular infections can precipitate the onset of a functional somatic syndromes such as IBS and CFS. However, the importance of the existence of an infectious precipitant remains unclear. Whilst certain infections place individuals at higher risk of developing CFS or IBS, the majority of individuals experiencing these acute infections will not go on to develop such chronic conditions.

Similarly, individuals with CFS or IBS have not all experienced an infectious precipitant. Individuals who develop post-infectious functional somatic syndromes are therefore subsets of a wider population of people with these conditions. In order to fully understand the interaction between biology and psychology in the development of post-infectious syndromes such as IBS and CFS, we need to know the relative importance of the infection in comparison to psychological variables and how that influence may change over time.

The conclusions of prospective studies such as these necessarily relate specifically to post-infectious subgroups. However, if it can be demonstrated that psychological factors are an important aetiological influence in groups with a known infectious precipitant, then such factors are also likely to be relevant to the same condition without such a biological precipitant. The small number of prospective studies that have looked at the importance of psychological predictors in the development of functional somatic syndromes have also been limited in their approach to the selection of predictors. Studies using post-infectious populations have confirmed the importance of psychological factors but have tended to focus on very broad measures of psychological functioning, such as a history of psychiatric diagnosis; or very specific ones, such as illness perceptions (Candy et al., 2003; Parry, Corbett et al., 2003; Rea et al., 1999).

Despite the importance of post-infectious samples in determining aetiological factors, untested theories regarding the relevance of the infectious precipitant abound. In chronic fatigue, the infection is viewed by many to be a physiological trigger in an otherwise psychologically vulnerable individual (White, 1997). In the case of IBS, some view the infection as a physiological cause of altered bowel function with psychological factors less important in this subgroup compared to those without prior infection (Spiller, 1994). It is clear from these examples that we need to confirm more precisely the influence of the infectious precipitant. Previous studies have found that the development of CFS is associated with a range of severe infections but not with milder illnesses. It is possible then, that the severity of the infection may be more important than the nature of the infection. Similarly, not all who experience these infections will go on to develop a functional somatic syndrome, suggesting that the infection needs to co-exist with certain psychological variables to become a trigger. By including two separate acute illness samples this study aims to shed light on these possibilities.

Stages of illness development.

Many of the methodological difficulties in the literature surrounding IBS and CFS stems from the differences found between the various subpopulations found in these disorders. Consulters vs. non-consulters, primary care vs. tertiary care, post-infectious vs. non-infectious, subthreshold vs. threshold conditions; many studies have provided contrasting results about these common disorders as a direct result of these distinctions. In addition, knowledge of the natural history of IBS and CFS is sketchy, particularly in the early stages prior to help-seeking and diagnosis (El-Serag, Pilgrim, & Schoenfeld, 2004). All of these issues, coupled with largely cross-sectional designs have led to a glossing over of the important issue of the impact of stage of development of these conditions. It is likely that a person who has experienced CFS or IBS for many years will have a very different set of symptoms and circumstances to someone who is in the early stages of developing such a condition.

Functional somatic syndromes such as CFS and IBS are most commonly seen in primary care settings, and it would appear that an even larger number of people with these conditions have never sought help for their symptoms, have never been diagnosed, and manage them of their own accord with varying degrees of success (Wilson et al., 2004). Despite this, much of the literature on classification, assessment and treatment of functional somatic syndromes has focused on those with well established conditions, rather than the newly diagnosed or those who never present with their symptoms. These studies are unable to tell us with any firm conviction what the precursors to the development of these conditions are, or what factors may influence their development over time.

Because of this selection bias, there has been more investigation of the perpetuating factors associated with somatic syndromes, particularly CFS (Vercoulen et al., 1998). Far less has been done to empirically investigate the predisposing and precipitating factors that could be useful in determining those at risk for these conditions. In order to provide strategies for prevention and early intervention, it is essential that we have a very clear picture of the factors that may influence the development of these conditions in populations that have not previously experienced bowel or fatigue problems. By targeting patients before the development of a functional somatic syndrome it is possible to elucidate the key features that invoke vulnerability, and use a wider population than can be found once patients have sought help for their symptoms

In order to remain relevant to the ever changing face of medicine, one of the great challenges for biopsychosocial approaches is to broaden their scope to include health promotion and prevention of illness (Ryff & Singer, 2000). The cognitive-behavioural model, with its distinction between predisposing, precipitating and perpetuating variables, is ideally placed to do this. In addition to providing information about predisposing and precipitating variables, prospective studies also enable the clarification of the existence of risk factors during the early stages of these syndromes. In this way it is possible to determine not only who is vulnerable to the development of IBS and CFS following acute infection, but what to target in terms of prevention and early intervention.

7.2. The design of this study.

In order to fill some of these gaps identified in the literature, this study focuses on two known infectious precipitants (*Campylobacter* and glandular fever) of two common functional somatic syndromes (IBS and CFS respectively). The existence of these acute infections will be verified through diagnostic testing in order to ensure as homogeneous population as possible. Prior to the main study, a measure of behavioural responses to illness will be developed and validated to ensure that this aspect of the cognitive-behavioural model is able to be tested. The main study employs a prospective, self-report questionnaire-based design in order to investigate between group differences with regard to the development of these two syndromes. Baseline measures will be completed at the time of acute illness, whilst three and six month follow-up questionnaires will determine outcome data with regard to caseness of IBS and CFS and their subthreshold conditions. Predisposing and precipitating psychological variables identified by the cognitive-behavioural models of IBS and CFS will be investigated as predictors of the development of these conditions following acute infection. The use of a prospective design will enable the investigation of the individual importance of a range of variables identified by the cognitive-behavioural model.

In order to determine the predictors of each individual syndrome and their relative importance, the sample will initially be split according to acute illness type and analysed separately. The analysis will be identical in order to provide comparison of results between the two functional somatic syndromes. Each of the variables to be measured will be considered independently with regard to its influence on the development of IBS and CFS, and then alongside the others to determine their relative importance. The sample will

then be considered as a whole in order to: a) compare psychological predictors of IBS and CFS, b) determine the relative risk of developing IBS and CFS following two distinct infections, and c) investigate the differences between threshold and subthreshold definitions with regard to predictors, patient characteristics and disability.

7.3. Specific hypotheses investigated.

1. Specific cognitive, behavioural and emotional risk factors operationalised from the cognitive-behavioural model will be significantly associated with the development of post-infectious IBS three and six months post-infection:

    (a) Cases of IBS will report higher levels of the following predisposing variables at the time of acute illness than non-cases: depression, anxiety, somatisation, and negative perfectionism.

    (b) Cases of IBS will report higher levels of perceived stress at the time of acute illness than non cases, reflecting the role of this variable as a precipitant in the development of IBS.

    (c) Cases of IBS will report higher levels of illness-related behaviours and cognitions at the time of acute illness that lead to the perpetuation of symptoms relevant to IBS, including: an oscillating pattern of activity and inactivity, limiting/resting behaviour, practical and emotional support seeking behaviour, as well as a range of negative illness beliefs (such as expectations of recovery time, perceived consequences and the emotional impact of the illness).

2. The same psychological risk factors as set out for IBS will also be significantly associated with the development of post-infectious CFS three and six months post-infection.

3. The odds of developing CFS will be significantly greater following glandular fever than *Campylobacter*; whereas the opposite will be true for IBS. However, the odds of these acute illness risk factors will be lessened from three to six months post-infection in relation to the odds of the psychological variables.

4. Cases of CFS will have lower prevalence rates, higher levels of associated disability and utilise health care more often than IBS cases, due to a greater emphasis on disability in the diagnostic criteria for this condition.

5. IBS will be more comparable with a wider group of fatigue cases that includes both CFS cases and those not significantly disabled by their fatigue, with respect to prevalence, the level of associated disability and health care utilisation. They will also be more comparable with regard to the psychological risk factors relevant to their development.

6. Patients experiencing bowel dysfunction or chronic fatigue post-infection that does not meet the threshold for established criteria, will nonetheless have a similar profile to cases of IBS and CFS with regard to psychological risk factors. Subthreshold conditions will, however, be distinguished according to the relative importance of these psychological variables and the extent of disability associated with them.

Chapter 8.

Preliminary study: The development and validation of the Behavioural Responses to Illness Questionnaire.

The aim of this study was to design a self-report measure of behavioural responses during the acute phase of an illness, in order to assess the importance of these behaviours in the development of ongoing medically unexplained syndromes. As outlined in the introduction to this thesis, the cognitive-behavioural model proposes that behaviour during the acute stage of an illness may contribute to the early development and perpetuation of functional somatic syndromes. Behaviours of particular interest include a limiting pattern, where activity is avoided, and an oscillating or all-or-nothing pattern, where bursts of activity are followed by prolonged rest periods.

Despite the theoretical and clinical interest in these behaviours, there has been little empirical research to support their existence, largely due to difficulties measuring this concept. The following chapter outlines the development and validation of a questionnaire designed to measure these behaviours in the context of post-infectious irritable bowel syndrome (IBS). Section one describes how an initial pool of items derived from theoretical models and clinical observation was piloted on a group of 312 university students to assess the factor structure of the scale and the best fit items. Section two outlines the further validation of the scale using 758 patients from the main study of this thesis who were experiencing *Campylobacter* gastroenteritis. Finally, section three provides a brief summary and discussion of the results of the study.

8.1. Initial item selection.

Methodology

Selection of items

Seven possible subscales were devised based on models of illness behaviour described in the literature, the retrospective accounts of patients with functional somatic syndromes

regarding acute illness behaviour, and clinical reports of common activity styles during acute illness. The initial subscales were labelled as follows: balanced approach (e.g. "I would know just what needs to be done and what can wait until I am feeling better"), limiting behaviour (e.g. "I would put parts of my life on hold"), denial of illness (e.g. " I would continue to work and play as I do normally"), all-or-nothing behaviour (e.g. "I would overdo things, then need to rest up for a while"), medical help-seeking (e.g. "I would take some medicine to make me feel better"), social/emotional support seeking (e.g. "I would ring people close to me for sympathy"), and practical support seeking (e.g. "I would rely on my family and friends to look after me"). A complete list of items is found in Table 4.

Participants

The questionnaire was piloted on 312 university students; including first year Human Biology students (a composite of medical, nursing, pharmacy, and health science students) and a smaller class of fifth year medical students at the University of Auckland, New Zealand. The sample was predominantly female (73.5%) and young (M=21.7 years; SD=5.8). A separate group of a further 51 students from the Human Biology course was used to collect the test-retest data. Once again this group was largely female (74.5%) and was of a similar age to the previous group (M=21.6 years; SD=7.2).

Procedure

Students were asked to complete an anonymous questionnaire during class-time, including questions regarding age and gender (see Appendix 1). Participants were asked to answer the questions according to what they would do if they were to experience a moderately severe acute illness such as food poisoning or influenza. Items were scored according to a frequency scale ("not at all", "rarely", "some days", "most days", and "every day") in order to emphasise the behavioural nature of the items. That is, participants were asked to recall the amount of time actually engaged in a particular behaviour rather than rate their belief in the usefulness of that behaviour. The test-retest data was once again collected during class-time, with one week between the completion of each questionnaire.

Table 4. Proposed subscales and items used in the pilot study.

BALANCED APPROACH
I would pace myself in what I need to do
I would carry on with some of my daily activities but take more time to rest
I would carry on with my usual daily activities but at a slower pace
I would know just what needs to be done and what can wait until I am feeling better
I would take time out from my usual activities so that I can get back to normal quicker
LIMITING OF ACTIVITY
I would avoid physical exercise
I would put parts of my life on hold
I would avoid my usual activities
I would go to bed during the day
I would not be able to carry on with my usual level of activities
DENIAL OF SICKNESS
I would continue to work and play as I do normally
I would take time off even if my work or other responsibilities may suffer (reverse scored)
I would keep up my normal level of exercise
I would feel obliged to carry out all my responsibilities, no matter how bad I feel
I wouldn't slow down, I would just carry on as normal (reverse scored)
ALL-OR-NOTHING BEHAVIOUR IN THE FACE OF ILLNESS
I would overdo things, then need to rest up for a while
I would push myself as hard as ever until I can not push myself anymore
I would carry on with things as normal until my body could not cope any longer
I would try to do too much and feel even worse as a result
I would find myself rushing to get everything done before I crashed
MEDICAL HELP-SEEKING
I would go to the chemist for advice
I would take some medicine to make me feel better
I would use herbal remedies
I would look for information about my illness
I would speak to my doctor or practice nurse about my illness
SOCIAL/EMOTIONAL SUPPORT SEEKING
I would talk to others about how bad I feel
I would ring people close to me for sympathy
I would tell people around me how miserable I feel in the hope that they feel sorry for me
I would want people to acknowledge how sick I am
I would want people to understand how awful I feel
PRACTICAL SUPPORT SEEKING
I would rely on my family or friends to look after me
I would ask for help from my family or friends
I would make sure I had someone to look after me
I would try to find someone to help me out
I would ask my family and friends to carry out my usual responsibilities

Results

Structural Validity

SPSS version 12.0.1 for Windows computer software programme was used to explore the factor structure of the questionnaire and to determine which items best represented the proposed subscales. Principal components analysis (PCA) with varimax rotation was conducted on the student data collected for the 35 items. The first analysis produced eight factors with an eigenvalue greater than 1, accounting for 61% of the variance. Item analysis of the rotated factors indicated that while most of the items from the proposed subscales loaded onto independent factors, the items from the proposed limiting and balanced subscales were spread over two factors each. In addition, the items from the proposed denial of illness subscale were spread across factors representing the proposed all-or-nothing and limiting subscales. Examination of the scree plot also suggested that a five factor solution may be more appropriate.

In order to clarify the nature of the factor structure, a five factor solution was imposed. A much clearer factor structure was obtained, with the five factors accounting for 50% of the variance. The majority of items had loadings greater than .5 on one of the five factors and less than .45 on the others. The items from the proposed balanced subscale, however, performed poorly, with four of the five items obtaining factor loadings less than .5, and the remaining item loading onto the limiting factor. Results remained inconsistent for the proposed denial of illness subscale as well, with some items loading negatively onto the limiting factor and others onto the all-or-nothing factor. All items with factor loadings less than .5 were deleted, including one item each from the denial of illness, practical support and medical help-seeking subscales. In addition, the only two remaining negatively loaded items were deleted to avoid the confusion of only two reverse scoring items, leaving a total of 26 items. No item loaded onto more than one factor.

Internal Reliability

Cronbach's alpha was used to determine the internal reliability of the preliminary subscales. Four of the five subscales obtained alpha coefficients ranging from .81 to .87 (see Table 5). Inter-item correlations indicated that none of the subscales would have been significantly enhanced by the removal of any further items. In contrast, the medical help-seeking subscale obtained a comparatively low alpha coefficient of .66, with no

improvements to be made by removing any items. Consequently, this subscale was removed from further analysis.

Table 5. Principal components analysis of the Behavioural Responses to Illness Questionnaire: Pilot study, student sample (n=314).

	I	II	III	IV
ALL-OR-NOTHING BEHAVIOUR (α = .82)				
I would overdo things, then need to rest up for a while	**.59**	-.01	-.01	.01
I would push myself as hard as ever until I could not push myself any more	**.77**	-.01	.00	.00
I would carry on with things as normal until my body could not cope any longer	**.74**	-.15	.00	.00
I would feel obliged to carry out all my responsibilities, no matter how bad I feel	**.54**	-.45	.00	-.01
I would try to do too much and feel even worse as a result	**.76**	-.11	.01	-.12
I wouldn't slow down, I would just carry on as normal	**.67**	-.40	.00	-.01
I would find myself rushing to get everything done before I crashed	**.69**	.00	.01	.00
LIMITING BEHAVIOUR (α = .81)				
I would avoid exercise	-.01	**.59**	.01	.01
I would put parts of my life on hold	-.12	**.69**	.27	.12
I would avoid my usual activities	.00	**.84**	.00	.00
I would go to bed during the day	-.15	**.61**	.11	.17
I would not be able to carry on with my usual level of activities	-.13	**.72**	.25	.11
I would take time out from my usual activities so that I can get back to normal quicker	-.39	**.64**	-.01	.19
EMOTIONAL SUPPORT SEEKING (α = .85)				
I would talk to others about how bad I feel	.00	.01	**.70**	.24
I would ring people close to me for sympathy	.00	.19	**.56**	.38
I would tell people around me how miserable I feel in the hope that they feel sorry for me	.01	.01	**.83**	.11
I would want people to acknowledge how sick I am	-.01	.12	**.83**	.16
I would want people to understand how awful I feel	.00	.20	**.83**	.11
PRACTICAL SUPPORT SEEKING (α = .87)				
I would rely on my family or friends to look after me	-.01	.12	.14	**.81**
I would ask for help from my family and friends	.00	.13	.20	**.84**
I would make sure I had someone to look after me	.00	.12	.20	**.81**
I would try to find someone to help me out	.00	.14	.21	**.79**

Structural validity of the revised questionnaire

A final PCA was conducted on the remaining 22 items, producing a clear four factor solution accounting for 58% of the total variance. Factor loadings ranged from .56 to .84 (see Table 5). The items from each factor loaded no more than .45 on the other factors with the majority obtaining loadings of less than .20. Alpha coefficients (see Table 5) and inter-item correlations remained consistent leaving a seven-item all-or-nothing subscale, a six-item limiting subscale, a five-item emotional support seeking subscale, and a four item practical support seeking subscale.

Test-retest reliability

Data was collected from the second student sample to investigate the test-retest reliability of the 22-item questionnaire over a one week period. Pearson's correlations were computed between the four subscales at the two time points. Each subscale showed acceptable stability over this period with correlations of .61 for the all-or-nothing subscale, .76 for the limiting subscale, .79 for the practical support seeking subscale, and .87 for the emotional support seeking subscale.

8.2. Validation of the questionnaire.

Method

Participants

Following the pilot study using university students, the 22-item questionnaire was validated using a clinical sample drawn from the main study. Because the methodology for that study is outlined in detail in the following chapter, only brief details relevant to the current study are given here.

The sample included 758 patients who had recently or were currently experiencing an episode of *Campylobacter* gastroenteritis. All patients 17 years and older, with *Campylobacter* isolated from stool culture were identified by the major provider of clinical diagnostic services for the greater Auckland area between 1st of March, 2002 and 10th March, 2002. Due to the need to maintain privacy of health information, questionnaires were sent directly from the laboratory to general practitioners (*N*=2547), who were then

asked to post these on to their patients. At least one patient reply was received from 59% of those doctors sent questionnaires. Assuming that 60% of doctors sent on all questionnaires for their patients, it is estimated that approximately 1500 questionnaires were received by patients. A total of 758 replies were returned, giving an estimated response rate of 51%.

The mean age of the sample was 44.6 years (*SD*=16.6), of whom 57% were female. The sample was predominantly New Zealand European (90%), and well educated, with 56% tertiary qualified. The majority of the sample reported being married or in a de-facto relationship (70%) and in some form of paid employment (76%).

Procedure

The 22-items were completed as part of a larger questionnaire examining predictors of recovery from acute infection which invited patients to complete a baseline questionnaire at the time of illness, in this case *Campylobacter* gastroenteritis (see Appendix 10). Three months after returning a positive stool sample, patients were sent a follow-up questionnaire. A total of 701 questionnaires were returned at this point giving a response rate of 92%.

Measures

The 22 items from the pilot study were adapted so that participants answered according to how often they had carried out the behaviours since their illness began. The larger questionnaire (see Appendix 10) asked for details about the person's illness, treatment, days off work, and details of past health problems in order to exclude any participants with a previous history of IBS or other chronic bowel condition. Patients were asked to indicate on a symptom checklist if they had experienced the main symptoms of *Campylobacter* (nausea, fever, vomiting, diarrhoea, stomach pain, blood in faeces, headache and aching muscles), and a *Campylobacter* symptom total was computed by summing these responses. The days off work variable and symptom total were used to assess criterion validity, that is, to determine whether behaviours were largely independent of illness severity.

The three month follow-up questionnaire included questions to determine whether or not patients met diagnostic criteria for IBS. Symptoms were elicited using questions developed from the Rome I and Rome II criteria for IBS (Thompson et al., 1992; Thompson et al., 1999) as described in Chapter 3. Participants were asked about the frequency of their bowel movements, and if they experienced urgency, straining, bloating,

mucus in the stools or a change in consistency of their stools more than 25% of the time. They were also asked if they experienced abdominal pain, and whether or not this pain was related to their bowel movements. Based on the answers to these questions, each participant was scored to determine whether they fulfilled Rome I or Rome II criteria for IBS. In recent years, there has been ongoing debate as to the usefulness of the distinctions made by these criteria (Boyce et al., 2000; Mearin et al., 2004; Saito et al., 2000). Because of this, and in order to gain the most representative group of IBS cases, participants who met Rome I and/or Rome II criteria were included as cases.

Results

Structural Validity and Internal Reliability

PCA with varimax rotation was used to validate the factor structure found in the student sample. This analysis produced similar results with four factors accounting for 61% of the variance. Item analysis indicated that all items loaded onto the expected factors, with the exception of two items. One of these items ("I have talked to others about how bad I feel") loaded equally onto the limiting and emotional support seeking subscales, whereas previously it had loaded strongly on the emotional support seeking subscale alone, and was deleted as a result. The other item ("I haven't slowed down, I've just carried on as normal") which had previously loaded clearly on the all-or-nothing factor, was now loading negatively on the limiting factor and was transferred to that subscale as a reversed scored item.

A final PCA was conducted on the remaining 21 items, producing four factors accounting for 62% of the variance with factor loadings ranging from .61 to .83 (see Table 6). The items loaded no more than .38 on the other factors, with the majority below .20. The final Behavioural Response to Illness Questionnaire (BRIQ) comprised a 6-item all-or-nothing subscale, a 7-item limiting subscale, a 4-item emotional support seeking subscale, and a 4-item practical support seeking subscale.

Reliability analysis:

The internal reliability of the subscales as measured by Cronbachs' alpha ranged from .81 to .89 (see Table 6).

Table 6. Principal components analysis of the Behavioural Responses to Illness Questionnaire: *Campylobacter* sample (n=758).

	I	II	III	IV
ALL-OR-NOTHING BEHAVIOUR (α = .81)				
I have overdone things, then needed to rest up for a while	**.64**	.14	.14	.00
I have pushed myself as hard as ever until I can not push myself any more	**.73**	-.13	.00	.01
I have carried on with things as normal until my body can not cope any longer	**.75**	.00	-.11	-.01
I have felt obliged to carry out all my responsibilities, no matter how bad I feel	**.70**	-.26	.00	-.12
I have tried to do too much and felt even worse as a result	**.77**	.10	.17	.00
I find myself rushing to get everything done before I crash	**.66**	.00	.24	.01
LIMITING BEHAVIOUR (α = .89)				
I have avoided physical exercise	.00	**.74**	.00	.15
I have put parts of my life on hold	.01	**.73**	.25	.17
I have avoided my usual activities	.00	**.83**	.10	.17
I have gone to bed during the day	.00	**.70**	.12	.30
I have not been able to carry on with my usual level of activity	.14	**.79**	.13	.15
I haven't slowed down, I've just carried on as normal	.38	**-.61**	-.12	-.16
I have taken time out from my usual activities so that I can get back to normal quicker	-.13	**.77**	.01	.15
EMOTIONAL SUPPORT SEEKING (α = .81)				
I have rung people close to me for sympathy	.00	.17	**.69**	.15
I have told people around me how miserable I feel, in the hope that they feel sorry for me	.00	.01	**.79**	.15
I have wanted people to acknowledge how sick I am	.10	.01	**.81**	.18
I want people to understand how awful I feel	.17	.18	**.77**	.01
PRACTICAL SUPPORT SEEKING (α = .84)				
I have relied on my family or friends to look after me	.00	.35	.00	**.79**
I have asked for help from my family or friends	.00	.28	.25	**.75**
I have made sure I had someone to look after me	.00	.24	.14	**.80**
I have tried to find someone to help me out	.00	.16	.39	**.65**

Inter-correlations between the subscales

Pearsons' correlations were computed between the subscales in order to investigate the inter-relationships between them. Results are presented in Table 7, indicating that the all-or-nothing subscale was relatively independent of the practical support seeking subscale, demonstrated a small negative correlation with limiting behaviour, and a small positive correlation with emotional support seeking. There were positive associations between the

limiting subscale, and both practical support seeking and emotional support seeking. The latter two subscales were also correlated.

Table 7. Correlation Matrix of the BRIQ subscales, *Campylobacter* sample (*n*=758).

	All-or-nothing	Limiting	Emot.SS
Limiting	-.07		
Emotional Support Seeking	.22**	.37**	
Practical Support Seeking	.01	.56**	.44**

NB. ** p <.01

Criterion validity

The relationship between the BRIQ subscales and severity of illness was also investigated. Pearson's correlations showed that *Campylobacter* symptom total was positively correlated with all the BRIQ subscales. The strength of these correlations ranged from small, for all-or-nothing (r=.08; p=.05) and emotional support seeking (r=.23; p<.001), to moderate for practical support seeking (r=.33; p<.001) and limiting (r=.40; p<.001). Because the variable "days off work" was not normally distributed, Spearman's rho correlations were used to determine its relationship with the BRIQ subscales. Results indicated that all-or-nothing behaviour demonstrated a small negative correlation with the number of days off work (r_s=-.11; p<.01). Both the limiting (r_s=.27; p<.001) and practical support seeking (r_s=.20; p<.001) subscales demonstrated small positive correlations with this variable. Emotional support seeking, however, (r_s=.07; p=.07) was not associated with days off work.

Predictive Validity

The predictive validity of the BRIQ was tested through the development of new onset IBS following *Campylobacter* infection. Consequently, all participants who reported a previous diagnosis of IBS or a serious bowel condition were excluded from further analysis. This included 109 participants who indicated they had been diagnosed with IBS in the past, and 18 people who indicated they had other bowel conditions (e.g. Colon cancer, Crohn's disease). Of the remaining 631 participants at baseline, there were 43 non-responders at follow-up. Analysis of the remaining sample of 588 people found a total of 99 (16.8%) new cases of IBS based on those who met Rome I and/or Rome II criteria,

consistent with previous reports of post-infectious IBS which range from 7% - 30% (Gwee, 1996; Neal et al., 1997; Parry, Stansfield et al., 2003).

An independent-samples *t* test showed IBS cases were significantly younger than non-cases (t (584) = 3.28; p<.001), while chi-square analysis indicated they were more likely to be female (χ^2 (1, N = 588) = 24.74, p<.001). With regard to illness variables, the IBS group reported a slightly higher number of *Campylobacter* symptoms (t (586) = -2.15, p=.03), but did not differ from the non-cases according to the rate of prescription for antibiotic treatment (χ^2 (1, N=580) =.10, p=.75). The Mann-Whitney U test showed that there was no difference between cases and non-cases with regard to the reported number of days off work (z=-1.24, p=.22). Consequently, further predictive analyses were conducted controlling for age, gender and *Campylobacter* symptom total.

Table 8. Results from the analyses of covariance across new IBS cases and non-cases for the BRIQ subscales.

	IBS cases (n=99) ***M (SE)***	**Non-cases(n=481)** ***M (SE)***	***F***	***p***
All-or-nothing	51.4 (1.68)	44.3 (.75)	14.78	<.001
Limiting	60.5 (1.87)	66.2 (.83)	7.73	<.01
Emotional support seeking	22.1 (1.02)	22.5 (.45)	.13	.72
Practical support seeking	26.5 (1.35)	30.1 (.60)	5.72	.02

N.B. means are percentage scores using marginal estimated means controlling for age, gender and *Campylobacter* symptom total

The ability of the BRIQ to predict the development of IBS post-infection was tested in two separate analyses. To compare the different levels of behaviour at the time of infection in IBS cases and non-cases, analyses of covariance (ANCOVAs) for each subscale controlling for age, gender and *Campylobacter* symptom total were conducted; with each of the BRIQ subscales measured at baseline as the dependent variables, and IBS caseness measured at follow-up as the fixed factor. Because each subscale had a different number of items, the individual BRIQ subscale totals were converted into percentage scores in order to provide meaningful comparison between the different subscales. The estimated marginal means and F values for the ANCOVA data are presented in Table 8, demonstrating that those who went on to develop IBS reported significantly higher levels of all-or-nothing behaviour at the time of infection than those who did not. The levels of

limiting behaviour and practical support seeking were significantly lower in those who went on to develop IBS. There was no significant difference in the levels of emotional support seeking behaviour between the two groups.

Table 9. Results from logistic regression analysis of the BRIQ subscales, gender, age and *Campylobacter* symptom total, with regard to new cases of IBS 3 months post-illness.

	IBS caseness	95%Confidence Interval (CI)	*P*
Gender	2.95	1.74-4.99	<.001
Age	.98	.97-.10	.02
Campylobacter symptom total	1.13	.97-1.30	.12
All-or-nothing	1.09	1.03-1.14	.001
Limiting	.97	.93-1.01	.11
Practical support seeking	.95	.88-1.02	.15
Emotional support seeking	1.02	.93-1.11	.73

To investigate the relative importance of the BRIQ subscales as predictors of IBS, a logistic regression was carried out with all four subscales as predictors and IBS caseness as the criterion (coded 0 for "no IBS" and 1 for "IBS"), with age, gender, and *Campylobacter* symptom total also entered into the equation. Results of the logistic regression demonstrated that even when demographic differences and illness severity were taken into account, all-or-nothing behaviour was a significant risk factor for the development of IBS, as was being female and younger in age (Table 9). None of the other BRIQ subscales were significant.

8.3. Discussion.

This study provides a valid and reliable measure of patients' behavioural responses to acute infection, and a useful predictor of the development of IBS. The development of this questionnaire differed from previous measures in a number of ways. First, the scale focused on frequency of actual behaviour rather than the strength of illness attitudes or cognitions. Second, it measured behaviour in both a student sample and an acute illness sample, rather than in a chronic condition, such as somatisation or chronic pain. Finally,

inclusion of data from the main study allowed examination of not only the psychometric properties of the scale, but also the usefulness of the construct as a predictor of IBS.

Certain limitations should be noted. The self-report nature of the questionnaire means that it is difficult to determine how accurately it reflects actual behaviour. The student sample questionnaire used a hypothetical situation rather than a real episode of illness, which may have impacted on results. In addition, due to the postal survey design aimed at achieving a large sample size, the determination of IBS caseness is based on self-report of IBS symptoms at follow-up rather than clinical assessment, which may have impacted on the integrity of the IBS diagnostic grouping.

Despite these limitations the results clearly demonstrate that the BRIQ subscales have good construct validity and internal reliability. Of the seven subscales originally proposed, four (all-or-nothing, limiting, practical and emotional support seeking) demonstrated good internal reliability and acceptable test-retest reliability. Items from the proposed balanced and denial of illness subscales either failed to load on any one factor, or loaded onto the limiting or all-or-nothing subscales respectively. The medical help-seeking items, whilst loading together as one factor, had poor internal reliability and were therefore discarded. It is possible that these items in particular were affected by the use of both the hypothetical scenario and a student population in study one. They may have performed better in a clinical sample and warrant further investigation.

With regard to construct validity, the correlations between the four remaining subscales were only small to moderate in size. The limiting, practical support seeking and emotional support seeking subscales demonstrated small to moderate positive associations between them. The greatest overlap was between limiting behaviour and practical support seeking, suggesting that people who limit their activities in response to illness are more likely to call on others for practical support. These two coping styles were also moderately correlated with the number of *Campylobacter* symptoms experienced at the time of infection, as well as days off work, suggesting that these strategies are associated with a delayed convalescence and possibly a more severe illness, or the perception of a more severe illness.

In contrast, the all-or-nothing subscale was largely independent of the others, demonstrating no association with practical support seeking, a slight negative association with limiting behaviour and a small positive correlation with emotional support seeking. All-or-nothing behaviour describes a pattern of alternating extremes of behaviour,

characterised by a cyclical response of pushing oneself to keep going until this feels no longer physically possible. The findings suggest that patients who engage in all-or-nothing behaviour attempt to be self-reliant when ill rather than impose on others. This is not a reflection of having a less severe illness, as all-or-nothing behaviour showed a slight positive association to *Campylobacter* symptoms at the time of infection. All-or-nothing behaviour also showed a small negative association with days off work, suggesting that these patients' attempts to keep going are reflected in their reluctance to take time off work.

The importance of this new scale lies in its predictive validity. The prospective data analysis showed that in accordance with models based on clinical accounts (Moss-Morris & Wrapson, 2003; Surawy et al., 1995), patients who went on to develop new onset IBS three months post-infection were significantly more likely to have responded to the acute infection with an all-or-nothing behavioural style than those who did not. When all four of the BRIQ subscales were entered into a single predictive analysis, all-or-nothing behaviour was shown to be the most significant predictor of IBS. The identification of all-or-nothing behaviour as an independent and measurable construct is an important validation of the cognitive-behavioural model of FSS, and provides new avenues of investigation. By measuring this behaviour, it may be possible to access relevant cognitions that are associated with it, such as perfectionistic beliefs, which may cause poorer outcomes for patients. It also provides some insight as to the mechanisms by which cognitive-behavioural interventions may be succeeding. Most of the successful trials for CFS, a condition that shows some overlap with IBS, encourage a graduated and consistent return to activity levels (Whiting et al., 2001).

As discussed in the introduction, much of the prior focus on acute illness behaviour has been on the commonly prescribed practice of bed rest, which has been found to be of little benefit and even harmful in some cases (Allen et al., 1999; Candy et al., 2002). In contrast, this study suggested that limiting activity levels, but not bed rest per se, at the time of acute illness decreased the likelihood of developing IBS three months following infection. In addition, a similar benefit was demonstrated for those with higher levels of practical support seeking.

There may be several reasons for this discrepancy. Limiting behaviour in the short term may well be adaptive, but prolonged use may prove to be maladaptive. Alternatively, it is also possible that there are different predictors for different functional somatic syndromes,

such that limiting behaviour may be somewhat protective for IBS, but a risk factor for other conditions such as chronic fatigue. Certainly, days off work, which correlated with limiting behaviour in this study, failed to predict IBS, whereas an early study showed that absence from work was a predictor of chronic fatigue following infectious mononucleosis (Thompson, Godleski, & Herman, 1969). Finally, measurement issues make comparisons difficult. Criteria by which caseness is determined for functional somatic syndromes and outcome variables often differ across studies. Poor physical functioning and de-conditioning at the time of infection are often interpreted to be signs of lengthy convalescence; however, these factors may reflect premorbid status rather than a specific behavioural response to the illness. More work is needed to unravel this relationship.

Future research should focus on the use of the BRIQ in other acute illness populations to determine the generalisability of these findings. The subscales that appear to be most relevant are those that measure all-or-nothing and limiting behaviours. Investigating the relative risk of these two behavioural patterns in other at-risk groups may reveal patterns in the development of other functional somatic syndromes. These behaviours may also be relevant to the course of any chronic illness, regardless of aetiology. Future studies should monitor these behaviours over the course of an illness in order to determine whether there are significant changes in behaviour that impact on outcome. Information about individual behavioural responses to illness can also be used to guide preventative interventions in the acute stages of an illness. By focusing on identifying and changing behaviour at this time, it may be possible to prevent the development of a chronic somatic complaint in those patients that are vulnerable. In an era where our most significant medical costs derive from chronic illness, it is clear that any intervention that may prevent this occurring merits further investigation.

Chapter 9.

Methodology: Main study.

The following section describes the method used in the main study of this thesis; a prospective study of the role of psychological factors in the development of IBS and CFS, following the acute infections of *Campylobacter* gastroenteritis and glandular fever. It includes detail about the sample used in the study; including the selection of eligible participants, response rates, and relevant demographic information about the groups. The procedure for the study is then outlined including the recruitment of participants and their follow-up. Finally, the measures used in the study to gather psychological information relevant to the previously outlined hypotheses for the study are described. For this purpose, the description of the measures are separated according to the questionnaire in which they appear; that is, the original questionnaire, the three month follow-up questionnaire or the final six-month follow-up questionnaire.

9.1. Sample information.

Participants

A power analysis based on previous research was conducted to determine the sample size needed. Calculations for the glandular fever sample were based on the only prospective study of fatigue following glandular fever to report rates of new onset CFS as opposed to idiopathic chronic fatigue, which reported a conservative estimate of 9% (White et al., 1998). With regard to the *Campylobacter* sample, calculations were based on a study which used a similar recruitment method and criteria to diagnose IBS following *Campylobacter,* and reported prevalence rates of 17% (Parry, Stansfield et al., 2003). Using 80% power and the .05 level of significance, a sample of 780 (195 glandular fever and 585 *Campylobacter*) was needed to detect a true difference in the proportions becoming a case of 9% and 17%.

Participants were recruited through Diagnostic Medlab Auckland, the major provider of community clinical diagnostic services for the greater Auckland area, encompassing a population of 1.5 million. Over 2,000 medical professionals use their services. Laboratory

staff carried out consecutive sampling of all confirmed cases of *Campylobacter* gastroenteritis between 1st March 2002 and 10th December 2002. Similarly, all consecutive cases of infectious mononucleosis (glandular fever) were sampled between 1st March 2002 and 19th November 2003. Blood and stool specimens were received from as far north as Whangarei, and as far south as Huntly. Each week a list of patients with either of the two target illnesses was generated from the Diagnostic Medlab database.

Inclusion criteria

Participants were included if they were experiencing an acute case of *Campylobacter* gastroenteritis or glandular fever and were over 16 years of age. A total of 2547 *Campylobacter* gastroenteritis cases were identified where *Campylobacter* species were isolated from stool culture using standard procedures. Faeces were inoculated onto charcoal-cefoperazone-deoxycholate agar and incubated in a microaerophilic atmosphere for 72 hours. Plates were examined at 48 and 72 hours for typical colonies. Suspect colonies that were oxidase positive and revealed gram-negative curved bacilli after gram staining were reported as *Campylobacter* species.

A total of 737 glandular fever cases over the age of 16 were identified using either the infectious mononucleosis screen (monospot), which tests for heterophile antibodies in the blood, or the more specific Epstein-Barr virus (EBV) serology test, which measures viral capsid antigen (VCA) IgM and IgG antibodies. Presence of VCA IgM antibodies in the blood indicates current infection, whereas the VCA IgG antibodies persist for life following infection. For a number of patients with suspected glandular fever, their GP had requested both monospot and EBV tests. Those patients with positive results for both tests were entered as a positive EBV test result. Those patients who returned a positive monospot but had a negative VCA IgM result, however, were not invited to participate in the study as their illnesses were not considered to be due to acute EBV infection.

Dr Susan Taylor of Diagnostic Medlab screened each patient's test result and age prior to sending out the initial questionnaire (see Appendix 10). All participants who met the above inclusion criteria were invited to participate. All who chose to do so completed the entire questionnaire and were sent subsequent follow-up questionnaires at three and six months (see Appendices 11 and 12). In this way, data relevant to exclusion criteria could be gathered at all three time points.

Exclusion criteria

For the purposes of this study it was important to establish which cases of IBS or CFS identified during the study period were of new onset. In order to achieve this, exclusion criteria were formulated to exclude any individual who prior to initial infection or during the course of the six month follow-up period, reported a pre-infectious history of IBS or CFS, or any medical condition known to cause bowel or fatigue symptoms. Individual medical screening for such a large sample was beyond the resources of this study, therefore participants were excluded on the basis of self-report information. Following postal return of the completed questionnaires, information was collated from the general health section of the initial questionnaire, which specifically asked if the individual had ever been diagnosed with CFS or IBS, or if they currently had any other major medical problem that may affect their recovery. In the three and six-month follow-up questionnaires participants were asked if they had any diagnosis to explain current symptoms. More specifically, this included:

1. Participants who stated they had been diagnosed by a doctor with IBS or CFS at any time in the past.

2. Participants without a history of IBS or CFS who disclosed on any questionnaire that they had a current diagnosis of a major medical condition judged likely to impact on levels of fatigue and /or bowel function. Table 10 lists reported conditions on which basis patients were excluded for this study. These conditions were drawn from exclusions established in case definitions of IBS (Schmulson & Chang, 1999; Vandvik et al., 2004) and CFS (Fukuda et al., 1994). Other medical conditions were verified as having the potential to cause altered bowel function or significant fatigue by medical consultants to the study.

3. Participants not already excluded were also screened for any excessive time lag between their period of acute illness and filling in the questionnaire, by subtracting the date the baseline questionnaire was filled out from the date the stool specimen was taken. All those whose questionnaires were completed more than 60 days after their lab test date were excluded from further analysis.

Table 10. Medical conditions known to impact on bowel function or fatigue that were present in the original sample and because of which patients were excluded.

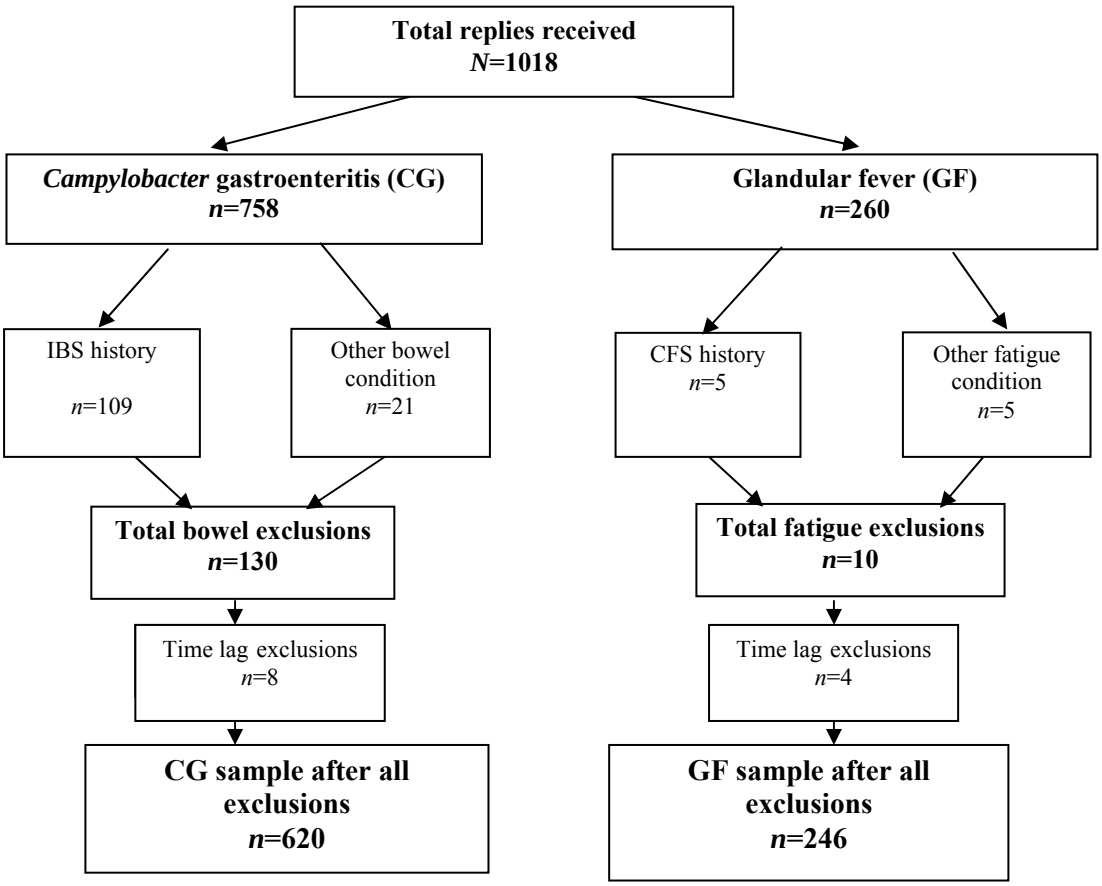
Bowel-related conditions	Fatigue causing conditions
Abdominal adhesions	Anaemia
Bowel cancer	Cancer of any type
Crohn's disease	COPD/emphysema
Celiac disease	Fibromyalgia
Colostomy	Head injury
Colitis	Hepatitis
Colon cancer	Hypothyroidism
Diverticulitis	Meningitis
Ileostomy	Multiple Sclerosis
Perforated bowel	Neutropenia
Polyps removed from bowel	Shingles
Stomach ulcers	Systemic Lupus Erythematosus

As set out in Figure 3, 109 people in the *Campylobacter* gastroenteritis group (14%) were excluded due to a history of IBS, and five people in the glandular fever group (2%) were excluded due to a history of CFS. These numbers are consistent with previous general population prevalence rates for IBS which range from 10-15% (Hungin et al., 2003; Saito et al., 2000), and CFS which range from 0.01-2.8% (Afari & Buchwald, 2003). Twenty-one people were excluded from the *Campylobacter* gastroenteritis group because of serious bowel conditions, and a further five from the glandular fever group who were experiencing medical conditions likely to cause fatigue. A further 12 people (eight with *Campylobacter* and four with glandular fever) were excluded due to an excessive time lag between their acute illness and answering the questionnaire. In total, analyses were conducted on 620 participants with *Campylobacter* and 246 participants with glandular fever group.

The data for each illness was then combined into a total post-infectious sample regardless of illness type, and exclusions for both bowel and fatigue-related conditions were reassessed. Of the 1018 participants, 171 were excluded from the total sample analyses because they reported either a positive history of confirmed or suspected CFS and/or IBS or a medical condition known to produce similar symptoms to these syndromes. Ninety-nine reported a history of IBS, 17 reported a history of CFS, 21 reported medical conditions known to cause bowel symptoms (e.g. bowel cancer, Chrohn's disease) and 21 reported conditions related to fatigue (e.g. multiple sclerosis or fibromyalgia). A further six people who had a history of both IBS and CFS were excluded, along with seven who

had IBS and a fatigue-related medical condition. Individuals who completed questionnaires more than 60 days after their laboratory specimen was collected were also excluded from further analysis (n=12). After these 183 exclusions, 835 people were included in the total sample.

Figure 3. Exclusions for *Campylobacter* gastroenteritis group and glandular fever group.



Response rate

Campylobacter gastroenteritis group

During the nine-month recruitment period for the *Campylobacter* gastroenteritis participants, 2547 patients were identified and letters sent to their general practitioners (GPs). Of these 36 were returned as the individual was no longer at the address and the forwarding address was unknown. Seven questionnaires were returned without consent forms and were therefore unable to be included in the study. A total of 758 usable questionnaires were returned from the *Campylobacter* group and entered into the study giving a response rate of 30%. However, it is estimated that approximately 40% of GPs

did not forward the information packs to their patients, as records indicated that there were no participants recruited from this proportion of GPs. Based on this information it is estimated that approximately 1,500 questionnaires actually reached participants, with a resulting estimated response rate of 51% for this group.

Glandular fever group

During the 23-month recruitment period for the glandular fever participants, 737 patients were identified and information packs sent to their GPs. Of these, two questionnaires were returned without consent forms and were therefore unable to be included in the study. A total of 260 usable questionnaires were returned and entered into the study giving a response rate of 35% for this group. A similar analysis of response rates from patients of individual GPs as conducted with the *Campylobacter* gastroenteritis group, estimated that again approximately 40% of GPs failed to forward the questionnaires to their patients. It was therefore estimated that approximately 440 questionnaires actually reached participants, with a resulting estimated response rate of 59% for this group.

Total combined sample

Combining the two illness groups gave a total sample of 1018 participants, an actual response rate of 31% and an estimated response rate of 52% calculated in a similar manner as before.

Demographics

Campylobacter gastroenteritis group

A total of 138 participants were excluded from the *Campylobacter* gastroenteritis group on the basis of the exclusions listed above. After these exclusions, this group (n=620) had slightly more females (55%) than males and a mean age of 43.4 years (range 17-88; SD=16.4). The majority were New Zealand European (93%) with the next largest group Maori (4%). A total of 20 people (3%) failed to answer this question while the remainder identified as being Pacific Islanders, Asian, Indian or other. With regard to marital status, 70% of participants stated they were married or in a de facto relationship, 22% single, 5% divorced or separated, and 3% widowed. The majority of participants (63%) had at least one child (range 0-13; SD=1.6). The *Campylobacter* gastroenteritis group was relatively well educated, with 27% stating their highest qualification was a University degree. A further 30% had a polytechnic qualification, and 37% had a secondary school qualification.

A large proportion of the sample (79%) reported they were in some form of paid work. Analysis of the kind of work indicated that this was largely skilled work.

Glandular fever group

In the glandular fever group a total of 14 participants were excluded on the basis of the exclusions listed above. This group (*n*=246), in contrast to the *Campylobacter* gastroenteritis group, had a majority of females (62%) and a much lower mean age of 22.8 years (range 17-67; *SD*= 8.3). The majority were New Zealand European (96%) with the next largest group Asian (2%). A total of 6 people (2%) failed to answer this question while the remainder identified themselves as Maori, Pacific Islanders, Indian or other. In this group, the majority of participants were single (82%), with only 15% of participants stating they were married or in a de facto relationship, 3% divorced or separated, and one person widowed. Most had no children (90%), and only 26 had at least one child (range 0-6; *SD*=0.7). The largest educational qualification group for the glandular fever sample was those with secondary school qualifications (60%), with 19% stating their highest qualification was a University degree. A further 16% had a polytechnic qualification. A similarly large proportion of the sample (79%) reported they were in some form of paid work, although analysis of the kind of work indicated that this tended to be lower paid or part-time employment reflecting the younger age group in this sample.

Total combined sample

In this group a total of 120 people were excluded due to a reported history of IBS or major bowel disorder, 36 due to a history of CFS or other fatigue-related condition, 13 people who had both fatigue and bowel exclusions and a further 12 with time lag exclusions. The total remaining sample (*N*=835) had a demographic profile that reflected the combination of the two illness groups, with 56% of the sample female and a mean age of 37.2 (range 17-88; *SD*=17.2). Ethnicity was very similar with 94% NZ European and 3% Maori. Just over half the sample were married or in a de-facto relationship (54%), and 40% were single. Approximately half the sample had no children (52%). The population was well educated (university=26%, polytechnic=26%, secondary=43%), and 79% were in some form of paid work.

9.2. Procedure

Recruitment

Test results ordered by a doctor on behalf of their patient are deemed to be confidential under the provisions of the Privacy Act (1993). Diagnostic Medlab was therefore unable to give contact details for patients directly to the researcher. Instead, participants were indirectly approached via their GP. A pre-prepared envelope for each participant with either *Campylobacter* gastroenteritis or glandular fever was posted to their GP. A covering letter from Diagnostic Medlab (see Appendix 3) informed the GP of the study, and requested that they address the envelope to their patient and post on. This envelope included an information pamphlet describing the study (see Appendix 5), consent form (see Appendix 6), questionnaire (see Appendix 10) and a reply-paid envelope. Each envelope sent out by the lab was documented according to the kind of positive test result, the initials of the patient, the date their specimen was taken, and the name of the GP the envelope was sent to. Ethical approval for this procedure was sought and obtained from the Ministry of Health's Auckland Ethics Committee on 14 December 2001 (see Appendix 2).

Each week, the above information recorded for each envelope was faxed to the principal investigator. In this way incoming completed questionnaires could be matched to ensure accurate specimen dates were recorded for each participant. Response rates from individual GPs were also monitored in this way. During the first six months of the study, GP practices that had been sent questionnaires were contacted by phone according to this information to ensure that they were receiving the questionnaires and understood what was expected of them. Practice nurses handled most of these calls, and the majority were aware and appeared supportive of the study. Those who were experiencing difficulties were mainly the larger 24-hour emergency surgeries that had large numbers of visiting doctors. In most of these cases, a practice manager was able to be identified who agreed to deal with all future envelopes that came to their practice. In only one case did a practice refuse to pass the envelopes on, stating that they did not have the resources to complete this task. In an attempt to maximise the possibility that GPs would pass on the information to their patients, publicity was arranged through the Diagnostic Medlab newsletter sent to all GPs, and a short article was sent to all Independent Practitioners Associations (IPAs) in the Auckland region for inclusion in their regular newsletters (see Appendix 5).

The principal investigator assembled all information that was sent out to participants and their referring practitioners, and handled all subsequent enquiries from them. Dr Susan Taylor from Diagnostic Medlab was responsible for the collating and screening of all diagnostic tests and the initial mailing out of questionnaires to GPs. Participants completed the questionnaires in their own home and posted them back to the principal investigator at their convenience. Ten people were given the questionnaire prior to the study start date to estimate the time taken to fill it in. Times varied from 16 minutes to 30 minutes with an average time of 23 minutes taken to complete the questionnaire. Based on this it was stated on the information pamphlet that the questionnaire would take each participant between 20 and 30 minutes to complete. Each group completed identical questionnaires answering all questions relevant to them.

The data collection phase of the study was terminated for the *Campylobacter* gastroenteritis sample once 750 cases had been recruited (a further 8 patients returned questionnaires after this). Because of the high incidence of *Campylobacter* gastroenteritis during that time, the period of recruitment was nine months (1/3/02–10/12/02). Recruitment for the glandular fever group was much slower due to lower numbers of test results than anticipated coming through Diagnostic Medlab during the study period. Recruitment continued for a total of 21 months (1/3/02–19/11/03), at which point 260 cases of glandular fever had been recruited into the study.

Follow-up

When each baseline questionnaire and consent form was received, a thank you letter welcoming the participant to the study was sent, and the date of their laboratory sample noted to obtain independent verification of the period of illness. Three and six months after their test result date, patients were sent a shorter follow-up questionnaire (see Appendices 11 and 12). Participants received a phone call informing them that the questionnaire was coming. If no reply was received at ten days after mail out, a reminder phone call was made, followed by a reminder letter at two weeks (see Appendix 9), and a further phone call three weeks after mail out.

Follow-up response rates were high with 581 responses from the *Campylobacter* group at three months (94%) and 561 (90%) at six months. From this group there were 39 non-responders at three month follow-up and 59 at six month follow-up who were excluded from individual analyses. Independent samples *t*-tests indicated that non-responders in the

Campylobacter group were significantly younger at both three ($t(616) = 3.19$, $p = .001$) and six month follow-up ($t(616) = 3.43$, $p = .001$). Contingency table analyses comparing gender between responders and non-responders, however, found no significant difference at either three (Pearson χ^2 (1, $n = 620$) $= 2.0$, $p = .16$) or six months (Pearson χ^2 (1, $n = 620$) $= 0.78$, $p = .38$).

The glandular fever group had a similar follow-up response rate, with 224 questionnaires returned at three months (91%) and 217 (88%) at six months. In this group there were 22 non-responders at three month follow-up and 29 at six month follow-up who were excluded from individual analyses. Independent samples *t*-tests indicated that there was no significant difference in the glandular fever sample between responders and non-responders with regard to age, at either three ($t(243) = -.54$, $p = .59$) or six month follow-up ($t(243) = -.04$, $p = .97$). Contingency tables and chi-square analyses comparing gender between responders and non-responders found no significant difference at three month follow-up (Pearson χ^2 (1, $n = 246$) $= 2.7$, $p = .10$). At six months, however, there was a significant association between gender and response, with non-responders twice as likely to be male as female and the opposite true for responders (Pearson χ^2 (1, $n = 246$) $= 10.4$, $p = .001$).

The total sample had 775 questionnaires returned at three months (93%) and 748 (90%) at six months. In this group, there were 60 non-responders at three months and 87 non-responders at six months who were excluded from individual analyses. Independent samples *t*-tests indicated that there was a significant association between response status and age in the total sample, at both three ($t(70.9) = 3.09$, $p = .003$) and six months post-infection ($t(117.3) = 3.88$, $p < .001$), with non-responders significantly younger at both time points. Contingency tables with chi-square analyses comparing the gender ratio of responders and non-responders found there was a significant association between gender and response status at both three month follow-up (Pearson χ^2 (1, $n = 835$) $= 4.2$, $p = .04$) and six months, with non-responders more likely to be male than female (Pearson χ^2 (1, $n = 835$) $= 6.03$, $p = .01$).

9.3. Measures

Initial Questionnaire

The content of the baseline questionnaire (Appendix 10) was designed to gather self-report information on variables relevant to the cognitive-behavioural model, with regard to illness-related physiology, cognitions, behaviours, and emotions; which are outlined in this section. It included a range of established psychological measures, the newly developed measure of illness behaviour described in the previous chapter, and a number of self-report questions regarding general health and demographics. Demographic variables were also measured including; gender, age, ethnicity, place of residence, marital status, number of children, highest educational qualification obtained, paid work, and the nature of that work.

Physiological and general health measures

The type of laboratory test result and date the initial specimen was taken, were both documented to provide objective evidence of the type of illness and approximate date of illness onset. General health questions included a checklist of symptoms associated with *Campylobacter* (including nausea, headache, fever, vomiting, diarrhoea, stomach pain, blood in faeces and aching muscles), and glandular fever (sore throat, loss of appetite, weight loss, headache, fever, swollen glands, fatigue/tiredness, and rash). Replies on these questions were totalled to reflect number of *Campylobacter* symptoms and glandular fever symptoms. In addition, a number of non-specific symptoms (sore eyes, loss of strength, feeling off colour, breathlessness, joint pain, dizziness, unrefreshing sleep, racing heartbeat, and feeling worse after exertion) were also included in the checklist as a measure of general somatisation and were totalled to reflect the number of somatic symptoms. This symptom checklist was organised according to the Illness Perceptions Questionnaire–Revised format (described in the following section), with participants asked to check yes or no according to whether they had experienced each individual symptom since their acute illness began.

Specific details about the individual's acute illness were also gathered, including the onset, treatment and advice given by the individual's GP. Antibiotic use was recorded so as to control for any gastrointestinal effects caused by this medication. As mentioned earlier, questions regarding any history of CFS, IBS or serious physical illness were used to exclude people from the study.

Cognitive measures

The **Illness Perceptions Questionnaire-Revised** (IPQ-R, Moss-Morris et al., 2002) was included in the initial questionnaire in order to determine whether particular illness-related cognitions at the time of acute illness were influential in the development of IBS and CFS. The IPQ-R measures the five components of illness representations that make up Leventhal's Self-Regulatory Model; that is, **identity** (the number of symptoms the individual ascribes to their illness), **consequences** (what impact they believe their illness will have on their everyday life), **timeline** (how long they believe their illness will last), **control/cure** (how much control they believe they have over their illness and it's treatment, and **cause** (what they believe caused their illness) (Weinman et al., 1996). In addition, it measures **emotional representations** (the perceived emotional impact of their symptoms) and **illness coherence** (how well the individual believes they understand their illness) (Moss-Morris et al., 2002).

The IPQ-R and its earlier version have been used to measure the impact of illness perceptions on a wide variety of chronic illnesses such as psoriasis, heart disease, diabetes and CFS. The IPQ-R has been found to have a good factor structure, internal reliability, and test-retest reliability. In addition, individual subscales of the IPQ-R have been proven to be distinct from affective disposition, able to discriminate between acute and chronic illness samples, and predict adjustment to illness (Moss-Morris et al., 2002). An earlier version of the IPQ-R has been used to demonstrate the influence of illness representations on the development of functional gastro-intestinal disorders following gastroenteritis (Parry, Corbett et al., 2003) and post-infectious fatigue (Candy et al., 2003).

For the purposes of the current study, the IPQ-R was modified to reduce the overall size of the scale and to make it more relevant to the acute illnesses being studied, in concordance with the original authors' recommendations. The illness identity scale was modified to double as a symptom checklist and included additional symptoms of *Campylobacter* gastroenteritis and glandular fever (as specified earlier). The treatment control subscale and the cyclical timeline subscale were removed due to their limited relevance to the illnesses of *Campylobacter* gastroenteritis and glandular fever, as were two items from the coherence subscale and one from the timeline subscale. Remaining subscales included the timeline, consequences, personal control, emotional representation, and illness coherence subscales for which items were rated by participants on a five point Likert scale ranging from strongly disagree to strongly agree. Causal beliefs were assessed using the open

format, which asked participants to list in rank order the three most important factors that they believed had caused their illness.

The **Perceived Stress Scale** (PSS) was included to determine how participants' perceptions of their levels of stress at the time of acute infection may impact on the development of a functional somatic syndrome. The PSS was designed to measure the degree to which situations are perceived to be currently stressful for the individual, as opposed to the frequency of stressful life events in a specified time period (Cohen et al., 1983). Construction of this scale originated with the idea that stressful life events themselves are not a sufficient cause of pathology but instead are filtered through an individual's appraisal of those events. The PSS has been used in a wide range of health-related research both as an outcome measure and a predictor. For example, it has been used to measure stress levels in caregivers of the chronically ill (Schwarz & Dunphy, 2003) and has been found to be an independent predictor of the speed of wound healing (Ebrecht et al., 2004), increased acne severity (Chiu, Chon, & Kimball, 2003), and antibody status after vaccination (Burns, Drayson, Ring, & Carroll, 2002).

Items on the PSS are rated on a five point Likert scale for frequency, and relate to how often an individual has felt their lives to be unpredictable, uncontrollable and overloading over the course of the previous month, with higher scores reflecting greater levels of perceived stress. The original 14 item scale was found to have good reliability and was correlated with a number of psychological variables such as depression, social anxiety and life event scores, despite evidence that it was measuring a different construct. It was also found to be a better predictor of outcome measures than life-events and was independent of depressive symptomatology (Cohen et al., 1983). Further validation of the scale on a large probability sample indicated that a ten-item version of the scale improved the psychometric quality of the instrument and was recommended for future use (Cohen & Williamson, 1988). In the current study the 10-item scale was used with excellent internal consistency, as indicated by a Cronbach's alpha score of .89.

Perfectionism has been linked with disabling fatigue and many authors have commented on CFS patients' retrospective reporting of related personality features (Magnusson et al., 1996; Van Houdenhove et al., 2001). For this reason the **Positive and Negative Perfectionism Scale** (PANPS) was included in the initial questionnaire. The PANPS was designed to measure perfectionism from the theoretical perspective of traditional learning theory, with the assumption that different forms of perfectionism may reflect the intended

consequences of the behaviour rather than the behaviour itself (Slade & Owens, 1998). It was also designed for use in the general population, in contrast to previous scales used solely in clinical populations that had a more negative or pathological focus.

The 40-item questionnaire is split into two broad factors encompassing positive and negative perfectionism. Positive perfectionism is hypothesised to be motivated by a desire to improve self-concept, whereas negative perfectionism is motivated by a desire to avoid impairing self-concept. The initial validation resulted in a two factor structure and demonstrated good discriminant validity with different groups scoring differently on each of the two dimensions. Athletes scored highly on positive perfectionism, depressed participants scored highly on negative perfectionism, while eating-disordered women scored highly on both, all in comparison to a normal control group (Terry-Short, Owens, Slade, & Dewey, 1995). Further validation in two studies using athletes confirmed the factor structure and found good internal consistency for each of the scales as indicated by Cronbach's alpha scores of .83 to .84 and .83 to .88 for the positive and negative scales respectively (Haase, Prapavessis, & Owens, 1999, 2002).

In all of the studies cited it was the negative perfectionism scale that proved to have the strongest predictive validity and for this reason only this part of the scale was used in the current study. In addition, the authors of the original instrument had been working on a short form of the questionnaire which reduced the number of items from 40 to 20 (Glynne Owens; personal communication; December 2000). Due to space restrictions in the current study, this short form of the PANPS negative perfectionism subscale was used. Analysis of the short form of this subscale in the current study indicated that the 10 items loaded onto one factor accounting for 53% of the variance with excellent internal reliability, as evidenced by a Cronbach's alpha score of .90.

Behavioural measures

As described earlier in this thesis, there were no existing measures reported in the literature that examined acute illness behaviour in the general population. Prior measures had focused on abnormal aspects of illness behaviour in populations that were experiencing chronic ill health (Pilowsky, 1993; Rief et al., 2003), rather than measure how people behave when they are acutely unwell. As a result the **Behavioural Responses to Illness Questionnaire** (BRIQ) was developed prior to the main study using a healthy sample and validated on the *Campylobacter* gastroenteritis sample (as presented in Chapter 8). This scale aimed to measure behavioural responses during the acute phase of an illness, in order

to assess the importance of these behaviours in the development of ongoing functional somatic syndromes. The 21-item self-report scale consists of four subscales measuring all-or-nothing behaviour, limiting behaviour, practical support seeking, and emotional support seeking. All items are rated on a five point Likert scale reflecting the amount of time the individual has spent engaging in each behaviour (not at all, rarely, some days, most days, every day).

The validation of the BRIQ indicated that it had a sound four factor structure with good construct validity and internal reliability. Predictive validity was also good with several subscales predicting the development of a medically unexplained syndrome. In the current study when all subjects were included, the factor structure and internal consistency remained strong.

Measures of emotion

Anxiety and depression have long been associated with the functional somatic syndromes, with many assigning a causal role while others maintain such emotional consequences are secondary to the somatic condition. Much of this work, however, has been either retrospective or has demonstrated a link once the somatic condition has been established. For the purposes of this study it was important to find an instrument that could measure anxiety and depression unrelated to the acute illness. The **Hospital Anxiety and Depression Scale** (HADS) is one such scale, designed to assess the presence and severity of anxiety and depression in physically ill populations (Zigmond & Snaith, 1983). Previous instruments such as the Beck Depression Inventory (Beck & Steer, 1993) and the State-Trait Anxiety Inventory (Spielberger, 1983) have been found to be inappropriate in populations whose physical symptoms of illness might mimic or mask those of depression and anxiety.

The HADS is a 14-item scale rated on individual four point Likert scales measuring frequency or severity, with some items reverse scored. It can be administered singly or on separate occasions to monitor change over the course of treatment. In a recent review of 747 studies that explored the psychometric properties of the HADS, Bjelland and colleagues (Bjelland, Dahl, Haug, & Neckelmann, 2002) found that its internal consistency was high and that the two-factor structure was largely confirmed, despite a small number of studies finding a three or four factor structure. The HADS performed well with regard to its case finding abilities, with the identified threshold value of 8+ as a cut off for possible cases showing very little variability across studies. With regard to concurrent

validity, the HADS was found to have medium to strong correlations with other screening measures of anxiety and depression despite it's brevity in comparison to those measures. Bjelland and colleagues (2002) concluded that the HADS performed well across a range of populations with screening properties as good as other more comprehensive measures of anxiety and depression. In the current study the factor structure and the internal consistency of the anxiety and depression subscales was confirmed, with Cronbach's alphas of .82 for both scales.

As mentioned earlier, the symptom checklist adapted from the IPQ-R was used as a measure of general somatisation, based on the total number of symptoms unrelated to either of the acute illnesses in the study. For each illness type, a more specific somatic symptom total was calculated using all symptoms not related to the individual illness (non-glandular fever symptoms and non-*Campylobacter* symptoms). Somatisation has often been linked with anxiety and depression. This has lead many to regard it as a means of expressing underlying emotional distress; achieved by reporting multiple physical symptoms unrelated to actual disease or pathology.

Three month Follow-up Questionnaire

The three-month follow-up questionnaire (Appendix 11) was primarily designed to identify participants who had developed IBS and/or CFS. In order to determine this, outcome measures were designed to gather information regarding general symptoms, specific bowel and fatigue-related symptoms. Levels of associated disability were also measured at this time point, along with a number of factors hypothesised to be associated with the perpetuation of somatic syndromes.

Outcome measures

Symptom-related scales

The symptom checklist and illness identity scale taken from the IPQ-R (Moss-Morris et al., 2002) was repeated in the three months questionnaire without alteration. Participants were asked to indicate what symptoms they had experienced in the previous month and whether or not they believed these symptoms were related to their illness three months before. In order to determine the frequency of health care utilisation in the months following initial infection, participants were asked the number of times they had sought help for any complaint or problem in the prior three months, from any health professional; including doctor, naturopath, medical specialist, acupuncturist or other.

Fatigue-related measures

The key fatigue-related outcome measures were caseness of CFS and chronic fatigue, as determined by analysis of self–report information regarding fatigue-related symptoms gathered in section two of the three- and six-month follow-up questionnaires. The two established definitions of CFS, the Fukuda Criteria (Fukuda et al., 1994) and the British criteria (Sharpe et al., 1991), were both used to determine CFS caseness in this study. Clinical evaluation was beyond the scope of this study, therefore a self-report questionnaire was designed to approximate as closely as possible the above mentioned criteria from which a designation of caseness was made.

As outlined in more detail in Chapter 3, the Fukuda criteria states that an individual must be suffering from clinically evaluated fatigue that is unexplained, persistent or relapsing, of new or definite onset, and which is not the result of exertion or alleviated by rest. The fatigue must result in a substantial reduction in activity levels and be accompanied by at least four of seven symptoms. The British criteria stipulate that fatigue must be the main symptom which has been present for at least six months, and for at least 50% of the time. The fatigue must be of definite onset, it must be severe, disabling and should affect both physical and mental functioning.

These criteria were operationalised in the following way (see Appendix 11). An initial screening question asked participants if they were experiencing fatigue or excessive tiredness so that those without fatigue could omit this section. If affirmative, the participant was asked to rate the severity of their fatigue (mild, moderate or severe), and answer a range of questions derived from the Fukuda and British criteria for CFS. Questions included the type of fatigue experienced (physical or mental), the onset of the fatigue (whether there was a definite start to the fatigue and length of time since onset), the extent of the fatigue (proportion of time affected by fatigue, and their ability to ignore it), any moderating effects experienced (i.e. impact of rest, excessive exercise) and the impact of fatigue on their daily activities such as work, self-care, family life, and leisure activities. In addition, participants were asked if they suffered from any of the seven symptoms specified in the Fukuda criteria as being associated with CFS.

Using the information provided in this section, a SPSS syntax file was created to code participants according to whether they fulfilled criteria for the Fukuda and/or the British definitions of CFS. As set out in Table 11, to be included as a case of CFS based on the Fukuda criteria, participants had to be experiencing fatigue that was not alleviated by rest,

that was not due to excessive exercise, that resulted in a substantial reduction in activity (disabling or stops from doing things would like to do) and report at least four of the specific related symptoms outlined by this criteria. Similarly, to fulfil the British criteria, participants needed to report moderate or severe mental and physical fatigue present more than 50% of the time. The six month time criterion was not applied at three month follow-up as the study was focused on new cases of post-infectious fatigue, but was used to determine cases at six-month follow-up.

Table 11. Self-report information used to determine caseness groupings for CFS and chronic fatigue.

Symptom	Fukuda criteria	British criteria	Chronic fatigue
Presence of fatigue	✓	✓	✓
Experiencing moderate to severe fatigue		✓	✓
Disabled by fatigue	✓	✓	
Not alleviated by rest	✓		
Not related to excessive exercise	✓		✓
Four or more of defined CFS-related symptoms	✓		
Experiencing both physical and mental fatigue		✓	
Tired more than half the time		✓	
At least six months duration (Time 3 only)	✓	✓	✓

Although participants were asked whether or not the onset of their fatigue was definite, this criterion was not used to determine cases, as it was felt that this particular question had been open to misinterpretation. Both the Fukuda and British criteria state that the fatigue must be of "new or definite onset (has not been lifelong)" (Fukuda et al., 1994, p.956). It was considered that the wording of this question ("was there a definite start to this fatigue") in the follow-up questionnaires of the current study was too restrictive, and that many individuals who may not have regarded their fatigue as having had a distinct onset, would not have been experiencing lifelong fatigue either. In addition, because all participants with a history of CFS had been excluded, it was decided that this aspect of the criteria would not be helpful in determining cases.

All participants who met criteria for either of the Fukuda or British definitions were classified as cases of CFS for the purposes of analysis in this study. In addition, criteria for a subthreshold condition of chronic fatigue were created based on the idiopathic chronic

fatigue category outlined in the Fukuda criteria (Fukuda et al., 1994, p.956). This category has provision for those cases of unexplained chronic fatigue that fail to meet the full Fukuda criteria. As outlined in Table 11, this group was defined as those with moderate to severe physical and mental fatigue, which was not due to excessive exercise, and had been present for six months (this last criterion was excluded for the three-month follow-up). Individuals in this group were regarded as cases of chronic fatigue for the purposes of analysis in this study.

Bowel-related measures

The key outcome measures with regard to bowel symptoms were developed in a similar manner to those for fatigue, that is, whether or not patients met established diagnostic criteria for IBS or were experiencing ongoing disturbed bowel function. As outlined in Chapter 3 the accepted criteria for IBS have undergone several revisions since first proposed by Manning and colleagues in the late 1970s (Manning et al., 1978). The original Rome criteria stated that patients must be experiencing continuous or recurrent abdominal pain that is relieved by defecation or associated with a change in frequency or consistency of stool, **and/or** two or more symptoms of disturbed defecation (Thompson et al., 1989). This was subsequently modified to include a minimum three-month criteria and the requirement of both pain and disturbed defecation (Thompson et al., 1992). The current Rome II criteria cites abdominal pain or discomfort as the cardinal feature and requires it to be associated with two of three aspects of defecation (Thompson et al., 1999). The Rome II criteria also stipulate that the abdominal pain should have been present for at least 12 weeks in the preceding twelve months, although not necessarily consecutively.

For the purposes of the current study, these criteria were converted into a self-report format in order to elicit bowel symptoms. All participants were asked about the frequency of their bowel movements, and if they experienced urgency, straining, abdominal bloating, mucus in the stools or a change in consistency of their stools more than 25% of the time. They were also asked if they experienced abdominal pain, and whether or not this pain was alleviated by bowel movements, or related to their frequency or consistency. Because of the self-report format and the desire to gather information regarding both Rome I and Rome II criteria, the abdominal pain question was not widened to include abdominal discomfort as stated in the Rome II criteria. Participants were also asked if their bowel symptoms impacted on their daily activities using the same questions asked in relation to fatigue, and whether they were able to ignore their symptoms. Based on the answers to

these questions, each participant was scored to determine whether they fulfilled Rome I or Rome II criteria for IBS (see Table 12).

Table 12. Self-report information used to determine caseness groupings for IBS.

Symptom	Rome I criteria	Rome II criteria	Disturbed bowel function
Two or more abdominal pain-related symptoms e.g.; Relief from pain after bowel movement More frequent bowel movements with pain Less frequent bowel movements with pain Pain-related loose/watery stools Pain-related hard/lumpy stools		✓	
One or more pain-related symptoms as above	✓		**Either**
Two or more symptoms of disturbed defecation e.g. Abnormal stool frequency Abnormal stool form Abnormal stool passage Abdominal bloating Mucus in stools	✓		**Or**
At least three months of disturbed bowel function		✓	

Rome I was determined by using the modified option that requires both pain-related symptoms **and** the disturbed defecation criteria. Rome II was calculated based on the presence of two or more abdominal pain-related symptoms present for 3 months or more. In recent years, there has been ongoing debate as to the usefulness of the distinctions made by these criteria (Boyce et al., 2000; Mearin et al., 2001; Saito et al., 2000). Because of this debate, and in order to gain the most representative group of IBS cases, it was decided to determine as one category, those participants who met either Rome I modified or Rome II criteria as cases of IBS. In order to provide a larger comparison group similar to that of the chronic fatigue cases in relation to CFS, a less restrictive definition was also calculated by using the original Rome I criteria which requires **either** abdominal pain-related symptoms **or** disturbed defecation. Individuals in this subthreshold group were regarded as cases of disturbed bowel function for the purposes of analysis in this study.

Disability measures

A range of disability measures were included in the follow-up questionnaires in order to compare the levels of disability associated with CFS and IBS in relation to non-cases. To

obtain a more standardised assessment of the ongoing level of impairment associated with the participants' initial illness, the **Work and Social Adjustment Scale** (WSAS) was included in the follow-up questionnaire (Marks, 1986). This scale aims to provide information about an individual's perception of their functional impairment due to an identified problem. In this study participants were asked whether or not the illness they experienced three or six months ago had had any ongoing impact on their daily life. Subjects were asked to rate their level of impairment due to this illness for five separate functional areas including work/study, home management, social and leisure activities, private leisure activities, and the ability to form and maintain relationships. Items were scored on a nine point Likert scale ranging from no impairment to very severe impairment and totalled to provide an overall impairment score.

The WSAS was initially designed for use in populations with mental disorder such as depression, and was validated using a depressed population and those undergoing treatment for obsessive-compulsive disorder (Mundt, Marks, Shear, & Greist, 2002). Data indicated that the WSAS had strong psychometric properties within these populations with high internal consistency that improved with repeated presentations and good test-retest reliability over a two week period. Principal component analysis found a single factor with factor loadings ranging from .66 to .93. The WSAS was found to have moderate to strong correlations with symptom severity indicating good convergent validity. It was also able to discriminate between individuals according to mild, moderate and severe symptomatology groupings, and global impressions of perceived improvement. The scale has subsequently been used in physical health settings with patients with chronic fatigue and rheumatoid arthritis (Chalder et al., 2003; Wood & Wessely, 1999).

Principal components analysis of the current study sample found one factor with an eigenvalue of 3.8 at both three and six months post illness accounting for 75% and 76% of the variance respectively. Cronbach's Alpha scores of .91 and .92 indicated excellent internal consistency in this sample.

The **Five-item Mental Health Scale** (MHI-5) was included to gather information about the participants' general mental health status. This instrument was developed from the five items that best predicted the summary score of the 38-item Mental Health Inventory which was developed to measure psychological distress and wellbeing (Veit & Ware, 1983). The MHI-5 was subsequently included as the mental health measure for the Short Form 36 (SF36) questionnaire and has been used extensively to measure psychological distress in a

wide variety of both psychiatric and general health surveys (McHorney, Ware, Lu, & Sherbourne, 1994). Like the HADS, it is said to be uncontaminated by the physical symptoms of distress. It includes items measuring the frequency of anxious and depressive states, as well as general psychological wellbeing over the past month, and is scored on a six point Likert scale ranging from all of the time to none of the time.

Over the years the MHI-5 has performed well with high internal consistency, good construct validity and good discriminant validity (McCabe, Thomas, Brazier, & Coleman, 1996). It has also been demonstrated to have moderate one year retest stability (Veit & Ware, 1983). Comparisons with other more extensive measures of psychological distress have consistently demonstrated the validity of this instrument as a screening tool for mood disorders (Berwick et al., 1991; Rumpf, Meyer, Hapke, & John, 2001). In the current data set, internal consistency was high in this sample at three and six months post illness with Cronbach's alpha scores of .83 and .85 respectively.

Illness perpetuators

An additional question was included in the three month follow-up questionnaire in order to determine the impact of **illness attributions** on participant outcome six months post-illness. It was intended to investigate the effect of illness attributions in the perpetuation of symptoms. In order to investigate this, all participants who were experiencing any symptoms at the time of three-month follow-up were asked if they had a name or a diagnosis to explain these symptoms. This was followed by a five point Likert scale adapted from a previous study looking at illness attributions for depression and chronic fatigue (Powell, Dolan, & Wessely, 1990). Participants were asked to choose the statement that best applied to how they saw their current symptoms. Options included: (a) my symptoms are physical, (b) my symptoms are mainly physical, (c) both physical and psychological factors are involved in my symptoms, (d) my symptoms are mainly psychological, and (e) my symptoms are psychological in nature.

Finally, the same measure of **exercise** frequency and intensity used in the initial questionnaire was included in order to monitor changes over time.

Six month Follow-up Questionnaire

The six month and final follow-up questionnaire (Appendix 12) was the shortest of the three questionnaires. Focused mainly on outcome measures, it included the symptom and

identity checklists described above, the fatigue and bowel-related symptoms sections, the MHI-5, the WSAS, and the same exercise measure. Three additional general health questions were added as a global measure of health, and were taken from the Centers for Disease Control and Prevention's population assessment of health-related quality of life (US Department of Health and Human Services, 2000). These questions asked separately how many days in the past month had the participants' physical and mental health been not good, followed by a question asking how many days did poor physical or mental health keep them from their usual activities.

The health care utilisation question from the previous questionnaire was also included as were two additional questions regarding help-seeking behaviour specific to fatigue and bowel-related symptoms. Participants who were experiencing general symptoms, fatigue or bowel problems were also asked if they had a name or diagnosis to explain these separate groups of symptoms in order to further screen for exclusions. The specific fatigue and bowel-related disability questions were removed. Finally, a space was included in which participants could add any further comments about their illness, how they had managed it and/or recovered from it. A total of 309 (34%) of participants chose to make some comment.

Chapter 10.

Results: Main study.

The following chapter describes the analyses and subsequent results for each of the hypotheses outlined in the rationale section of the introduction. The initial section describes preliminary analyses carried out to screen the total data set, and data reduction procedures to reduce the number of variables for use in later analyses. Sections two and three investigate the first two hypotheses, examining each acute illness population separately with regard to the importance of psychological variables in the development of irritable bowel syndrome (IBS) and chronic fatigue syndrome (CFS) respectively. In the remaining sections, the two acute illness population data sets are combined and all cases of IBS and CFS are examined, regardless of the type of acute illness initially experienced. Section four examines the odds of developing either IBS or CFS following either of the two acute illnesses recruited for this study. The influence of acute illness type in the development of post-infectious IBS and CFS is compared, with and without the inclusion of the previously identified psychological risk factors in order to determine their relative importance. Similarities and differences with regard to the importance of the psychological variables as risk factors for IBS and CFS are also examined in this section.

Section five investigates the fourth hypothesis, whereby IBS and CFS cases in the total sample are compared with regard to prevalence, patient characteristics, health care utilisation and disability levels, in order to further explore the similarities and differences between the two syndromes. Section six then compares post-infectious IBS with an expanded chronic fatigue group, by omitting disability criteria from the CFS definition. The possibility that differences between IBS and CFS are a function of the level of disability associated with diagnosis, rather than the diagnosis per se, is explored in this way. The final section of the results compares patients in the total sample identified as having subthreshold fatigue and bowel conditions to those who meet established criteria for CFS and IBS, with regard to disability levels and psychological characteristics.

10.1. Data screening and preliminary analyses.

All data analyses were performed on the SPSS version 12.0.1 for Windows computer software programme. The data file was separated into three distinct files according to acute illness type; *Campylobacter* sample after exclusions (n=620), glandular fever sample after exclusions (n=246) and a combined total sample which excluded participants with either fatigue or bowel-related exclusions (n=835). Prior to analysis all variables were examined using the SPSS explore function. Most variables had few missing values and their distributions demonstrated a good fit with normality. In instances where less than 25% of items from a composite variable were missing, the variable was computed by replacing the missing items with a mean score calculated from the existing items. Where more than 25% of items were missing from composite variables and where single item scales were missing, analyses were performed with a listwise deletion of cases.

The main outcome measure, presence or absence of IBS and/or CFS, was measured categorically. All of the continuous outcome variables at three and six months, however, were highly positively skewed including the MHI-5, the WSAS, the various healthcare utilisation measures and the CDC's general health measures, with skewness ranging from 1.13 to 6.16 for these measures. Transformation of these variables was attempted using common transformation strategies and their distributions were rechecked in each of the three data files. In most cases, transformation altered the skew of the distribution so that it was no greater than + or -1, however Kolmogorov-Smirnov tests of normality indicated that all distributions were still significantly different from normal. Because of this, these variables were categorised according to clinically relevant levels and analysed using non-parametric tests. These procedures are described in more detail in section 10.5. Parametric tests were deemed appropriate in all other cases.

Two single-item variables were excluded from the main analysis due to concerns about the interpretability of the data, including the causal beliefs question from the initial questionnaire and the attributional belief question from the three month follow-up questionnaire. The causal beliefs question from the IPQ asked what participant's believed were the three most important factors that caused their illness. The majority of participants (55%) listed one causal factor, with only 17% listing three or more reasons. With regard to the most important causal belief; 77% listed a physical cause (e.g. contaminated food or drink, bacteria, contact with an infected person), 10% stated they had been "doing too much" and the remaining 13% provided a range of answers that were spread across four

smaller causal categories. Because the variance was so limited, and "doing too much" was difficult to categorise as a psychological or physical belief, it was felt that further analysis of these causal factors may be misleading. Similar problems were found with the attributional beliefs question regarding ongoing symptoms in the three month follow-up questionnaire, however in this case the interpretability of the variable was further complicated by a large amount of missing data. Of the 660 participants reporting one or more symptoms at three month follow-up, 39% did not answer this question. Of those that did answer the question, 71% believed their symptoms were physical or mainly physical, whereas less than 5% believed their symptoms were psychological or mainly psychological.

This study employed a prospective design to test the importance of psychological variables operationalised through the cognitive-behavioural model as potential risk factors for the development of functional somatic syndromes. Because of the predictive nature of the hypotheses to be tested and because the key outcomes were categorical (IBS or non-IBS, CFS or non-CFS), logistic regression was the primary statistical analysis used to answer many of the research questions in this study. The results of logistic regression can be distorted by multicollinearity, that is, where variables included in the equation are highly correlated with each other. Due to the large number of psychological variables measured and the fact that they were measuring sometimes related concepts, it was important to first determine whether these variables could be combined into larger groupings.

In order to check the size of the relationships between the variables, correlation coefficients were computed among the 18 psychological variables measured at the time of acute illness (see Table 13) including; the various measures of somatisation captured by symptom scores related and unrelated to the participants' individual acute illnesses (including number of symptoms, non-*Campylobacter* symptoms (non-CG), non-glandular fever symptoms (non-GF) and somatic symptoms); the four BRIQ subscales (all-or-nothing, limiting, practical and emotional support seeking (SS) scales); the IPQ subscales (illness identity, timeline, consequences, illness coherence, emotional representations and personal control); the Hospital Anxiety and Depression subscales, the Perceived Stress Scale (PSS) and the Negative Perfectionism scale.

Table 13. Pearsons correlations among the psychological variables (N=975).

	Perc. Stress	Neg. perfect.	Anxiety	Depres.	Timel.	Conseq.	Illness coher.	Emot. repr.	Pers. control	Illness identity	No. of sympt.	Somatic sympt.	Non GF sympt.	Non CG sympt.	Limiting	Pract. SS	Emot. SS
Negative perfectionism	.53*																
Anxiety	.65*	.51*															
Depression	.41*	.31*	.50*														
Timeline	.26*	.19*	.24*	.30*													
Consequences	.28*	.23*	.29*	.38*	.54*												
Illness coherence	-.21*	-.18*	-.23*	-.20*	-.37*	-.35*											
Emotional representations	.37*	.33*	.47*	.40*	.47*	.69*	-.44*										
Personal control	-.01	-.01	-.02	-.05	-.09*	.02	.14*	-.05									
Illness identity	.12*	.07	.13*	.17*	.17*	.31*	-.05	.22*	.04								
No. of symptoms.	.18*	.12*	.20*	.21*	.19*	.33*	-.09*	.25*	.02	.88*							
Somatic sympt.	.17*	.11*	.21*	.21*	.21*	.32*	-.12*	.25*	.04	.76*	.88*						
Non GF sympt.	.13*	.08*	.20*	.19*	.11*	.28*	-.07	.23*	-.06	.82*	.93*	.87*					
Non CG sympt.	.23*	.15*	.21*	.23*	.30*	.35*	-.15*	.26*	.12*	.73*	.86*	.93*	.75*				
Limiting	.13*	.12*	.09*	.26*	.17*	.44*	-.06	.27*	.05	.42*	.40*	.31*	.33*	.31*			
Practical SS	.17*	.11*	.16*	.18*	.18*	.38*	-.06	.28*	.01	.32*	.33*	.27*	.30*	.26*	.57*		
Emotional SS	.30*	.29*	.28*	.18*	.20*	.33*	-.14*	.38*	-.03	.19*	.23*	.18*	.19*	.21*	.35*	.45*	
All-or-nothing	.22*	.18*	.25*	.13*	.17*	.16*	-.17*	.19*	-.03	.15*	.21*	.25*	.21*	.23*	-.11*	-.02	.17*

***p≤ .001**

The results of the correlational analyses are presented in Table 13, and indicate a large number of correlations significant at the $p \leq .001$ level. However, because of the large sample size and number of correlations computed, only those correlations with Pearson correlation coefficients of more than .40 were considered to be moderate to large. As would be expected given that the somatisation measures came from the same set of scores, a cluster of large correlations were found between the various symptom scores computed for each sample, including number of symptoms, somatic symptoms, non-glandular fever symptoms and non-*Campylobacter* symptoms, all of which ranged from .75 to .93. These scores were also highly correlated with the illness identity score at .73 or higher. Another cluster was represented by the IPQ subscale scores including timeline, consequences, illness coherence and emotional representations, with only personal control found to be independent of the others. Two BRIQ subscales, limiting and practical support seeking, were also highly correlated at .57 as were the two support seeking scales at .45. Finally, results indicated correlations of .51 or higher between the HADS anxiety, perceived stress and negative perfectionism scales respectively. HADS depression was also moderately correlated with the PSS (.41) and the HADS anxiety scale (.50).

Because of these moderate to strong correlations a principal components analysis (PCA) with varimax rotation was carried out using all 18 subscales, in an attempt to reduce the number of psychological variables into a smaller number of factors. It was expected that each factor obtained would be measuring an underlying construct relatively independent of the others, and therefore of use in further logistic regression analyses. This process was undertaken using the total sample before exclusions in order to ensure the largest data set possible, and because the data reduction process was seen to be independent of outcome. For the purposes of these analyses IPQ personal control and illness coherence were reverse scored to ensure that they would be measured in the same direction as the other IPQ subscales.

The first analysis produced five factors with eigenvalues greater than one, accounting for 71% of the variance. Analysis of the rotated factors indicated that most of the variables loaded onto four independent factors. These included: a general somatisation factor encompassing the various symptom scores and illness identity; a general psychological distress factor including anxiety, depression, negative perfectionism and perceived stress; an illness perceptions factor including the IPQ subscales timeline, consequences, illness

coherence and emotional representations; and an illness behaviour factor incorporating limiting behaviour and practical and emotional support seeking behaviours. Only IPQ personal control loaded onto a factor alone, whereas the BRIQ all-or-nothing subscale did not load satisfactorily on any factor. Because all-or-nothing behaviour was deemed to be of greater importance theoretically than the belief in personal control over an acute illness, it was decided to delete personal control and re-run the analysis. This second analysis produced four factors with eigenvalues greater than one, however examination of the scree plot and the fact that all-or-nothing was still not satisfactorily loading onto any factor, suggested that a five-factor solution may be more appropriate.

Table 14. Principal components analysis of the psychological variables: Total sample (N=1012).

	I	II	III	IV	V
Somatisation (α = 0.96)					
Number of symptoms	.95	.09	.08	.17	.03
Somatic symptoms	.94	.09	.13	.07	.08
Non GF symptoms	.93	.07	.04	.12	.05
Non CG symptoms	.88	.12	.19	.07	.07
Illness Identity	.88	.02	.06	.20	-.03
Psychological distress (α = 0.79)					
Anxiety	.11	.84	.19	.04	.09
Perceived Stress Scale	.08	.81	.13	.11	.10
Negative Perfectionism	.01	.74	.07	.14	.15
Depression	.16	.62	.33	.02	-.32
Illness Perceptions (α = 0.78)					
Timeline	.11	.11	.77	.06	.01
Consequences	.22	.16	.73	.37	-.09
Illness coherence	.01	.09	.72	-.07	.17
Emotional Representations	.12	.34	.71	.26	.05
Illness Behaviour (α = 0.71)					
Practical support seeking	.21	.06	.10	.80	-.10
Emotional support seeking	.05	.24	.13	.74	.35
Limiting behaviour	.31	.06	.15	.69	-.37
All-or-nothing behaviour					
	.20	.18	.17	-.06	.80

In order to clarify the factor structure, a five factor solution was imposed and results of this PCA indicated that 74% of the variance was accounted for by the five factors; with all variables producing factor loadings greater than .62 (see Table 14). The factors were labelled somatisation, psychological distress, illness perceptions, illness behaviour and all-or-nothing behaviour. The subscales making up each factor loaded no more than .37 on any other factor with most obtaining loadings of less than .20. The alpha coefficients ranged from .71 to .96 (see Table 14), with no gains to be made in the reliability of the factor scores by deleting any variables. Based on this analysis, these five factors were then added to the list of variables for use in analyses where a large number of highly correlated variables may have produced misleading results.

10.2. Risk factors for IBS: *Campylobacter* group.

Hypothesis one: Specific psychological risk factors operationalised from the cognitive-behavioural model will be significantly associated with the development of post-infectious IBS three and six months post-infection.

As described earlier in the methodology section, analysis for the *Campylobacter* group was conducted using a sample of 620 participants, following exclusions for current or prior history of bowel problems and late completion of questionnaires. In this group there were 39 non-responders at three month follow-up and 59 at six month follow-up who were excluded from individual analyses. All analyses in this section compared new cases of IBS (as defined by the Rome I modified or Rome II definitions described in the methodology section) with non-cases, at three and six month follow-up. Analysis of the remaining sample at each time point found a total of 90 (16%) new cases of IBS at three months and 65 (11%) at six months. Of these cases, 49 (8%) met criteria for IBS at both three and six months, leaving 41 participants who met criteria at three months only, and 16 at six months only. This meant there were 494 (84%) non-cases at three months and 504 (87%) at six months.

Before hypothesis one was tested, a number of demographic and illness severity variables that may have independently influenced outcome were compared between the IBS cases and the non-cases. Mean scores were compared using independent samples *t*-tests and dichotomous variables were compared using two-way contingency tables with chi-square

analyses. Table 15 outlines the result of these analyses. IBS cases at three months were significantly younger than non-cases ($t(577) = 3.2$, $p<.001$), but those cases at six months were not ($t(557) = 1.77$, $p<.08$). Chi-square analysis using two variables, gender (male and female) and outcome (IBS and non-IBS), indicated that cases at both three months (Pearson χ^2 (1, n=581) = 21.9, $p<.001$) and six months (Pearson χ^2 (1, n=561) = 8.82, p=.003) were significantly more likely to be female than non-cases. Despite a relatively even gender balance within the non-cases group at each time point, over 70% of IBS cases at three and six months were female.

With regard to illness variables, IBS cases at three months had reported a significantly higher number of *Campylobacter* specific symptoms at the time of acute illness than non-cases ($t(579) = -2.2$, $p<.03$), as had cases at six months ($t(559) = -2.1$, $p<.04$). IBS cases and non-cases at three and six months were also compared on the prescription of antibiotics at the time of acute illness (yes or no). Chi-square analyses showed that at three months the two groups did not significantly differ in the rate of prescription of antibiotics (Pearson χ^2 (1, n=573) = 0.01, p=.91), and nor did they at six months (Pearson χ^2 (1, n=553) = 0.52, p=.47).

Table 15. Comparison of IBS cases and non cases at three and six months post-*Campylobacter* on relevant demographic and illness variables.

	THREE MONTHS		SIX MONTHS	
	IBS cases *n*=90	**Non-cases *n*=494**	**IBS cases *n*=65**	**Non-cases *n*=504**
% of total	15.6	84.4	11.4	88.6
Gender (% female)	78%***	51%***	72%**	53%**
Mean Age (SD)	38.9(15.6)***	44.9(16.4)***	40.8 (15.4)	44.6 (16.5)
Campylobacter symptoms	5.2 (1.8)*	4.7 (1.8)*	5.2 (1.6)*	4.7 (1.9)*
Prescription of antibiotic (%prescribed)	52%	52%	55%	51%

***p*<.05, ** *p*<.01, ***p*<.001**

In summary, it would appear that of these demographic and illness variables, gender was the most important factor differentiating between cases of IBS and non-cases. Cases at three months were significantly younger, and at both time points cases also had a

significantly higher number of *Campylobacter* symptoms at the time of acute illness, indicating that these variables also needed to be considered in determining outcome. In light of these analyses, further hypothesis testing in this section was conducted controlling for age, gender and *Campylobacter* symptoms. These variables were included in all analyses so as to retain consistency and allow comparison across the multiple analyses conducted.

Descriptive statistics for each psychological variable at the time of acute illness were also computed prior to further analysis in order to provide a basic understanding of the pattern of results for the two groups. Mean scores and standard deviations are presented in Table 16 for both the IBS group and non-cases, at three and six months post-*Campylobacter*. Because of the large sample size, overall differences between the two groups were small, but detectable.

Table 16. Mean scores and standard deviations on each psychological variable for IBS cases and non-cases at three and six months post-*Campylobacter*.

	MEAN SCORES(SD) IBS		**MEAN SCORES(SD) NON-CASES**	
	(*n*=90)	**(*n*=65)**	**(*n*=491)**	**(*n*=490)**
Variable	**Three months**	**Six months**	**Three months**	**Six months**
Non CG symptoms	6.4 (2.5)	6.5 (2.6)	5.5 (2.4)	5.6 (2.4)
Illness identity	12.0 (4.4)	12.1 (4.8)	11.1 (4.5)	11.1 (4.5)
Perceived Stress	27.8 (5.6)	27.6 (5.7)	24.0 (5.8)	24.3 (5.8)
Negative Perfectionism	25.7 (8.3)	24.7 (7.4)	22.9 (7.4)	23.1 (7.5)
Anxiety	6.8 (3.8)	6.9 (4.2)	4.9 (3.6)	5.0 (3.5)
Depression	4.3 (3.4)	3.9 (3.5)	3.4 (3.2)	3.5 (3.5)
Timeline	12.3 (3.7)	12.0 (3.6)	10.8 (4.6)	10.9 (3.2)
Consequences	17.0 (4.3)	16.9 (4.4)	15.6 (5.0)	15.7 (4.4)
Personal Control	19.3 (4.2)	19.7 (3.7)	19.4 (4.3)	19.4 (4.3)
Illness Coherence	10.4 (2.8)	10.4 (2.9)	11.0 (2.4)	11.0 (2.4)
Emot. Representations	15.5 (5.5)	15.9 (5.9)	14.3 (4.5)	14.3 (4.5)
All-or-nothing	15.7 (4.7)	15.1 (5.3)	13.3 (5.0)	13.4 (5.0)
Limiting	21.6 (6.2)	22.1 (6.2)	23.1 (7.2)	22.9 (7.1)
Emotional SS	7.0 (2.8)	7.1 (2.9)	6.7 (3.2)	6.6 (3.1)
Practical SS	8.4 (3.5)	8.5 (3.7)	8.9 (4.3)	8.8 (4.2)

Cases of IBS at both three and six months post-infection had higher mean scores on almost all psychological variables in relation to non-cases, with the exception of lower IPQ illness coherence scores (in which lower levels are considered less desirable) and lower levels on two of the illness behaviour scales, limiting behaviour and practical support seeking. For non-cases, mean scores for the individual variables at three and six months stayed fairly consistent, with changes in the mean scores of no more than 0.3 points between three to six months follow-up. Whilst the majority of mean scores for the IBS group were again relatively stable from three to six months, greater variation was found than amongst the non-cases, with changes in the mean scores ranging from 0.1 to 1.0. Given that less than half the cases at three months were also included in the six month group, this stability in mean scores cannot be explained by consistency of group membership alone.

Psychological risk factors for the development of IBS: Results of univariate analyses.

In the first exploratory stages of analysis, the importance of each individual psychological variable as a risk factor for the development of IBS was examined. Individual binary logistic regression analyses were used to determine IBS outcome on the basis of each psychological variable. IBS outcome measured at three months was entered as the dependent variable (coded 0 for 'no IBS' and 1 for 'IBS') with each psychological variable measured at baseline entered into separate regression analyses as a covariate. Age, gender and *Campylobacter* symptoms were entered simultaneously as covariates with each psychological variable in order to ensure that any significant effect of the psychological variable was independent of these demographic and illness variables. This process was repeated for IBS outcome measured at six month follow-up.

Results from the logistic regressions at three and six months are presented in Table 17, along with separate odds ratios and 95% confidence intervals for each psychological variable. Because of the large number of analyses conducted, significance was set at $p \leq .01$ level. The statistics for the effect of age, gender and *Campylobacter* symptoms in each of the analyses are not presented in order to simplify comparison between individual variables. This information can be summarised, however, over the 15 analyses for each time point. Age and *Campylobacter* symptoms were not significant risk factors for the development of IBS for any of the individual analyses at either three or six month follow-

up. In contrast, gender was a significant risk factor in all analyses at both three and six month follow-up, with the exception of the two analyses considering stress (the perceived stress scale) and anxiety (HADS anxiety).

Table 17. Individual logistic regression analyses of IBS outcome at three and six months post-*Campylobacter* as a function of individual psychological variables.

VARIABLE	THREE MONTH FOLLOW-UP			SIX MONTH FOLLOW-UP		
Non-cases vs. IBS cases	**Odds Ratio**	**95% C.I.**	***p***	**Odds Ratio**	**95% C. I.**	***p***
Non CG symptoms	1.14	1.02-1.28	.02	1.16	1.02-1.31	.02
Illness identity	1.01	.93-1.10	.76	1.01	.92-1.10	.91
Perceived Stress	1.10	1.06-1.14	**<.001**	1.09	1.04-1.14	**<.001**
Negative Perfectionism	1.04	1.01-1.07	**.01**	1.02	.99-1.06	.19
Anxiety	1.12	1.05-1.19	**<.001**	1.12	1.05-1.20	**.001**
Depression	1.06	1.00-1.13	.05	1.02	.95-1.10	.55
Timeline	1.15	1.07-1.23	**<.001**	1.10	1.02-1.19	.02
Consequences	1.06	1.01-1.12	.03	1.06	.99-1.12	.09
Personal Control	1.01	.95-1.07	.77	1.03	.97-1.10	.31
Illness Coherence	0.91	.83-.99	.05	0.91	.82-1.00	.06
Emot. Representations	1.04	.99-1.09	.13	1.06	1.00-1.12	.04
All-or-nothing	1.10	1.05-1.20	**<.001**	1.06	1.01-1.12	.02
Limiting	0.94	.91-.98	**.002**	0.96	.92-1.00	.05
Emotional SS	0.99	.92-1.07	.82	1.01	.93-1.10	.78
Practical SS	0.93	.87-.99	.02	0.95	.88-1.02	.14

Variables significant at the $p \leq .01$ level in bold.

Overall results indicated that a range of cognitive, behavioural and emotional variables were risk factors in the development of IBS following *Campylobacter*. With regard to cognitive and emotional variables, perceived stress, negative perfectionism and anxiety were all significant risk factors for the development of IBS three months following infection, with IBS cases more likely to have reported higher levels on these variables at the time of acute illness. The IPQ timeline subscale was also a significant risk factor, with cases of IBS at three months more likely to have had higher scores on this scale. This indicates that participants who went on to develop IBS at three months were more likely to believe at the time of their acute illness that their illness would last a long time. Finally, illness behaviour at the time of acute infection also placed an individual at greater risk of

developing IBS three months following that infection. All-or-nothing and limiting behaviour were significant risk factors for the development of IBS, with IBS cases more likely to have reported an all-or-nothing behavioural pattern in response to their illness, and less likely to have limited their activity levels at the time of that illness.

At six months the pattern of results was similar (see Table 17), however there were fewer significant results at the $p<.01$ level. Perceived stress and anxiety remained strong risk factors for the development of IBS six months post-*Campylobacter*; however, negative perfectionism, IPQ timeline, all-or-nothing behaviour, and limiting behaviour were no longer significant risk factors. The remaining psychological variables were not risk factors for the development of IBS at either three or six months post-infection; including somatisation (non-CG symptoms), illness identity, depression, IPQ consequences, personal control, illness coherence and emotional representations, and the two support seeking scales from the BRIQ.

Relative importance of psychological risk factors in the development of IBS: Results of multivariate analysis.

The univariate analyses suggested that a number of individual psychological variables are related to the development of IBS. Investigating the relative importance of these variables in relation to each other is complicated by the previously discussed high inter-correlations between some of the most significant variables. Entering all these significant variables into a single logistic regression analysis could create the problem of multicollinearity, compromising valid interpretation of the results. In order to reduce the number of competing (and correlated) variables, the psychological factor scores computed and defined earlier were instead entered simultaneously into a logistic regression analysis to determine the relative importance of each group of variables.

The five factor scores (somatisation, psychological distress, illness perceptions, illness behaviour and all-or-nothing behaviour) were entered as covariates along with gender, age and *Campylobacter* symptoms into two separate regressions, with IBS outcome at either three or six months as the dependent variable (coded 0 for 'no IBS' and 1 for 'IBS'). For the purposes of these analyses, significance was set at the conventional $p\leq .05$ level. Results are presented in Table 18, and indicate that psychological distress, illness perceptions, and all-or-nothing behaviour were all significant risk factors for the

development of IBS at three months, with those reporting higher levels of these variables at the time of acute illness more likely to develop IBS. Illness behaviour was also a significant predictor; however on this factor lower levels were associated with IBS. Finally, gender and age were also both significant risk factors for the development of IBS at three months, with women and younger people more likely to develop IBS.

At six months post-*Campylobacter*, psychological distress, illness perceptions, all-or-nothing behaviour in response to illness and gender, all remained significant risk factors for the development of IBS. Once again, females and those with higher levels of these psychological variables were at greater risk. Age and illness behaviour, however, were not significant risk factors at this point.

Table 18. Logistic regression analyses of IBS outcome at three and six months post-*Campylobacter*; as a function of psychological factor scores, gender, age and *Campylobacter* symptoms at the time of acute illness.

VARIABLE	THREE MONTH FOLLOW-UP			SIX MONTH FOLLOW-UP		
Non-cases vs. IBS cases	**Odds Ratio**	**95% C.I.**	***p***	**Odds Ratio**	**95% C. I.**	***p***
Gender (M vs. F)	2.78	1.58-4.89	**<.001**	2.03	1.12-3.70	**.02**
Age	0.98	0.96-0.10	**.02**	0.99	0.98-1.01	.45
CG symptoms	1.08	0.87-1.34	.47	1.09	0.86-1.37	.48
Somatisation	1.11	0.77-1.60	.57	1.16	0.78-1.72	.48
Psychological distress	1.65	1.30-2.10	**<.001**	1.47	1.13-1.93	**.01**
Illness perceptions	1.35	1.05-1.72	**.02**	1.33	1.01-1.76	**.04**
Illness behaviour	0.61	0.45-0.81	**.001**	0.76	0.55-1.03	.08
All-or-nothing	1.57	1.22-2.02	**<.001**	1.41	1.08-1.85	**.01**
Constant	0.05		.001	0.04		.001

Variables significant at the $p \leq .05$ level in bold

Viewed in conjunction with the univariate analyses, these results suggest that there is good evidence for cognitive-behavioural factors in the development of IBS post-infection. In particular, psychological distress and illness behaviour were consistent risk factors across all analyses. The univariate analyses indicate that higher levels of perceived stress, negative perfectionism, anxiety, and all-or-nothing behaviour, along with lower levels of limiting behaviour are particularly important. Illness perceptions were also significant, although it is interesting to note that this effect was strongest when the individual subscales

were analysed together as a group. In the univariate analysis, only negative beliefs about timeline were found to be significant. Finally, gender was also an important risk factor throughout all analyses, with females twice as likely to develop IBS as males.

10.3. Risk factors for CFS: Glandular fever group.

Hypothesis two: Specific psychological risk factors operationalised from the cognitive-behavioural model will be significantly associated with the development of post-infectious CFS three and six months post-infection.

Analysis for the glandular fever group was conducted using a sample of 246 participants, following exclusions for current or prior history of fatigue inducing conditions, and late completion of questionnaires. In this group there were 22 non-responders at three month follow-up and 29 at six month follow-up who were excluded from individual analyses. All analyses in this section compared new cases of CFS (as defined by the Fukuda or British definitions described in the methodology section) with non-cases, at three and six month follow-up. Analysis of the remaining sample at each time point found a total of 21 (9.4%) new cases of CFS at three months and 17 (7.8%) at six months. Of these cases, only seven (2.8%) met criteria for CFS at both three and six months; leaving 14 participants who met criteria at three months only, and 10 at six months only. This meant there were 203 (90.6%) non-cases at three months and 200 (92.2%) at six months.

As with the *Campylobacter* group, before hypotheses two was tested, a number of variables that may have influenced outcome were compared between the CFS group and non-cases. Mean scores were compared using independent samples *t*-tests or two-way contingency table analyses in the same manner as for the *Campylobacter* group. Results are presented in Table 19. Independent-samples *t*-tests showed that CFS cases at three months did not differ in age from non-cases ($t(222) = 0.26$, $p=.79$), but that cases at six months were significantly younger than non-cases ($t(102) = 5.18$, $p<.001$). Chi-square analysis using two variables, gender (male and female) and outcome (CFS and non-cases), indicated that CFS cases at three months were not significantly different from non-cases with regard to gender (Pearson χ^2 (1, $n=224$) = 3.08, $p=.08$), however by six months, cases were significantly more likely to be female (Pearson χ^2 (1, $n=217$) = 6.71, $p<.01$). Unlike the *Campylobacter* sample in which the non-cases had a relatively even gender balance,

the non-cases in the glandular fever sample had a slight gender imbalance, with over 60% of non-cases female. Despite this, a much larger majority of the CFS cases were female with 81% of cases at three months being female, rising to over 90% at six month follow-up.

Table 19. Comparison of CFS cases and non cases at three and six months post glandular fever on relevant demographic and illness variables.

	THREE MONTHS		SIX MONTHS	
	CFS cases *n*=21	Non-cases *n*=203	CFS cases *n*=17	Non-cases *n*=200
%	9.3	90.7	7.8	93.2
Gender (% female)	81%	62%	94%**	63%**
Mean Age (SD)	22.2 (8.2)	22.7 (8.2)	19.1 (1.9)***	23.1 (8.7)***
Glandular fever symptoms	6.0 (1.3)	6.1 (1.4)	6.4 (0.8)	6.0 (1.4)
Prescription of antibiotic (%prescribed)	38%	26%	41%	26%

**p<.01, ***p<.001

With regard to illness variables, CFS cases at three months reported a similar number of glandular fever specific symptoms at the time of acute illness as non-cases ($t(222) = 0.2$, $p=.84$), whereas a similar pattern was found at six months ($t(219) = -1.13$, $p=.26$). Chi-square analyses using the variable 'prescription of antibiotics' (yes or no), was performed as an additional indicator of illness severity. CFS cases at three months did not significantly differ from non-cases in the rate of antibiotic prescription (Pearson χ^2 (1, $n=223$) = 1.48, $p=.22$), nor did they at six months (Pearson χ^2 (1, $n=216$) = 1.79, $p=.18$). In summary, unlike the *Campylobacter* sample, there were fewer differences between CFS cases and non-cases in the glandular fever sample on these variables. However, further predictive analyses were still conducted controlling for age, gender and glandular fever symptoms in order to be consistent with the analyses previously conducted on the *Campylobacter* sample.

Descriptive statistics for each psychological variable at the time of glandular fever were also computed prior to further analysis in order to give a basic understanding of the pattern of results for CFS cases and non-cases. Mean scores and standard deviations are presented

in Table 20 for both the CFS group and non-cases at three and six months post glandular fever. As was the case for the *Campylobacter* sample, mean scores at three and six months were largely consistent for non-cases, with changes in the mean scores of no more than 0.2 points between three and six month follow-up. Cases of CFS at both three and six months post-infection, like IBS cases, had higher scores on almost all psychological variables in relation to non-cases, with the exception of IPQ personal control and illness coherence, where mean scores were lower. As was the case for the IBS group, greater variation was found between mean scores for the CFS group between three and six months than was found amongst the non-cases, with change scores ranging from 0.1 to 2.0. In this sample only one-third of cases at three months were also included in the six month CFS group, once again indicating that the similarities in mean scores cannot be explained by the consistency of group membership alone.

Table 20. Mean scores and standard deviations on each psychological variable for CFS cases and non-cases at three and six months post glandular fever.

	MEAN SCORES(SD) CFS		MEAN SCORES(SD) NON-CASES	
	(n=21)	(n=17)	(n=203)	(n=200)
Variable	Three months	Six months	Three months	Six months
Non GF symptoms	9.5 (2.3)	9.1 (2.6)	6.9 (3.1)	7.1 (3.1)
Illness identity	14.0 (2.9)	14.4 (2.7)	12.3 (4.3)	12.3 (4.3)
Perceived Stress	30.5 (5.5)	29.7 (7.0)	27.9 (6.3)	28.2 (6.2)
Neg. Perfectionism	28.5 (8.1)	30.5 (8.4)	25.8 (7.6)	25.6 (7.3)
Anxiety	8.6 (3.4)	8.9 (4.2)	5.8 (3.6)	5.9 (3.8)
Depression	6.9 (3.1)	7.1 (2.7)	4.5 (3.1)	4.6 (3.2)
Timeline	16.1 (2.2)	16.5 (2.9)	13.8 (3.3)	13.9 (3.3)
Consequences	20.2 (3.0)	19.5 (4.7)	18.1 (4.4)	18.3 (4.3)
Personal Control	20.6 (3.4)	20.6 (3.7)	22.3 (3.2)	22.2 (3.3)
Illness Coherence	8.7 (2.0)	8.6 (2.6)	10.3 (2.3)	10.3 (2.2)
Emot. Representations	19.7 (4.4)	19.2 (4.8)	16.0 (4.9)	16.0 (5.0)
All-or-nothing	16.7 (3.9)	17.2 (5.8)	13.8 (4.7)	13.7 (4.5)
Limiting	26.4 (5.6)	26.6 (7.6)	24.8 (6.2)	24.9 (6.0)
Emotional SS	8.3 (3.0)	7.8 (3.0)	7.7 (3.1)	7.8 (3.2)
Practical SS	10.1 (4.1)	11.1 (4.8)	9.6 (3.7)	9.6 (5.6)

It is interesting to compare these mean scores to that of the *Campylobacter* group as presented in Table 16. At both time points the mean scores for the non-cases in the glandular fever sample are more comparable with the mean scores for the IBS cases than they are for the non-cases in the *Campylobacter* sample. With the exception of anxiety and all-or-nothing behaviour, all mean scores for the non-cases in the glandular fever sample are either similar or higher than that reported by the IBS cases in the *Campylobacter* sample. This result indicates possible differences in the two sample populations either related to the experience of the two acute illnesses or related to characteristics of individuals that get one illness as opposed to the other. These possibilities will be commented on further in the discussion.

Psychological risk factors in the development of CFS: Results of univariate analyses.

Separate binary logistic regression analyses were again used to examine the usefulness of each psychological variable, this time as risk factors for the development of CFS. Fatigue-related outcome measured at three months was entered as the dependent variable (coded 0 for 'no CFS' and 1 for 'CFS') with each psychological variable measured at baseline entered into separate regression analyses as a covariate. Age, gender and glandular fever symptoms were entered simultaneously as covariates with each psychological variable, in order to ensure that any significant effect was independent to that of these demographic and illness variables. Once again, as for the *Campylobacter* sample, the same analyses were repeated using cases identified at six month follow-up.

Results from the logistic regression analyses according to outcome at three and six months respectively are presented in Table 21, along with separate odds ratios and 95% confidence intervals for each individual variable. Once again, because of the large number of analyses, significance was set at the $p \leq .01$ level. Age, gender and glandular fever symptom statistics for each individual analysis indicated that none of these variables were significant risk factors for the development of CFS outcome in any of the individual analyses at either three or six month follow-up and as such are not presented here.

Results indicated that, as was the case for IBS post-*Campylobacter*, a range of cognitive, behavioural and emotional variables were risk factors for the development of CFS following glandular fever. With regard to cognitive variables, several illness specific

beliefs as measured by the IPQ were found to be significant risk factors for the development of CFS including timeline, illness coherence and emotional representations. These results indicate that participants who went on to develop CFS at three months were more likely to believe that their initial acute illness would last a long time, were less likely to feel that they understood the nature of that illness, and were more likely to think of it in terms of its emotional impact. Behaviourally, an all-or-nothing pattern of behaviour at the time of acute illness was also a significant risk factor with cases reporting higher levels of this behaviour than non-cases. With regard to emotional variables, anxiety and depression at the time of acute illness were also associated with the development of CFS, with cases at three months reporting higher levels than those who did not develop CFS. Finally, somatisation (as measured by the total number of non-glandular fever related symptoms reported at the time of acute illness) was a significant risk factor with higher levels found in those who went on to develop CFS at three months.

Table 21. Individual logistic regression analyses of CFS outcome at three and six months post glandular fever as a function of individual psychological variables.

VARIABLE	THREE MONTH FOLLOW-UP			SIX MONTH FOLLOW-UP		
Non-cases vs. CFS cases	**Odds Ratio**	**95% C.I.**	***p***	**Odds Ratio**	**95% C. I.**	***p***
Non GF symptoms	1.40	1.16-1.69	**<.001**	1.24	1.02-1.51	.03
Illness identity	1.17	1.01-1.35	.03	1.14	.97-1.36	.12
Perceived Stress	1.06	.99-1.14	.12	1.01	.93-1.09	.88
Negative Perfectionism	1.05	.99-1.12	.12	1.08	1.01-1.16	.04
Anxiety	1.22	1.08-1.38	**.002**	1.18	1.03-1.34	.02
Depression	1.26	1.09-1.46	**.002**	1.26	1.06-1.50	**.01**
Timeline	1.30	1.09-1.54	**.004**	1.38	1.11-1.72	**.004**
Consequences	1.15	1.02-1.29	.03	1.06	.94-1.20	.36
Personal Control	.86	.75-.98	.02	.86	.74-1.01	.07
Illness Coherence	.75	.62-.92	**.01**	.77	.62-.95	**.01**
Emot. Representations	1.17	1.06-1.29	**.002**	1.11	1.00-1.24	.05
All-or-nothing	1.13	1.03-1.24	**.01**	1.14	1.02-1.26	.02
Limiting	1.05	.97-1.14	.26	1.04	.95-1.14	.43
Emotional SS	1.05	.91-1.22	.49	.96	.81-1.14	.64
Practical SS	1.04	.92-1.17	.57	1.08	.94-1.24	.29

Variables significant at the $p \leq .01$ level in bold

The pattern was similar for cases at six months (see Table 21); however, there were fewer significant results, as was the case for the *Campylobacter* group. Depression, IPQ timeline and IPQ illness coherence remained strong risk factors, whereas somatisation, anxiety, IPQ emotional representations, and all-or-nothing behaviour were no longer significant risk factors for the development of CFS six months post glandular fever. A number of psychological variables were not significantly related to the development of CFS at either three or six months, including illness identity, perceived stress, negative perfectionism, IPQ consequences, IPQ personal control, limiting behaviour, and the two behavioural support seeking scales.

Relative importance of psychological risk factors in the development of CFS: Results of multivariate analysis.

As with the *Campylobacter* group, the factors defined earlier were used to reduce the number of competing variables in order to determine the relative importance of each group of psychological variables. The five factor scores (somatisation, psychological distress, illness perceptions, illness behaviour and all-or-nothing behaviour) were entered as covariates along with gender, age and glandular fever symptoms into two separate regressions, with CFS outcome at either three or six months post glandular fever as the dependent variable (coded 0 for 'no CFS' and 1 for 'CFS'). Significance was set at the $p \leq .05$ level. The initial results of the six month analysis indicated an unusually large 95% confidence interval with regard to the variable gender, suggesting that the model was unstable and the results likely to be invalid. Two way contingency table analysis of gender and CFS outcome indicated that this instability was most likely due to a very small cell size for male cases of CFS (of the 17 cases of CFS at six months, only 1 was male). Because of this gender was excluded from the six month analysis.

Results are presented in Table 22, and indicate that glandular fever symptoms, somatisation, psychological distress, and illness perceptions were all significant risk factors for the development of CFS at three months, with cases more likely to have higher scores on all of these variables. Age, gender, illness behaviour and all-or-nothing behaviour were not significant risk factors. By six months post glandular fever, however, the only significant risk factor for the development of CFS was illness perceptions, with all other variables non-significant, indicating that those with higher levels of illness perceptions were most at risk for the development of CFS six months post glandular fever.

Table 22. Logistic regression analyses for CFS outcome at three and six months post glandular fever as a function of psychological factor scores, gender, age and glandular fever symptoms at the time of acute illness.

VARIABLE	THREE MONTH FOLLOW-UP			SIX MONTH FOLLOW-UP		
Non-cases vs. CFS cases	**Odds Ratio**	**95% C.I.**	***p***	**Odds Ratio**	**95% C. I.**	***p***
Gender (M vs. F)	1.67	.49-5.67	.41			
Age	1.01	.94-1.08	.89	.87	.72-1.04	.11
GF symptoms	.60	.38-.94	**.03**	.90	.56-1.44	.65
Somatisation	2.83	1.42-5.62	**.003**	1.88	.94-3.78	.08
Psychological distress	1.98	1.09-3.60	**.03**	1.56	.87-2.78	.14
Illness perceptions	2.50	1.40-4.47	**.002**	2.15	1.13-4.10	**.02**
Illness behaviour	1.15	.63-2.11	.65	.92	.48-1.77	.81
All-or-nothing	1.13	.64-2.00	.67	1.10	.62-1.94	.75
Constant	.24		.50	1.34		.90

Variables significant at the $p \leq .05$ level in bold.

In summary, these results suggest that there is also good evidence for cognitive-behavioural factors in the development of CFS post-infection, as was the case for IBS. Illness perceptions were consistently associated with the development of CFS across all analyses, in particular timeline, illness coherence and emotional representations, with stronger negative beliefs more likely in those who went on to develop CFS. Psychological distress was again a significant risk factor in the development of CFS, as it was for IBS; however in this case it reflected the influence of anxiety and depression, rather than perceived stress and negative perfectionism. These variables were not significant risk factors in the univariate analyses for CFS as they had been for IBS. Glandular fever symptoms and high levels of somatisation were significantly associated with the development of CFS at three months, in contrast to the results for IBS. Similarly, illness behaviour was not a strong predictor of CFS post glandular fever, whereas it was for IBS. With regard to behavioural factors, across all analyses only all-or-nothing behaviour was significantly associated with CFS in the univariate analysis three months post-infection. Limiting behaviour was not a significant risk factor at any point. Another striking difference from the IBS results was the relative unimportance of gender in the development of CFS. Whilst female gender was consistently associated with the

development of IBS across all analyses, it was not found to be significantly associated with the development of CFS in any of these analyses.

10.4. The importance of the nature of the infection in the development of post-infectious IBS and CFS.

Hypothesis three: The odds of developing CFS will be significantly greater following glandular fever than Campylobacter; whereas the opposite will be true for IBS. However, the odds of these acute illness risk factors will be lessened from three to six months post-infection in relation to the odds of the psychological variables.

Up to this point all analyses have been conducted on outcomes within each acute illness sample, that is IBS post-*Campylobacter* and CFS post glandular fever. Given that all subjects in the study completed both bowel and fatigue-related outcome measures, however, it is also possible to determine cases of CFS occurring after *Campylobacter* as well as cases of IBS occurring after glandular fever. Combining the two groups into one post-infectious sample makes it possible to compare the relative importance of the type of infection in the development of these conditions. We can also examine the relative risks of the type of infection in comparison to that of the psychological risk factors already identified. In addition, we are able to analyse commonalities regarding the relevance of psychological factors in the development of IBS and that of CFS, regardless of acute illness type.

These questions were investigated in several different ways. The first set of analyses described the ratio of the prevalence rates of IBS and CFS in the total sample according to acute illness type, after exclusions for history of fatigue and bowel-related problems. This approach aimed to present a simple picture of the rates of each functional somatic syndrome within each acute illness type. A second approach used multinomial logistic regression to compare the relative odds of developing IBS and CFS in comparison to non-cases, based on acute illness type. This analysis was able to determine more precisely the impact of two specific acute illnesses on the development of IBS and CFS, while also taking into account the impact of age and gender. Multinomial logistic regression was also used to determine the impact of the acute illness on the relative importance of the

psychological risk factors already identified. Finally, binary logistic regression was used with the total sample to specifically compare IBS and CFS cases in order to determine whether the psychological risk factors for the development of each condition were similar or not.

Comparison of prevalence rates.

The total sample included 835 participants following exclusions for current or prior history of either bowel or fatigue-related conditions and late completion of questionnaires. In this group, there were 60 non-responders at three months and 87 non-responders at six months who were excluded from individual analyses. In order to compare prevalence rates of IBS and CFS in these two acute illness populations, separate two-way contingency tables were run for each outcome at each time point, using two variables; laboratory test result (*Campylobacter* and glandular fever) and outcome (IBS and non-IBS, or CFS and non-CFS). Table 23 outlines the rates of IBS and CFS found in each acute illness population.

Table 23. Percentage and frequency of outcome according to acute illness type.

	Campylobacter	Glandular fever	Total sample
IBS three months			
No IBS	85% (471)	93% (205)	87% (676)
IBS	15% (83)	7% (16)	13% (99)
IBS six months			
No IBS	89% (475)	92% (197)	90% (672)
IBS	11% (59)	8% (17)	10% (76)
CFS three months			
No CFS	95% (528)	91% (201)	94% (729)
CFS	5% (26)	9% (20)	5.9% (46)
CFS six months			
No CFS	95% (508)	92% (198)	94% (706)
CFS	5% (26)	8% (16)	6% (42)

At three months post-infection, more than twice the rate of IBS was found in the *Campylobacter* group (15%) than was found in the glandular fever group (7%). Similarly, there was almost twice the rate of CFS in the glandular fever group (9%) as there was in

the *Campylobacter* group (5%). At six months, however, the results were slightly less striking. Whilst there were still more cases of IBS in the *Campylobacter* group than the glandular fever group and more cases of CFS in the glandular fever group than the *Campylobacter* group, the differences were less profound, with only a three percent difference between each illness type for each functional somatic syndrome. In addition, the overall number of cases of CFS and IBS remained relatively consistent from three to six months within each group with the exception of IBS in the *Campylobacter* group which dropped from 15% to 11%.

These figures include participants who had a dual diagnosis of both IBS and CFS. This amounted to 14 participants at three month follow-up (15% of the total IBS group and 30% of the total CFS group) and seven participants at six month follow-up (9% of total IBS and 16% of total CFS). For all remaining analyses in this section, these cases were excluded to ensure there was no overlap between the two groups. The remaining sample at three months follow-up had a total of 85 (11%) new cases of IBS and 32 (4.1%) new cases of CFS, with non-cases numbering 644 (83.1%). At six months follow-up there was a total of 69 (9.2%) new cases of IBS and 35 (4.7%) new cases of CFS, with non-cases numbering 637 (85.2%).

Acute infection type as a risk factor in the development of IBS and CFS.

Multinomial logistic regression was used to examine the impact of the acute illness type on IBS and CFS outcome at both three and six months. Separate analyses were carried out for outcome at three and six months. Outcome was entered as the dependent variable (coded 0 for 'no IBS or CFS', 1 for 'CFS' and 2 for 'IBS') with acute illness (*Campylobacter* and glandular fever) entered as a factor, and age and gender (coded 1 for 'male' and 2 for 'female') measured at baseline entered as covariates. 'No IBS or CFS' was nominated as the reference category. Results are presented in Table 24, and indicate that acute illness type was a significant risk factor in the development of IBS at both three and six month follow-up, with the odds of those experiencing *Campylobacter* 2-3 times those of patients experiencing glandular fever. This effect was most striking at three months with the odds of those who experienced *Campylobacter* developing IBS 3.5 times that of patients who experienced glandular fever. At six months, these patients still had twice the odds of developing IBS compared with glandular fever patients. Gender was also a significant risk

factor with females 2-3 times more likely to develop IBS than males. Whilst age was a significant risk factor in the development of IBS at three month follow-up, with younger participants at greater risk, it was no longer significant at six months.

Table 24. Multinomial logistic regression analyses of outcome (CFS and IBS compared to non-cases) at three and six months post-infection as a function of acute illness type, gender and age.

	THREE MONTHS			SIX MONTHS		
	Odds ratio	**95% C.I.**	***p***	**Odds ratio**	**95% C.I.**	***p***
IBS VS. NON-CASES						
Gender (M vs. F)	3.22	1.85-5.60	**<.001**	2.44	1.37-4.36	**.003**
Age	.98	.96-1.00	**.02**	.98	.97-1.00	.07
Acute illness type (GF vs. CG)*	3.45	1.75-6.67	**<.001**	2.22	1.11-6.67	**.02**
Intercept			.03			.02
CFS VS. NON-CASES						
Gender (M vs. F)	2.42	1.06-5.57	**.04**	1.50	.72-3.10	.28
Age	1.00	.97-1.03	.91	1.00	.97-1.02	.83
Acute illness type (CG vs. GF)	2.77	1.08-7.11	**.03**	1.48	.62-3.55	.38
Intercept			<.001			.001

Variables significant at the $p \leq .05$ level in bold
*** Odds ratios have been inverted to reflect the relative risk for GF vs. CG**

With regard to the development of CFS, illness type was again a significant risk factor for the development of CFS at three months, with the odds of those experiencing glandular fever going on to develop CFS almost three times that of those who had experienced *Campylobacter*. Similarly, gender was also a significant risk factor, with females more than twice as likely to develop CFS as males. These associations at three months for CFS were not as strong as had been found for IBS, however, and by six months neither the nature of the acute illness nor gender was significantly associated with CFS outcome. Age was not a significant risk factor for the development of CFS at either time point.

These results suggest that glandular fever and *Campylobacter* are important risk factors for the development of CFS and IBS respectively in the sub-acute phase of an illness; that is

up to three months post-acute illness. By six months following the acute illness, however, only *Campylobacter* illness type as opposed to glandular fever is a risk factor for the development of IBS, whereas glandular fever is no more of risk factor than *Campylobacter* in the development of CFS.

Comparison of infectious and psychological risk factors in the development of CFS and IBS post-infection.

In order to compare the relative odds of the nature of the acute infection with that of the psychological risk factors previously identified, multinomial logistic regression was used again. To investigate the impact the addition of the acute illness variable would make, outcome measured at three or six months was entered as the dependent variable (coded 0 for 'no IBS or CFS', 1 for 'CFS' and 2 for 'IBS') with acute illness (coded 1 for '*Campylobacter'* or CG, and 2 for 'glandular fever' or GF), age and gender (coded 1 for 'male' and 2 for 'female') measured at baseline again entered as covariates. Also included as covariates were the five factor scores developed earlier as summary psychological measures. 'No IBS or CFS' was once again nominated as the reference category and the results are presented separately for IBS and CFS.

Results for IBS outcome are summarised in Table 25 and demonstrate that for IBS, the inclusion of the psychological variables increased the odds ratio of the *Campylobacter* illness type. Once again, illness type was a significant risk factor in the development of IBS, with the odds of those experiencing *Campylobacter* five times that of those experiencing glandular fever at three months post-infection. While the odds had decreased somewhat by six months, *Campylobacter* cases still had over three times the odds of developing IBS in comparison to those who had experienced glandular fever.

Including illness type in the regression also had the effect of increasing the overall number of significant psychological variables as well. At three months, all the psychological variables were significant risk factors; including somatisation, psychological distress, illness perceptions, illness behaviour and all-or-nothing behaviour. While for most of these psychological variables higher scores were associated with the development of IBS, for illness behaviour lower levels were more likely to be found in those who developed IBS. By six months, however, the two illness-related behavioural factors were no longer significant risk factors in the development of IBS, whereas somatisation, psychological

distress and illness perceptions remained so, with higher levels of these variables associated with the development of IBS. Gender was also a significant risk factor at both time points with IBS cases 2-3 times more likely to be female.

Table 25. Multinomial logistic regression analyses according to IBS outcome at three and six months post-infection as a function of acute illness type, gender, age and psychological factor scores.

IBS vs. NON-CASES	THREE MONTHS			SIX MONTHS		
	Odds ratio	**95% C.I.**	***p***	**Odds ratio**	**95% C.I.**	***p***
Acute illness type (GF vs. CG)*	5.26	2.56-11.1	**<.001**	3.23	1.54-6.67	**.002**
Gender (M vs. F)	2.81	1.58-5.00	**<.001**	2.26	1.25-4.09	**.01**
Age	.98	.96-1.00	**.02**	.99	.97-1.01	.19
Somatisation	1.30	1.01-1.67	**.04**	1.37	1.05-1.80	**.02**
Psychological distress	1.56	1.22-2.00	**<.001**	1.50	1.12-1.92	**.01**
Illness perceptions	1.40	1.09-1.80	**.01**	1.34	1.02-1.78	**.04**
Illness behaviour	.66	.51-.86	**.002**	.80	.61-1.06	.12
All-or-nothing	1.52	1.19-1.94	**.001**	1.19	.92-1.53	.18
Intercept			.26			.07

Variables significant at the $p \leq .05$ level in bold.
*** Odds ratios have been inverted to reflect the relative risk for GF vs. CG**

In contrast, for CFS at both three and six months post illness (Table 26), a consistent pattern emerged whereby the odds of developing CFS following glandular fever as opposed to *Campylobacter* were reduced, when the nature of the infection was looked at in conjunction with the psychological variables. Acute illness type in the form of glandular fever as opposed to *Campylobacter* was not significantly associated with the development of CFS at three or six months when psychological factors were taken into account. Gender, illness behaviour and all-or-nothing behaviour were also not significant risk factors for the development of CFS at either time point. Instead, the psychological factors of somatisation, psychological distress and illness specific beliefs, were all significant risk factors at both three and six months post-illness, with higher levels of these variables associated with the development of CFS. These results indicate that these three psychological factor groupings were more important in the development of CFS at both

three and six months post illness than the nature of the infection, gender or illness-related behaviour at the time of acute illness.

Table 26. Multinomial logistic regression analyses according to CFS outcome at three and six months post-infection as a function of acute illness type, gender, age and psychological factor scores.

CFS VS. NON-CASES	THREE MONTHS			SIX MONTHS		
	Odds ratio	**95% C.I.**	***p***	**Odds ratio**	**95% C.I.**	***p***
Acute illness type (GF vs. CG)	1.64	.59-4.55	.34	.94	.35-2.50	.90
Gender (M vs. F)	2.04	.87-4.80	.10	1.32	.62-2.82	.48
Age	1.01	.97-1.04	.77	1.01	.98-1.03	.69
Somatisation	1.96	1.28-3.00	**.002**	1.69	1.15-2.49	**.01**
Psychological distress	1.95	1.35-2.82	**<.001**	2.52	1.77-3.60	**<.001**
Illness perceptions	1.76	1.20-2.60	**.004**	1.61	1.10-2.36	**.02**
Illness behaviour	.93	.61-1.42	.73	.98	.65-1.47	.91
All-or-nothing	.99	.69-1.42	.94	.77	.55-1.07	.12
Intercept			<.001			.003

Variables significant at the $p \leq .05$ level in bold.

In summary, the results of these analyses highlight the importance of psychological variables in the development of IBS and CFS and point to some important differences between the two conditions. Whilst the nature of the infection is important in the sub acute phase of the two illnesses, by six months this is only true of the impact of *Campylobacter* on IBS. It would appear that by six months psychological variables at the time of acute illness are more important in the development of CFS, than the physiological impact of having had glandular fever. In the development of IBS, despite the significance of the acute illness, psychological variables appear to strengthen the predictive ability of *Campylobacter* illness type by increasing the odds associated with the development of this condition.

Relative importance of psychological risk factors three and six months post-infection: Comparison of IBS vs. CFS.

The results of the previous section highlight some important differences in the role of psychological factors in the development of IBS and CFS. With the aim of clarifying these differences, binary logistic regression was used to determine whether any of the psychological variables could differentiate between those who went on to develop IBS as opposed to CFS. In order to do so, only cases of either CFS or IBS were selected, and non-cases filtered out. Outcome at three or six months was entered as the dependent variable (coded 1 for 'CFS' and 2 for 'IBS') and significance set at $p \leq .05$. Age, gender and the five factor scores were entered as covariates.

Table 27. Binary logistic regression analysis of CFS or IBS outcome at three months post-acute illness as a function of psychological factor scores, gender and age at the time of acute illness.

VARIABLE	CFS vs. IBS		
	Odds Ratio	**95% C I**	***p***
Gender (M vs.F)	1.80	.61-5.34	.29
Age	1.00	.97-1.04	.86
Somatisation	.56	.33-.95	**.03**
Psychological distress	.72	.46-1.12	.14
Illness perceptions	.70	.46-1.05	.09
Illness behaviour	.69	.39-1.19	.18
All-or-nothing behaviour	1.91	1.13-3.24	**.02**
Constant	1.14		.91

Variables significant at the $p \leq .05$ level in bold.

Results of these analyses are presented in Table 27, and indicate that the only significant risk factors for the development of CFS, as opposed to IBS, were somatisation and all-or-nothing behaviour, with cases of CFS more likely to have had higher levels of somatisation and lower levels of all-or-nothing behaviour than cases of IBS. Psychological distress, illness perceptions, and illness behaviour were unable to distinguish between the two groups, and nor could gender and age. These results indicate that whilst CFS and IBS share many similarities with regard to psychological and demographic risk factors, they also have some significant differences. Somatisation and all-or-nothing behaviour appear

to be the two psychological variables that can distinguish between the development of IBS and CFS at three months post-acute illness.

Results of the six month analysis indicate a slightly different pattern from that found at three months (Table 28). Once again all-or-nothing behaviour was a significant risk factor for the development of CFS as compared to IBS. However, at this point, psychological distress was also significant whereas somatisation (which had been significant at three months) was not. Cases of CFS at six months post-infection were more likely to have higher levels of psychological distress and lower levels of all-or-nothing behaviour than cases of IBS. Gender, age, somatisation, illness perceptions and illness behaviour were unable to differentiate between the development of IBS and CFS at this point.

Table 28. Binary logistic regression of CFS or IBS outcome six months post-acute illness, as a function of psychological factor scores, gender, and age at the time of acute illness.

VARIABLE	CFS vs. IBS		
	Odds Ratio	**95% C I**	***p***
Gender (M vs. F)	1.85	.66-5.19	.25
Age	1.01	.98-1.04	.59
Somatisation	.74	.46-1.19	.22
Psychological distress	.60	.39-.92	**.02**
Illness perceptions	.85	.53-1.34	.48
Illness behaviour	.92	.55-1.56	.77
All-or-nothing behaviour	1.60	1.05-2.42	**.03**
Constant	.76		.82

Variables significant at the $p \leq .05$ level in bold.

In summary, analyses in this section examined a range of infectious, demographic and psychological risk factors for IBS and CFS. These results suggest that whilst there are indeed some similarities in the risk factors for the development of these two conditions, there are also some key differences. In addition, the results suggest that the relative importance of some of these factors change over time. The acute illness of glandular fever appeared to be more important in the early stages of CFS, as were higher levels of somatisation. By six months, however, psychological distress at the time of acute infection appeared to be more closely associated with the development of CFS than either glandular fever illness type or somatisation. In contrast, *Campylobacter* illness type and all-or-

nothing behaviour appear to be more closely associated with IBS regardless of the time since infection. These key predictors also distinguish between IBS and CFS, with CFS predicted by somatisation and distress, whereas IBS is predicted by all-or-nothing behaviour.

10.5. IBS and CFS: Comparison of prevalence, demographics, disability, and health care utilisation in a post-infectious sample.

Hypothesis four: Cases of CFS will have lower prevalence rates, higher levels of associated disability and utilise health care more often than IBS cases, due to a greater emphasis on disability in the diagnostic criteria for this condition.

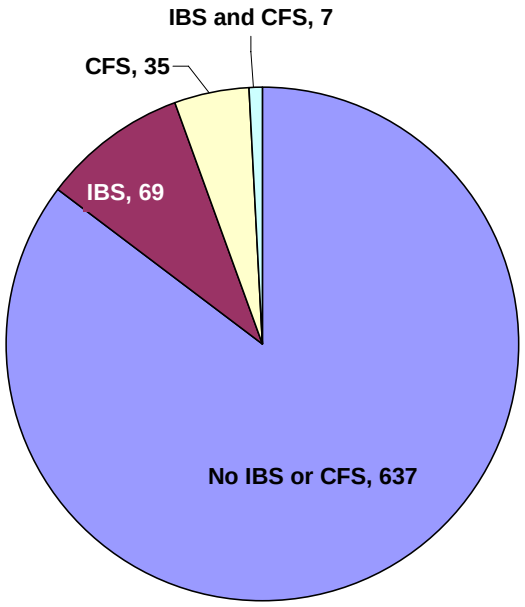
The previous section focused on the influence of psychological variables and the type of infection in the development of IBS and CFS. The combined total sample, regardless of acute infection, however, can also give us an indication of some of the more basic similarities and differences between the two syndromes, such as overall prevalence rates of each condition in a post-infectious sample, gender and age differences, levels of disability and health care utilisation. It is expected that the two conditions will differ with respect to a number of these variables because of differences in the way diagnostic criteria have been developed for the two conditions. The emphasis on disability criteria for CFS and the absence of such criteria for IBS suggests that CFS cases will be more severely disabled. This section aims to provide direct comparison between the two conditions as a means of testing this hypothesis.

In order to simplify presentation of results, only data from the six month follow-up are presented here. As in the previous section, the total sample after relevant exclusions, regardless of acute illness type, was used to identify cases of IBS and CFS six months post-infection, and those participants with neither condition. These three groups were then compared with regard to prevalence rates and patient characteristics, disability levels, and levels of health care utilisation. As before, the seven people with both IBS and CFS at six months follow-up were excluded from analyses so as to obtain mutually exclusive groups.

Prevalence, age and gender.

Rates of IBS and CFS regardless of infection type are presented in Figure 4, and indicate that by far the largest group were those non-cases who had not developed IBS or CFS (85.2%). The next largest group were those experiencing new onset IBS (9.2%), followed by those with new onset CFS (4.7%). Excluding the seven people with both IBS and CFS, comparisons were made between the remaining three groups with regard to age and gender. A one-way analysis of variance (ANOVA) was conducted to evaluate the relationship between group membership and age. Whilst non-cases (M=38.3, SD=17.6) were slightly older than both IBS cases (M=34.9, SD=18.8) and CFS cases (M=35.3, SD=15.6), the ANOVA was not significant, F (2,736) = 1.42 *p*=.24, indicating that there were no significant differences in the mean ages for each group.

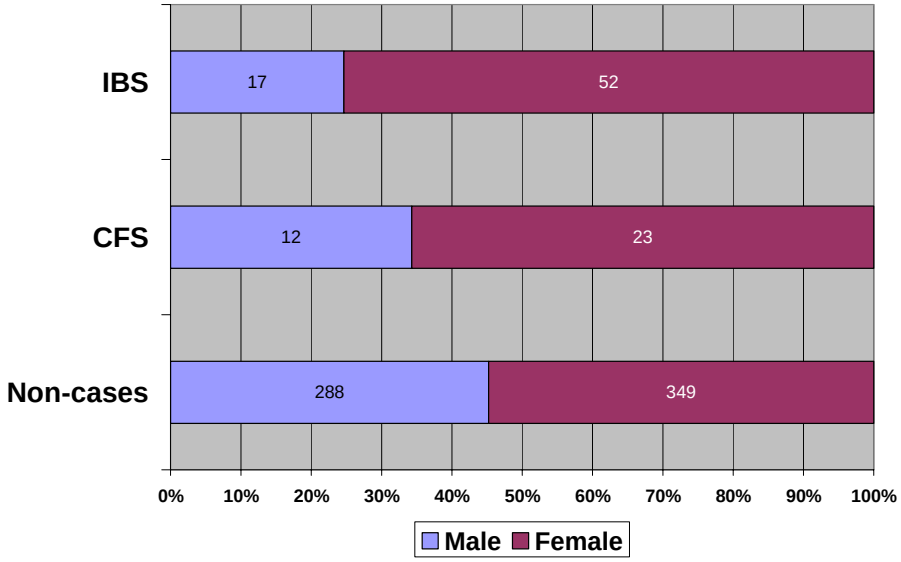
Figure 4. Frequency of IBS, CFS, and non-cases in the total sample (N=748).



A three by two contingency table was used to compare the three groups with regard to gender. Chi-square analysis indicated that group membership and gender were significantly associated (Pearson $\chi 2$ (2, n=741) = 11.85, p=.003). Results are reported in Figure 5 and indicate an increasing gender imbalance across groups. Non-cases had a relatively equal number of males and females, compared to the CFS group which had twice as many females than males. The IBS group had the greatest gender imbalance with three times as many females as males. Post hoc analyses comparing the individual groups found

that when comparing IBS cases with non-cases, there was a significant difference with IBS cases more likely to be female (Pearson $\chi 2$ (1, n=706) = 10.74, p=.001). However, the ratio of males to females was not significantly different when comparing IBS cases to CFS cases (Pearson $\chi 2$ (1, n=104) = 1.1, p=.30), or when comparing non-cases to CFS cases (Pearson $\chi 2$ (1, n=672) = 1.6, p=.21), indicating that these groups had more comparable gender ratios.

Figure 5. Gender ratio according to group membership six months post-infection.



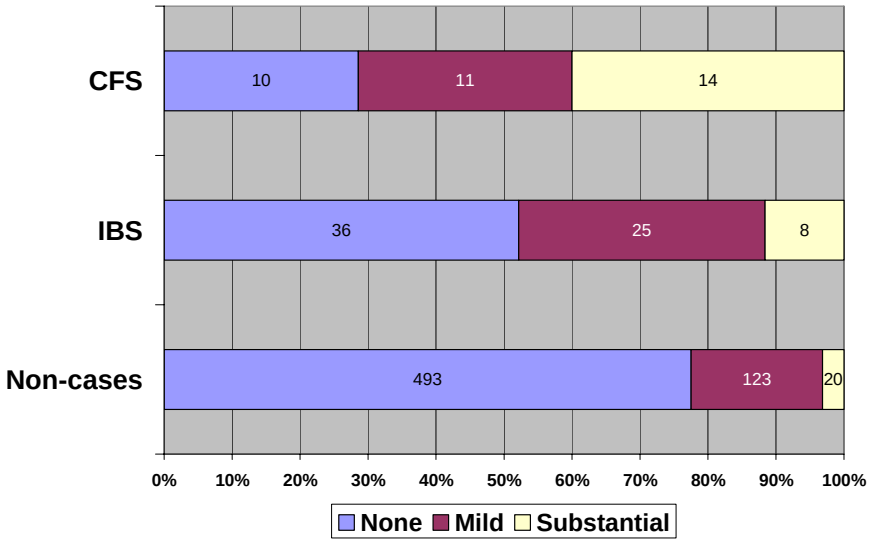
Disability levels and health care utilisation.

The various health-related measures completed at six month follow-up included: impairment related to the acute illness (WSAS total score), the MHI-5 measure of psychological wellbeing, the three CDC questions about general health (number of days experiencing poor physical health, number of days experiencing poor mental health, and inactive days due to poor physical or mental health), and the total number of occasions that health-related help was sought from any health professional in the past six months. Because the distributions of all these measures were skewed and on many of the measures a large number of respondents recorded zero, these variables were categorised and then compared across groups using non-parametric tests. In this way, the levels of disability and health care utilisation associated with each of the three groups (non-cases, CFS, and IBS) could be compared.

Scores on each measure were categorised with regard to published norms if available, or to reflect clinically meaningful criteria indicating no disability, mild disability and moderate to severe disability. Total scores on the WSAS of zero, one to ten, and 11 or higher, were categorised to reflect no impairment, mild impairment and substantial impairment respectively. In the case of the MHI-5 scores, raw scores were transformed according to accepted practice in order to obtain a score between 0 and 100. These scores were then categorised according to high levels of psychological wellbeing (71-100), medium levels of psychological wellbeing (51-70) and low levels of psychological wellbeing (0-50). The CDC and help-seeking scores were also categorised according to low, medium and high levels of poor health, inactivity and health care utilisation (equating to zero, 1-5, and more than five days or visits).

Three by three contingency tables and chi-square analyses were used to compare the groups on each of the categorical measures, and to determine whether there were significant differences between the groups. If the chi-square was significant, follow-up pairwise comparisons were conducted between non-cases and IBS cases, non-cases and CFS cases, and CFS and IBS cases to evaluate where the differences lay. The Holm's sequential Bonferroni method was used across each set of post hoc comparisons to control for Type I error at the .05.

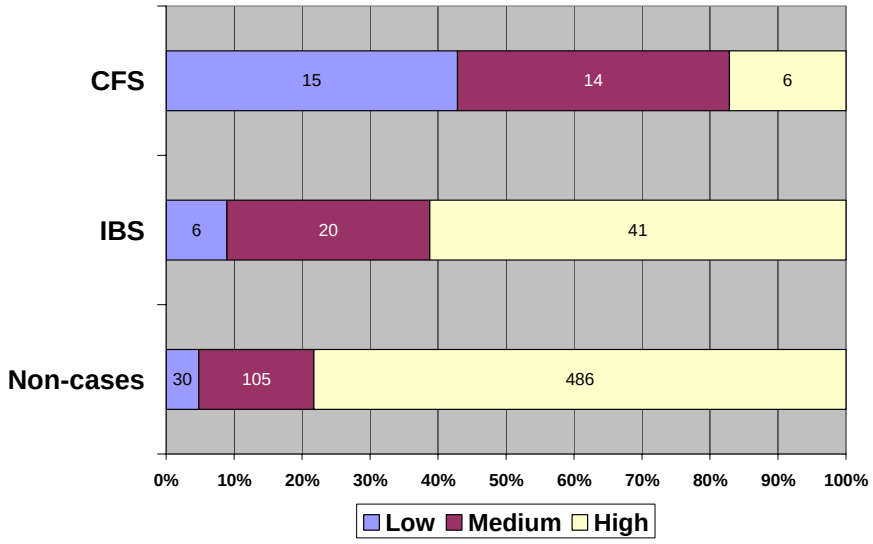
Figure 6. Frequency and percentage of cases according to level of WSAS impairment.



The WSAS total score at six month follow-up was used to determine the overall level of impairment or disability that participants attributed to their acute illness six months prior

(no impairment, mild or substantial impairment). Chi-square analysis indicated that there was a significant association between outcome and the three levels of impairment (Pearson χ^2 (4, n=740) = 109.42, p<.001). Results are presented in Figure 6, and indicate that only 3% of non-cases were reporting substantial impairment compared to 12% of IBS cases, and 40% of CFS cases. Post hoc analyses indicated that there were significant differences between all three groups with regard to their levels of impairment. CFS cases were significantly more likely to have higher levels of impairment than both non-cases (Pearson χ^2 (2, n=671) = 101.96, p<.001) and IBS cases (Pearson χ^2 (2, n=104) = 11.94, p=.003), whereas the IBS group was also more likely to have higher levels of impairment than non-cases (Pearson χ^2 (2, n=705) = 24.98, p<.001). The probability of a participant having substantial impairment was 13 times more likely if they were a CFS case as opposed to a non-case, four times more likely if they were an IBS case as opposed to a non-case, and three times more likely for CFS cases as opposed to IBS cases.

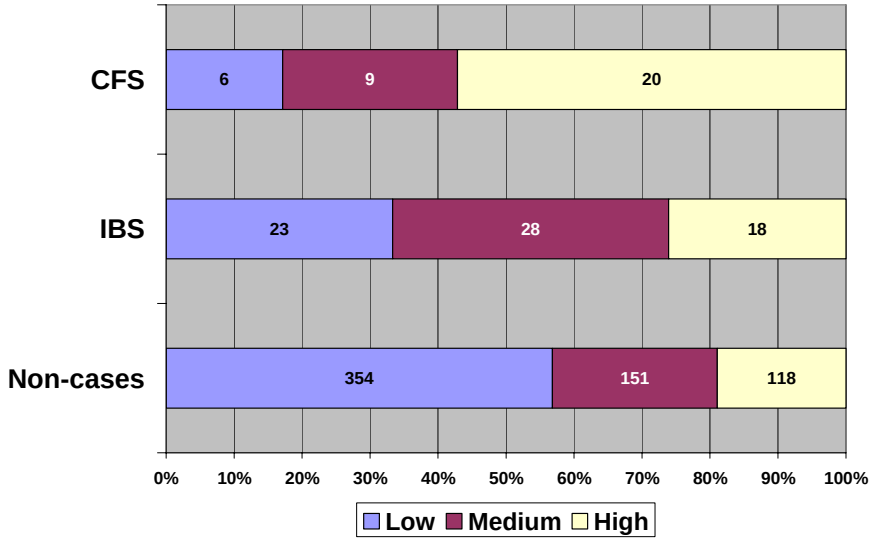
Figure 7. Frequency and percentage of cases according to level of MHI-5 psychological wellbeing.



The MHI-5 total score at six month follow-up was used to determine general mental health status six months following acute infection in order to compare the three groups with regard to their levels of psychological wellbeing (low, medium or high). Chi-square analysis indicated that there was a significant relationship between the three levels of psychological wellbeing and group membership (Pearson χ^2 (4, n=723) = 100.18, p<.001). Results are presented in Figure 7, indicating that 78% of non-cases were experiencing high levels of psychological wellbeing, compared to 61% of IBS cases and only 17% of CFS

cases. Post hoc analyses indicated that, once again, there were significant differences between all three groups on this measure. Non-cases were significantly more likely to be experiencing high levels of wellbeing in comparison to IBS cases (Pearson χ^2 (2, n=688) = 9.84, p=.01) and CFS cases (Pearson χ^2 (2, n=656) = 96.08, p<.001), whereas the IBS group also had a significantly higher levels of wellbeing than did the CFS group (Pearson χ^2 (2, n=102) = 23.23, p<.001). The probability of a participant experiencing high levels of psychological wellbeing was almost five times more likely if they were a non-case as opposed to a CFS case, almost four times more likely for IBS cases as opposed to CFS cases, and only 1.3 times more likely if they were a non-case as opposed to an IBS case. These results indicate that whilst IBS cases had significantly lower levels of wellbeing than non-cases, they were much closer to the levels found in non-cases than those for CFS cases.

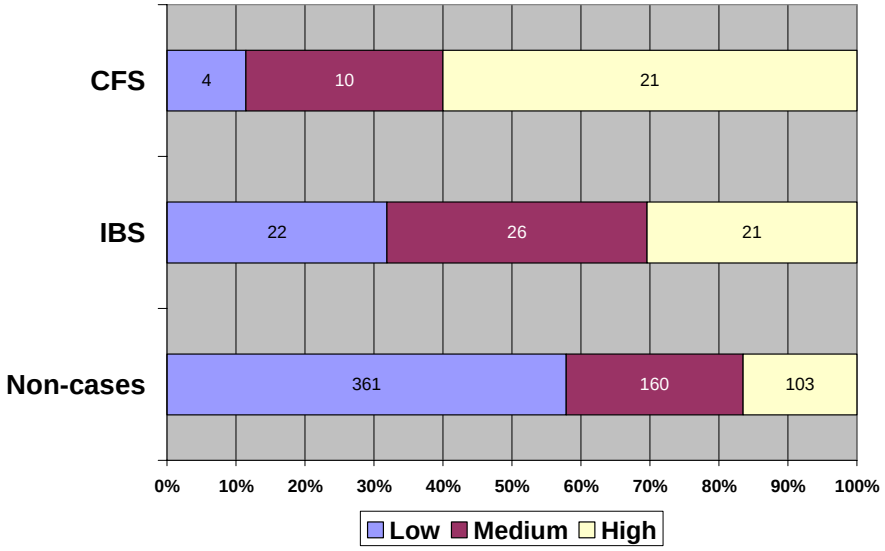
Figure 8. Frequency and percentage of cases according to level of poor physical health.



The CDC questions regarding general health at six month follow-up were also compared across groups. Scores were grouped according to the number of days participants had experienced poor physical or mental health, or inactivity due to poor physical or mental health (no days, one to five days, or more than five days). Chi-square analysis indicated that group membership was significantly associated with levels of poor physical health reported in the last month (Pearson χ^2 (4, n=727) = 45.04, p<.001). Results are reported in Figure 8 and demonstrate that 57% of the CFS cases had reported more than five poor physical health days in the previous month, compared to 26% of IBS cases and 19% of

non-cases. Post hoc analyses indicated that once again there were significant differences between all three groups. Cases of both IBS (Pearson χ^2 (2, n=692) = 14.32, p=.001) and CFS (Pearson χ^2 (2, n=658) = 32.63, p<.001) were significantly more likely to have reported high levels of poor physical health days in comparison to non-cases, whilst the CFS group were significantly more likely to report high levels of poor physical health days than the IBS group (Pearson χ^2 (2, n=104) = 9.76, p=.01). The probability of a participant experiencing more than five poor physical health days was 3 times more likely if they were a CFS case as opposed to a non-case, 2.2 times more likely for CFS cases as opposed to IBS cases and 1.4 times more likely if they were an IBS case as opposed to a non-case.

Figure 9. Frequency and percentage of cases according to level of poor mental health.

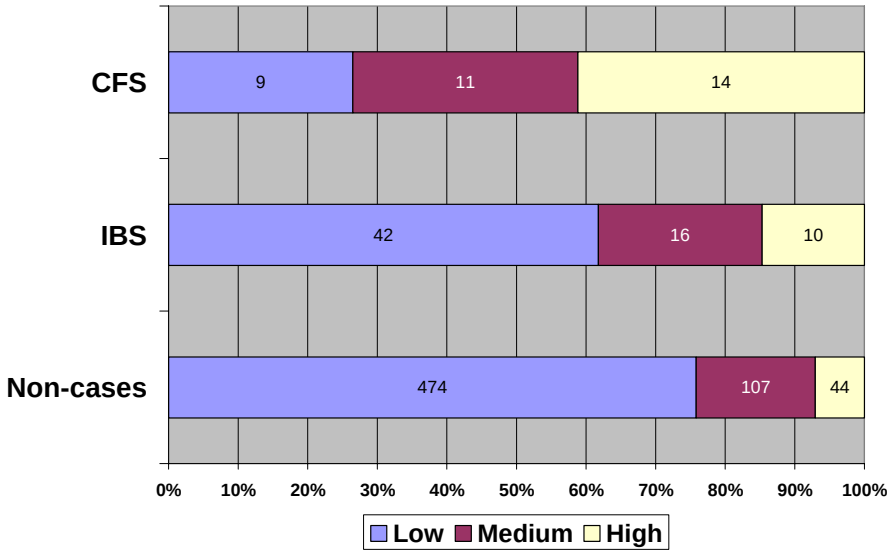


Frequencies and percentages for the level of poor mental health are reported in Figure 9 and the stepped pattern of disability according to group membership continues. Chi-square analysis indicated that group membership was once again significantly associated with levels of poor mental health (Pearson χ^2 (4, n=728) = 59.02, p<.001). The CFS group had 60% of cases reporting more than five days of poor mental health, compared to 30% of the IBS group, and only 17% of non-cases. Post hoc analyses indicated that both cases of IBS (Pearson χ^2 (2, n=693) = 17.67, p<.001) and CFS (Pearson χ^2 (2, n=659) = 46.32, p<.001) were significantly more likely to be experiencing high levels of poor mental health in comparison to non-cases, whilst the CFS group was more likely to do so than the IBS group (Pearson χ^2 (2, n=104) = 9.47, p=.01). The probability of a participant experiencing more than five poor mental health days was 3.5 times more likely if they were a CFS case

as opposed to a non-case, twice as likely for CFS cases as opposed to IBS cases and almost twice as likely if they were an IBS case as opposed to a non-case.

Frequencies for the level of inactivity due to poor physical or mental health are reported in Figure 10 and a similar pattern continues. Chi-square analysis indicated that there was a significant association between the level of inactivity and group membership (Pearson χ^2 (4, n=727) = 59.61, p<.001). Within the CFS group, 41% of cases were reporting more than five inactive days in the past month, compared to the IBS group which had only 15% of cases in this category and only 7% of non-cases. Once again, both IBS cases (Pearson χ^2 (2, n=693) = 7.68, p=.02), and CFS cases (Pearson χ^2 (2, n=659) = 57.60, p<.001) were more likely to be experiencing high levels of inactivity in comparison to non-cases, whilst the CFS group were also more likely to be reporting significantly higher levels of inactivity than the IBS group (Pearson χ^2 (2, n=102) = 13.06, p=.001). The probability of a participant experiencing more than five inactive days was almost six times more likely if they were a CFS case as opposed to a non-case, almost three times as likely for CFS cases as opposed to IBS cases and twice as likely if they were an IBS case as opposed to a non-case.

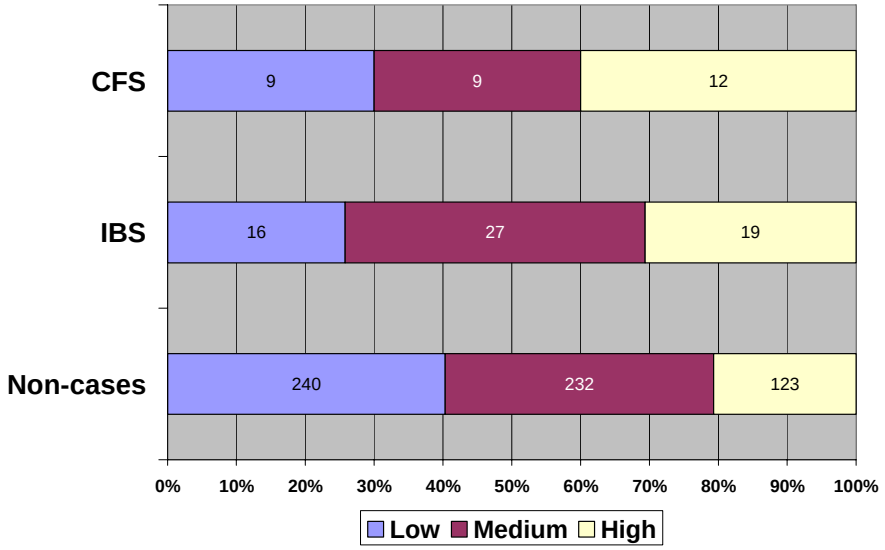
Figure 10. Frequency and percentage of cases according to level of inactivity due to poor physical or mental health.



Finally, the number of occasions that participants sought health-related advice from any health professional in the previous six months was compared across the three groups. Frequencies and percentages are reported in Figure 11, and indicate a slight variation on the previous results. Within the CFS group, 40% of cases reported more than five

occasions of health care utilisation, as compared to 31% of the IBS group and 21% of non-cases. Whilst chi-square analysis indicated that there was a significant association between group membership and the level of health care utilisation (Pearson χ^2 (4, n=687) = 11.44, p=.02), post hoc analyses using the Holm's sequential Bonferroni method failed to find any significant differences on these pairwise comparisons. These results indicate that although a similar pattern was found with health care utilisation as was found with disability levels, the frequency of health care utilisation was not significantly different across groups.

Figure 11. Frequency and percentage of level of help-seeking according to group membership.



In summary, a clear pattern emerges from these analyses with regard to levels of disability associated with IBS and CFS. Although both conditions had significantly higher levels of disability than was found in non-cases, this was much more pronounced for those with CFS than IBS. On all disability measures and the measure of psychological wellbeing, CFS cases had significantly higher levels of disability than IBS cases, consistent with the differences in criteria associated with each condition. Despite a significant association being found between levels of health care utilisation and the three groups, and a similar trend as was found for the disability measures, these pairwise differences did not reach significance. This would appear to indicate that despite higher levels of disability, the CFS and IBS groups did not have significantly higher levels of health care utilisation than those who were less disabled.

10.6. Comparing irritable bowel syndrome and chronic fatigue: Does removing disability-related criteria make a difference?

Hypothesis five: IBS will be more comparable with a wider group of fatigue cases that includes both CFS cases and those not significantly disabled by their fatigue, with respect to prevalence, the level of associated disability and health care utilisation. They will also be more comparable with regard to the psychological risk factors relevant to their development.

In previous sections, post-infectious IBS and CFS have been compared with regard to psychological risk factors, disability and health care utilisation. It is entirely possible that the only reason for these significant differences between CFS and IBS is simply that the CFS group is more disabled than the IBS group by definition alone. That is, CFS criteria specify disability whereas IBS criteria do not. By adding those participants experiencing significant fatigue that does not meet full criteria to the CFS group, and comparing this group with the IBS group, we can investigate whether this wider group is more comparable with the IBS group than the CFS group alone. In order to investigate this possibility further, a combined chronic fatigue group was created and compared with the IBS group with regard to age, gender, disability and the psychological factor scores used earlier to determine psychological risk factors for the development of IBS and CFS.

Additional analyses identified 34 subthreshold cases of chronic fatigue (CF) as defined in the methodology section (presence of moderate to severe physical and mental fatigue that is not due to excessive exercise and has been present for six months). These cases were then added to those with CFS to form a new CF/CFS group, and then compared with the IBS group. A total of 11 people met criteria for both CF/CFS and IBS and were excluded from these analyses. This left a total of 65 cases of CF/CFS and 65 cases of IBS for purposes of comparison. Due to the following section presenting results comparing subthreshold conditions with cases and non-cases, only those results specifically comparing the combined CF/CFS and IBS groups are presented here.

Patient characteristics.

ANOVA was used to compare age differences between the CF/CFS group, the IBS group, and the non-cases and found no significant difference, F (2,734) = 1.73, p=.18. Mean age and standard deviations are presented in Table 29. With regard to gender, a two by three contingency table and chi-square analysis indicated that while there was a significant difference in the gender ratio across the three groups (Pearson χ^2 (2, n=737) = 18.1, p<.001), post hoc tests found no significant difference in the gender ratio between CF/CFS and IBS (Pearson χ^2 (1, n=130) =.16, p=.69). As can be seen in Table 29, both CF/CFS (Pearson χ^2 (1, n=672) = 8.4, p=.004), and IBS groups (Pearson χ^2 (1, n=672) = 11.35, p=.001), had a significantly higher ratio of females to males than that found in non-cases, with approximately three times more females than males.

Table 29. Age and gender comparisons according to group membership six months post-infection.

	Age *M(SD)*	**Male** *%(n)*	**Female** *%(n)*
Non-cases	38.4 (17.6)	46.4% (281)	53.6% (325)
CF/CFS	35.2 (17.6)	27.7% (18)	72.3% (47)
IBS	35.4 (15.7)	24.6% (16)	75.4% (49)

Disability levels and health care utilisation behaviour.

Three by three contingency tables and chi square analyses using the categorical disability measures were again used to compare the non-cases, the CF/CFS group and the IBS group. Results are presented in Table 30 and demonstrate that, as was the case when comparing IBS and CFS cases, a similar pattern of disability emerges with the CF/CFS group more disabled than the IBS group who were in turn more disabled than the non-cases. Chi-square analyses indicated that there were significant differences at the p<.001 level across the three groups on all disability measures, including the MHI-5 and health care utilisation. Post hoc analyses specifically comparing the CF/CFS group and the IBS group indicated that they were also significantly different with regard to their levels of disability across all

analyses. Significant differences were found on the WSAS (Pearson χ^2 (2, n=130) = 7.08, p=.03), the MHI-5 (Pearson χ^2 (2, n=127) = 15.57, p<.001), the CDC measures of poor physical health (Pearson χ^2 (2, n=130) = 11.91, p=.003), poor mental health (Pearson χ^2 (2, n=130) = 9.74, p=.01), and inactivity related to poor health (Pearson χ^2 (2, n=128) = 11.83, p=.003). In all cases the CF/CFS group were more disabled than the IBS group as can be seen in the percentages found in Table 30. The levels of health care utilisation were not significantly different across these two groups, as had been the case when comparing the stricter definitions in the previous section (Pearson χ^2 (2, n=118) = 1.73, p=.42).

Table 30. Percentage and frequency of IBS cases, CF/CFS cases and non-cases according to level of disability measures.

Disability Measure	Non-cases	IBS	CF/CFS
WSAS level of impairment (total score)			
No impairment (0)	78.7% (476)	53.8% (35)	40% (26)
Mild (1-10)	18.8% (114)	35.4% (23)	30.8% (20)
Moderate (>11)	2.5% (15)	10.8% (7)	29.2% (19)
MHI-5 psychological wellbeing (total score)			
High (71-100)	79.9% (473)	61.9% (39)	29.7% (19)
Medium (51-70)	15.9% (94)	28.6% (18)	39.1% (25)
Low (0-50)	4.2% (25)	9.5% (6)	31.3% (20)
CDC poor physical health (no. of days)			
Low (0)	59.1% (350)	35.4% (23)	15.4% (10)
Medium (1-5)	23.6% (140)	38.5% (25)	30.8% (20)
High (>5)	17.2% (102)	26.2% (17)	53.8% (35)
CDC poor mental health (no. of days)			
Low (0)	60% (353)	32.3% (21)	13.8% (9)
Medium (1-5)	25.1% (149)	36.9% (24)	30.8% (20)
High (>5)	14.8% (88)	30.8% (20)	55.4% (36)
CDC inactivity (no. of days)			
Low (0)	77.3% (459)	64.1% (41)	37.5% (24)
Medium (1-5)	16.8% (100)	23.4% (15)	26.6% (17)
High (>5)	5.9% (35)	12.5% (8)	35.9% (23)
Health care utilisation (no. of occasions)			
Low (0)	41.9% (237)	26.7% (16)	20.7% (12)
Medium (1-5)	38.7% (219)	43.3% (26)	37.9% (22)
High (>5)	19.4% (110)	30% (18)	41.4% (24)

In summary, these results indicate that regardless of the differences in definition between IBS and CFS, the results regarding levels of disability and psychological wellbeing are very similar. Despite no significant differences in age and gender between the CF/CFS and IBS groups, they differ with regard to disability in the same manner as was found in the comparisons using the stricter definition of CFS. Taken together these results indicate that regardless of the differing levels of disability associated with the CFS criteria, the larger group of chronic fatigue cases in this study were still more disabled than IBS cases on a wide range of measures.

Psychological risk factors.

Despite the levels of associated disability being the same, it is still possible that the inclusion of those less disabled by their fatigue may highlight additional differences with regard to psychological risk factors for IBS and CFS. In order to compare the CF/CFS and IBS groups with regard to the relative importance of the psychological risk factors, these two groups were selected and binary logistic regression analysis used. As in the earlier analysis comparing the IBS and CFS groups, group membership at six months was entered as the dependent variable (coded 1 for 'CF/CFS' and 2 for 'IBS') and significance set at $p \leq .05$. The five factor scores were entered as covariates. On this occasion, age and gender were not entered as covariates as they were not significantly different across the two groups.

Table 31. Results of logistic regression analysis comparing CF/CFS group with cases of IBS at six months post-acute illness, as a function of psychological factor scores at the time of acute illness.

VARIABLE	CF/CFS vs. IBS		
	Odds Ratio	95% C I	*p*
Somatisation	.67	.44-1.01	.06
Psychological distress	.62	.43-.89	**.01**
Illness perceptions	.97	.69-1.37	.86
Illness behaviour	.88	.58-1.35	.57
All-or-nothing behaviour	1.48	1.03-2.14	**.04**
Constant	1.27		.25

Variables significant at the p≤ .05 level in bold.

Results are presented in Table 31, and like the disability measures, are identical to that found when comparing the IBS and CFS groups. Two of the psychological factor scores were significant risk factors regarding outcome with respect to these two groups, including psychological distress which had higher levels in the CF/CFS group and all-or-nothing behaviour which had higher levels in the IBS group. In summary, the same two psychological variables were also able to distinguish between IBS and the more inclusive definition of chronic fatigue. This indicates that the broader definition still differentiates fatigue patients from IBS patients on levels of psychological distress and all-or-nothing behaviour, and that these differences are not simply a function of differing disability criteria.

10.7. IBS, CFS and their subthreshold conditions: Comparison of prevalence, demographics, disability and psychological risk factors.

Hypothesis six: Patients experiencing bowel dysfunction or chronic fatigue post-infection that does not meet the threshold for established criteria, will nonetheless have a similar profile to cases of IBS and CFS with regard to psychological risk factors. They will be distinguished according to the relative importance of these psychological variables and the extent of disability.

With the exception of the previous section, all analyses to this point have compared non-cases with cases of IBS and CFS defined according to current recognised criteria. Although these definitions are well accepted and widely used in research, there are also large numbers of patients who experience significant fatigue and/or bowel disturbance that do not meet criteria for IBS and CFS. The large sample size in this study made it possible to compare those individuals experiencing subthreshold conditions with their labelled counterparts. In light of the findings in the previous section following the inclusion of those individuals experiencing significant fatigue, it is worth considering these subthreshold groups separately. By comparing these groups to the IBS and CFS cases, we can determine whether they meaningfully differ from their diagnosed counterparts or not. Once again, in order to simplify analyses, group membership was determined at six month

follow-up. Because non-cases have been extensively compared with cases in previous sections, comparisons were made between cases and subthreshold groups only, and those without significant fatigue or bowel symptomatology were filtered out from these analyses.

The total sample after relevant exclusions, regardless of acute illness type was used to identify cases and subthreshold cases of both CFS and IBS, as defined in the methodology section. Subthreshold cases of CFS were labelled 'chronic fatigue' (CF) and were defined according to the following criteria; presence of moderate to severe physical and mental fatigue, which was not due to excessive exercise, and had been present for six months. Subthreshold cases of IBS were labelled 'disturbed bowel function' (DBF) and were defined according to the following criteria; frequent abdominal pain with one or more related bowel symptom, or two or more symptoms of disturbed defecation more than 25% of the time.

Two separate sets of analyses (one each for bowel and fatigue groupings) compared two groups (subthreshold cases and cases) on prevalence, demographics, disability levels and psychological risk factors. In order to ensure that the bowel results were not influenced by those with severe fatigue, all cases of CFS were removed from the bowel analyses. This amounted to 24 participants with CFS (7 in the IBS group and 17 in the DBF group). For similar reasons, the 11 participants with IBS were excluded from the fatigue analyses (7 in the CFS group and 4 in the CF group).

Prevalence.

Prevalence rates for the bowel symptom groupings were determined by separating out those experiencing IBS from those with disturbed bowel function to ensure there was no overlap. As expected, all those with IBS also met the criteria for DBF. A similar process with fatigue symptoms found that whilst the majority of CFS cases met the CF criteria, there were five people who did not. Further investigation of these five participants indicated that whilst meeting criteria for either the Fukuda or British definitions of CFS, they had answered negatively to one of the questions required for CF. For example, one case was not reporting mental fatigue but met all requirements for the Fukuda criteria, whereas others reported that their fatigue occurred after excessive exercise but still met all requirements for the British criteria. Because these five cases were regarded as

classification anomalies rather than being qualitatively different, they were retained in the fatigue analyses.

Table 32. Frequency and percentage of bowel and fatigue symptoms in post-infectious sample according to standard criteria and subthreshold conditions.

Group membership (Six months post-infection)	Frequency (% of total sample)
Bowel symptoms	
Disturbed bowel function (DBF)	121 (17.1%)
Irritable bowel syndrome (IBS)	69 (9.8%)
Fatigue symptoms	
Chronic fatigue (CF)	30 (4.5%)
Chronic fatigue syndrome (CFS)	35 (5.2%)

Prevalence rates for each set of symptom groupings are set out in Table 32. As expected given the larger numbers of participants entering the study with *Campylobacter* and the generally higher rates of IBS in the general population, the largest group were those experiencing disturbed bowel function, followed by IBS. Of note, however, are the relative proportions; whilst there were slightly fewer participants with CF than with CFS, there was almost double the amount of participants with DBF than there was with IBS.

Demographics.

Age and gender were compared to determine if there were any significant differences between the symptom groupings. Separate one-way analyses of variances (ANOVA) were conducted to evaluate the relationship between bowel or fatigue symptom groups at six month follow-up, and age. The independent variable, group membership, included two levels in each analysis (DBF and IBS; or CF and CFS); the dependent variable was age. Whilst the DBF group were slightly younger (M=34.5) than the IBS group (M=35.3), and the CFS group were slightly younger (M=34.9) than the CF group (M=35.5), neither the bowel ($F(1,188) = .12$ $p = .89$) nor the fatigue ($F(1,188) = .12$ $p = .89$) group comparisons were significant, indicating that the two subthreshold groups were a similar age to those who were cases.

Table 33. Gender ratio according to group membership.

Group membership (6 mths post-infection)	Males	Females
Bowel symptoms		
Disturbed bowel function (DBF)	35.5% (43)	64.5% (78)
Irritable bowel syndrome (IBS)	24.6% (17)	75.4% (52)
Fatigue symptoms		
Chronic fatigue (CF)	20.0% (6)	80.0% (24)
Chronic fatigue syndrome (CFS)	34.3% (12)	65.7% (23)

In order to compare the ratio of males to females according to the symptom groupings, separate two by two contingency tables were used to compare the relevant bowel and fatigue groups using two variables; gender (male and female) and symptom grouping (DBF and IBS for the bowel analysis; CF and CFS for the fatigue analysis). Results are reported in Table 33 and indicate that all groups had a higher ratio of females to males. The CF group had four times as many females as males, and the IBS group had three times as many. Both the CFS group and the DBF group had a similar ratio with almost twice as many females as males. Chi-square analyses indicated that gender and symptom groupings were not significantly associated for both bowel (Pearson χ^2 (1, n=190) = 2.42, p=.12) or fatigue analyses (Pearson χ^2 (1, n=65) = 1.65, p=.20), indicating a similar gender ratio between cases and subthreshold groups.

In summary, neither age nor gender differed significantly between cases and subthreshold cases for either bowel or fatigue groupings. These results indicate that both bowel and fatigue subthreshold groups are similar demographically to IBS and CFS cases respectively.

Disability levels and health care utilisation.

As in previous sections, in order to determine if there were significant differences between the two fatigue groups and the two bowel groups, two by three contingency tables and chi-square analyses were used to compare the categorical disability measures and health care utilisation at six month follow-up. All measures were categorised in the same manner as previously. The following two sections summarise the results; firstly for fatigue symptom

groups and then for bowel symptom groups. Frequencies and percentages for all measures according to fatigue group are reported in Table 34 and bowel symptom group in Table 35.

Fatigue-related symptom groupings

As reported in Table 34, 40% of CFS cases were reporting substantial impairment, compared to 17% of CF cases. Chi-square analysis indicated, however, that there was no significant difference between the two fatigue groups with regard to level of impairment on the WSAS (Pearson χ^2 (2, n=65) = 5.50, p=.06), although it is possible that the smaller cell sizes for the CF group may have affected this result, which did approach significance.

Table 34. Percentage and frequency of participants by level of disability according to fatigue-related symptom groupings six months post-infection (n=65).

Disability Measure	CF	CFS
WSAS level of impairment (total score)		
No impairment (0)	53.3% (16)	28.6% (10)
Mild (1-10)	30% (9)	31.4% (11)
Substantial (>11)	16.7% (5)	40% (14)
MHI-5 psychological wellbeing (total score)		
High (71-100)	44.8% (13)	17.1% (6)
Medium (51-70)	37.9% (11)	40% (14)
Low (0-50)	17.2% (5)	42.9% (15)
CDC poor physical health (no. of days)		
Low (0)	13.3% (4)	17.1% (6)
Medium (1-5)	36.7% (11)	25.7% (9)
High (>5)	50% (15)	57.1% (20)
CDC poor mental health (no. of days)		
Low (0)	16.7% (5)	11.4% (4)
Medium (1-5)	33.3% (10)	28.6% (10)
High (>5)	50% (15)	60% (21)
CDC inactivity (no. of days)		
Low (0)	50% (15)	26.5% (9)
Medium (1-5)	20% (6)	32.4% (11)
High (>5)	30% (9)	41.2% (14)
Health care utilisation (no. of occasions)		
Low (0)	10.7% (3)	30% (9)
Medium (1-5)	46.4% (13)	30% (9)
High (>5)	42.9% (12)	40% (12)

With regard to psychological wellbeing as measured by the grouped MHI-5 scores, Table 34 reports that 45% of those in the CF group were experiencing high levels of psychological wellbeing, compared to only 17% of those with CFS. Chi-square analysis indicated that the CFS group was significantly more likely to be experiencing lower levels of wellbeing than the CF group (Pearson χ^2 (2, n=64) = 7.44, p=.02). The probability of a participant experiencing low levels of psychological wellbeing was 2.5 times more likely for those in the CFS group compared to the CF group.

The CDC questions regarding general health at six month follow-up were compared between fatigue symptom groups in a similar manner as before. Chi-square analysis indicated that there was no significant difference between the CFS and the CF groups with regard to the three levels of poor physical health (Pearson χ^2 (2, n=65) = .94, p=.63), levels of poor mental health (Pearson χ^2 (2, n=65) = .73, p=.69), or levels of inactivity (Pearson χ^2 (2, n=64) = 3.82, p=.15). In addition, Chi-square analysis indicated that there was no significant difference in the level of health care utilisation in the previous six months between the CFS group and the CF group (Pearson χ^2 (2, n=58) = 3.66, p=.16).

In summary, when comparing results for the CFS group and the subthreshold fatigue group, there was no significant difference on any of the disability measures, with the exception of the levels of MHI-5 measured psychological wellbeing, on which the CFS group had lower levels than the CF group. These results indicate that apart from levels of psychological distress, the subthreshold group had similar levels of disability as the CFS group. Whilst the CF group generally had lower levels of disability and health care utilisation, there was no significant difference between the CF and CFS groups on these measures.

Bowel-related symptom groupings

A similar set of analyses were carried out with the bowel-related symptom groupings and the results of two by three contingency table analyses for each categorical disability measure are set out in Table 35 according to bowel symptom group. As reported in Table 35, 12% of cases of IBS were reporting substantial impairment as measured by the WSAS, compared to 7% of those in the subthreshold DBF group. Chi-square analysis indicated that there was no significant association between the three levels of impairment and bowel symptom group (Pearson χ^2 (2, n=190) = 2.56, p=.28), indicating that the subthreshold

cases were experiencing similar levels of acute illness associated disability as those who met criteria for IBS. Similarly, there was no significant difference between the IBS group and the subthreshold group in the levels of MHI-5 psychological wellbeing (Pearson χ^2 (2, n=186) = 0.67, p=.72).

Table 35. Percentage and frequency of participants by level of disability according to bowel-related symptom groupings six months post-infection (n=190).

Disability Measure	DBF	IBS
WSAS level of impairment (total score)		
No impairment (0)	63.6% (77)	52.2% (36)
Mild (1-10)	28.9% (35)	36.2% (25)
Substantial (>11)	7.4% (9)	11.6% (8)
MHI-5 psychological wellbeing (total score)		
High (71-100)	66.4% (79)	61.2% (41)
Medium (51-70)	24.4% (29)	29.9% (20)
Low (0-50)	9.2% (11)	9.0% (6)
CDC poor physical health (no. of days)		
Low (0)	42.7% (50)	33.3% (23)
Medium (1-5)	30.8% (36)	40.6% (28)
High (>5)	26.5% (31)	26.1% (18)
CDC poor mental health (no. of days)		
Low (0)	46.6% (55)	31.9% (22)
Medium (1-5)	25.4% (30)	37.7% (26)
High (>5)	28.0% (33)	30.4% (21)
CDC inactivity (no. of days)		
Low (0)	67.8% (80)	61.8% (42)
Medium (1-5)	22.0% (26)	23.5% (16)
High (>5)	10.2% (12)	14.7% (10)
Health care utilisation (no. of occasions)		
Low (0)	31.2% (34)	25.8% (16)
Medium (1-5)	42.2% (46)	43.5% (27)
High (>5)	26.6% (29)	30.6% (19)

The CDC questions regarding general health at six month follow-up were again compared, this time between the two bowel symptom groups. Table 35 demonstrates similar levels of poor physical health in the IBS and DBF groups, with over 25% of both the IBS and DBF

groups reported more than five days of poor physical health in the past month. Chi square analysis indicated that there was no significant difference between the IBS group and the DBF group with regard to levels of poor physical health (Pearson χ^2 (2, n=186) = 2.19, p=.33), poor mental health (Pearson χ^2 (2, n=187) = 4.57, p=.10), and levels of inactivity in the subthreshold group as compared to the IBS group (Pearson χ^2 (2, n=186) = 1.03, p=.60). Finally, the level of health care utilisation in the previous six months was compared according to bowel symptom group. Chi-square analysis indicated that again there were no significant differences between the two groups with regard to the number of participants seeking health-related help (Pearson χ^2 (2, n=171) = .64, p=.73).

In summary, those with IBS and subthreshold bowel conditions did not significantly differ from each other with regard to any six month outcome measure in this study. This indicates that those with subthreshold bowel conditions experience similar levels of psychological distress, disability and health care utilisation as those with diagnosable IBS.

Comparison of fatigue and bowel groups

Because of the large number of analyses already undertaken comparing the relevant groups on disability measures, further comparisons of the bowel and fatigue sub-groupings were not conducted. It is possible however, to get some indication of fatigue and bowel group similarities and differences by comparing the two sets of analyses. In general, the fatigue and bowel group analyses resulted in very similar patterns, with cases and their subthreshold counterparts having similar levels of disability and health care utilisation.

Comparing results from the two sets of contingency tables (Table 34 and Table 35), however, clearly indicate that the levels of disability are much higher in those with CFS than those with IBS. For example, with regard to levels of poor mental health, 60% of CFS cases were reporting more than five days of poor mental health, in comparison to 30% of IBS cases. Similarly, the subthreshold fatigue group was reporting higher levels of disability than both the subthreshold bowel group and the IBS group on most measures also. Using the same measure, 50% of CF cases were reporting this level of poor mental health compared to 26% of subthreshold bowel cases. This pattern is repeated on all measures with CFS cases most disabled, followed by the CF group, whereas the IBS and DBF groups appear to be much closer to the levels reported by non-cases in the previous sections than either the CF or CFS groups.

Importance of the psychological factor scores as risk factors for IBS, CFS and their subthreshold conditions.

Given that the subthreshold bowel and fatigue conditions bear many similarities to their diagnosed counterparts with regard to the disability measures in this study, one final set of analyses were conducted to determine whether the relative importance of psychological risk factors were also the same. In order to determine whether there were any differences in the significance of psychological risk factors between cases of IBS and CFS and their subthreshold conditions another set of binary logistic regression analyses were conducted. Data from the six month follow-up were used, and only the psychological factor scores analysed, in order to simplify results and aid comparison.

As in previous sections, the relative importance of each psychological factor was analysed using the factor scores, this time in two logistic regression analyses with the significance level set at $p \leq .05$; one for bowel-related symptoms and one for fatigue-related symptoms. The five factor scores, age and gender were entered as covariates in each analysis. For the first analysis, the two groups of fatigue at six months were entered as the dependent variable (coded 1 for 'CF', and 2 for 'CFS'). In the second analysis, the three groups of bowel symptoms were entered as the dependent variable (coded 1 for 'DBF', and 2 for 'IBS').

Fatigue-related symptom groupings

Results for the analysis comparing the subthreshold group of CF to the CFS group are presented in Table 36. When comparing the CF group with cases of CFS, the only factor able to discriminate between them was psychological distress at the time of acute infection, with lower levels of this variable associated with the CF group. This, in conjunction with the significant difference in MHI-5 levels six months post-infection, would appear to indicate that level of psychological distress is an important distinguishing factor between threshold and subthreshold categories of fatigue. None of the other psychological factor scores, age or gender, were able to discriminate between cases and subthreshold cases of chronic fatigue in the development of these conditions.

Table 36. Results of binary logistic regression analysis comparing fatigue symptom groupings at six months post-acute illness, as a factor of psychological factor scores, gender, and glandular fever symptoms at the time of acute illness.

VARIABLE	CFS vs. CF		
	Odds Ratio	95% C. I.	*p*
Gender (M vs. F)	.34	.09-1.33	.12
Age	1.00	.96-1.04	.84
Somatisation	1.03	.53-2.03	.92
Psychological distress	1.80	1.06-3.07	**.03**
Illness perceptions	1.54	.80-.2.94	.20
Illness behaviour	1.09	.57-2.08	.79
All-or-nothing	.71	.39-1.28	.25
Constant	5.49		.28

Variables significant at the p≤ .05 level in bold.

Bowel-related symptom groupings

Results for the analysis comparing the IBS group with the subthreshold DBF group are presented in Table 37. When comparing the ability of these variables to differentiate between IBS and DBF, none of the psychological factor scores, gender or age were able to do so. This result indicates that with regard to psychological risk factors, the threshold and subthreshold categories of bowel symptoms are very similar.

Table 37. Results of binary logistic regression analysis according to bowel symptom groupings at six months post-acute illness, for psychological factor scores, gender, and *Campylobacter* symptoms at the time of acute illness.

VARIABLE	IBS vs. DBF		
	Odds Ratio	95% C. I.	*p*
Gender (M vs.)	1.67	.83-3.36	.15
Age	1.01	.99-1.03	.57
Somatisation	1.22	.89-1.69	.22
Psychological distress	1.05	.78-1.43	.74
Illness perceptions	1.13	.83-1.52	.45
Illness behaviour	.80	.57-1.11	.17
All-or-nothing	1.15	.84-1.56	.39
Constant	.20		.04

Variables significant at the p≤ .05 level in bold

Overall these results appear to indicate that the cut-off levels for cases and non-cases of IBS and CFS may be somewhat arbitrary. Results from this study indicate that subthreshold conditions share many similarities with regard to demographics, disability levels and psychological risk factors. Of all the comparisons conducted, only levels of psychological distress at initial infection and those six months later were able to distinguish between CF and CFS. No other fatigue comparison was significant, and no variable was able to distinguish between IBS and subthreshold levels of disturbed bowel function.

Chapter 11.

Discussion of specific hypotheses investigated.

This thesis aimed to consolidate the evidence for the cognitive-behavioural models of IBS and CFS and to examine the appropriateness and utility of the current classification systems for these conditions. The use of a prospective design enabled the exploration of a range of possible predisposing variables, precipitants and early perpetuators hypothesised to contribute to the development of each condition. The recruitment of two separate acute illness samples made it possible to compare the results for each condition and to examine the role of the type of infection in the development of two distinct conditions. The results have been presented according to the six major hypotheses developed to investigate selected aspects of these two broad areas. In this chapter, the results pertinent to each of these hypotheses will be summarised and discussed in the context of the relevant literature identified in the introductory chapters of this thesis. The final chapter will then examine the limitations of this study, before discussing the theoretical and practical implications of the findings, and directions for future research.

Hypothesis 1:

Psychological variables operationalised from the cognitive-behavioural model of IBS will be significantly associated with the development of IBS following gastroenteritis.

The first hypothesis in this study was developed to examine the evidence for specific aspects of the cognitive-behavioural model of IBS. The assessment and follow-up of an acute gastroenteritis sample enabled the prospective investigation of a range of cognitive, behavioural and emotional variables relevant to the development of this condition. Overall, the results provided good support for the cognitive-behavioural conceptualisation of this condition, with a number of individual variables significantly related to the development of IBS. More specifically, predisposing variables found to be risk factors for

IBS included anxiety and perfectionism, however, contrary to expectations, depression and somatisation were not significantly related to the development of this condition. Perceived stress was also strongly associated with IBS at both three and six months, lending weight to the conceptualisation of this variable as an important precipitant of IBS. With regard to perpetuators, the belief that the acute illness would last a long time and an all-or-nothing behavioural pattern were both significant risk factors. In contrast, higher levels of limiting behaviour, such as resting, were found to be protective.

In order to compare the relative importance of these individual variables, multivariate analyses were conducted using five factors generated from a series of factor analyses. The factors consisted of groups of correlated variables that were conceptually related to each other. As expected, each of the individual negative illness beliefs as measured by the IPQ clustered together on one factor and were labelled negative illness perceptions. Similarly, those scales measuring the number of acute illness symptoms clustered together to represent a general somatisation factor. The behavioural variables (limiting, practical and social support seeking) also grouped together with the exception of all-or-nothing behaviour; confirming results from the preliminary study which indicated that this variable was measuring a construct independent of the other behavioural measures. The last factor grouped together a range of cognitive and emotional variables all reflecting aspects of psychological distress: anxiety, depression, perceived stress and negative perfectionism.

By using these factors, multivariate analysis was able to provide further weight to the findings of the univariate analysis. In these analyses, higher levels of psychological distress, illness perceptions and all-or-nothing behaviour were all significant predictors of IBS at both three and six months. The significance of the factor measuring psychological distress was expected, as the anxiety, perfectionism and perceived stress variables were all associated with IBS in the univariate analyses; however, it may also indicate that subthreshold levels of depression are important when considered in the presence of these other variables. In contrast, the significance of the illness perception factor was unexpected, given that the only individually significant variable in the univariate analysis was the belief the acute illness would last a long time. This result indicates that the existence of a range of negative beliefs may collectively represent a more powerful risk factor than any one belief on its own; that is, the greater the number of negative illness beliefs, the higher the associated risk.

The significance of the all-or-nothing behavioural factor in the multivariate analysis is particularly striking. This factor included only one individual subscale of the BRIQ, yet it remained significant when competing with the other factors made up of several variables. The other behavioural subscales incorporated in the illness behaviour factor represented a significant risk factor at three months post-infection. Lower levels on this factor were significantly associated with the development of IBS, once again reflecting the independence of all-or-nothing behaviour from the more traditional coping behaviours such as resting or seeking practical and emotional support. This factor was the only one to indicate a potential protective factor in the development of IBS, indicating that a degree of limiting and support seeking are beneficial at the time of acute illness. Somatisation was the only factor found to be unrelated to the development of IBS in all the analyses.

These results provide support for the overall conceptualisation of the cognitive-behavioural model of IBS, in that a wide range of psychological factors were related to the predisposition, precipitation and early perpetuation of this condition. Although these variables were all measured at the time of acute infection and prior to the development of IBS, this study has conceptualised them according to their impact as potential predisposing, precipitating and perpetuating variables as suggested by the cognitive behavioural model. For example, anxiety, depression, and perfectionism were all non-illness related and measured according to the preceding weeks prior to infection. In this respect, they were considered predisposing variables, and perfectionism in particular viewed as a stable personality construct. Questions regarding illness related behaviours and beliefs, in contrast, were specifically related to the acute infection, but seen to reflect likely responses to ongoing symptoms. These variables were therefore considered as early perpetuators.

With regard to the investigation of more specific aspects of the cognitive behavioural model, there was both confirmation and conflict with previous empirical findings. The investigation of predisposing variables with regard to IBS, for example, revealed some interesting results. Negative perfectionism, proposed in the model as a risk factor for IBS, had not been studied prospectively before. This study demonstrated that it was indeed significantly associated with IBS at three months, but not at six months. This result indicates that the predisposition to IBS may be mediated by cognitions regarding unrealistic personal expectations, but that the influence of this variable may fade over time.

Anxiety was also a strong predictor at both time points, in keeping with other studies of post-infectious IBS (Dunlop, Jenkins, Neal et al., 2003; Gwee et al., 1996).

In contrast, depression and somatisation were not significant predictors of IBS in any of the analyses conducted. The rates of depression in this group were in fact very similar to those reported by non-cases, lending weight to studies that have found anxiety to be more important than depression in the development of IBS (Creed, 1999; Haug et al., 2002; Sykes et al., 2003). These results contrast, however, with the findings of Gwee and colleagues (1996) who demonstrated that anxiety, depression and somatisation were all associated with the development of IBS three months following infection, and those of a later study which found that both anxiety and depression were important risk factors for IBS (Dunlop, Jenkins, Neal et al., 2003).

This discrepancy may be the result of different sampling methods used in these studies. The first study investigated a cohort (n=139) of patients admitted to hospital with gastroenteritis (Gwee et al., 1996). Very few cases of gastroenteritis are admitted to hospital and the factors associated with hospitalisation itself (such as the severity of their physical illness and a possible lack of social support available to care for them in the community) may have resulted in a sample of more distressed patients. The second study had a similar recruitment method to the current study, but had a much smaller sample size (Dunlop, Jenkins, Neal et al., 2003). Of 103 new onset IBS cases three months post-*Campylobacter*, only 30 were recruited into the study. Participants were asked to attend a physical examination, including sigmoidoscopy and rectal biopsy as well as complete questionnaires. Given the invasive nature of these examinations, it is possible only those more concerned about their ongoing symptoms would have participated, which may also have impacted on the results regarding depressive symptoms.

One other aspect of the influence of depression and anxiety in these post-infectious studies warrants mention. Both previous studies reported that the levels of depression and anxiety found to be predictive of IBS were below traditional cut-off scores associated with categorical diagnoses (Dunlop, Jenkins, Neal et al., 2003; Gwee et al., 1996). The mean level of anxiety found in the IBS cases in the current study was in accordance with these findings. Whilst non-cases had a mean score on the HADS anxiety scale that was just under 5, the IBS cases were just under 7, still below the recommended cut off score of 8 for a possible case of anxiety disorder using this scale. Like the earlier studies, these

findings suggest that it is important not to overstate the role of psychopathology in IBS. Conversely, it is also important that subthreshold levels of anxiety in this condition are not ignored with regard to their impact on the development of IBS.

Based on these results, it is possible that the emphasis on categorical measures of depression and somatisation in the predisposition to IBS may have been simplistic. The importance afforded these variables in the cognitive-behavioural model of IBS may have been the result of investigating samples of more severely affected cases as described above. Other methodological problems discussed in the introduction, such as the reliance on cross-sectional research with participants with well established conditions may also have influenced the results. Alternatively, depression and somatisation may be more relevant as perpetuators of IBS rather than as predisposing variables.

In contrast to the large amount of research considering predisposing variables such as depression, possible precipitants identified in the cognitive-behavioural model have had less empirical attention. As outlined in the introduction, stress has been considered an important precipitant of IBS in this model, however the empirical evidence has been inconsistent. Several studies have measured the impact of life events on the development of IBS, with no definitive findings; however, the concept of perceived stress has not previously been investigated. The robustness of the association between perceived stress and IBS in the current study contrasts with the ambiguous findings of those studies using life events as a measure of stress. These results indicate that the individual's interpretation of stressful events may be more important than the nature of those events in the development of IBS.

With regard to potential perpetuators of IBS, the significance of the illness perceptions factor is in accordance with the only other prospective study of functional gastrointestinal disorders (FGID) to measure illness perceptions (Parry, Corbett et al., 2003). This study found that new onset FGID cases had reported higher levels on subscales measuring beliefs about timeline and consequences at the time of acute illness, compared to non-cases. The same findings were displayed in those who had a FGID prior to infection. Both groups were reporting beliefs about their acute illness, however, as mentioned earlier it is possible that such beliefs may be associated with a more consistent pattern of thinking that is applied to other symptoms and illnesses. The findings from the current study and that of Parry and colleagues indicate that negative beliefs about an acute illness are indeed

important in the early perpetuation of IBS, and may also be maintained over time. Further investigation is required, however, to determine if this is the case. It will also be important to determine how malleable these beliefs are in treatment, and whether a change in beliefs can impact positively on outcome.

The investigation of behavioural factors in the early perpetuation of IBS has been a neglected area, with very few studies examining the impact of specific behaviours in the development of this condition. In an attempt to address this issue, the current study considered a range of behaviours using a measure specifically designed for this study. Despite being largely drawn from the literature regarding CFS, the acute illness behaviours measured in this study were also important predictors of IBS. All-or-nothing behaviour was found to be one of the most consistent risk factors for the development of IBS across time and different analyses, whereas lower levels of limiting and practical support seeking were also associated with greater risk. These results are an important contribution to the cognitive-behavioural model. In contrast to previous studies that have considered bed rest at the time of acute illness as a potential barrier to recovery (Allen et al., 1999; Sharpe & Wessely, 1998), this study found that in relation to the development of IBS, limiting behaviour, along with seeking practical support, was actually protective. Instead the most important behavioural risk factor appeared to be the oscillating pattern, that is, limiting behaviour in conjunction with bursts of activity, rather than limiting behaviour on its own.

Although behaviours such as these have not previously been examined with regard to IBS specifically, the current findings lend weight to previous speculation that individuals with functional somatic syndromes have a need to be self-sufficient whilst also pleasing others (Van Houdenhove, 2005). It is possible that recovery from acute gastroenteritis is impaired by prematurely returning to previous activity levels before completely well, thereby increasing the risk of IBS. The current results relate to behaviour at the time of acute illness, but it is also possible that these behaviours, like the negative illness beliefs discussed earlier, represent patterns that endure over time. Individuals with an all-or-nothing response to acute illness may have a similar approach to IBS symptoms, and therefore be at greater risk of perpetuating those symptoms. In order to clarify the role of behaviour in the perpetuation of IBS, the findings from the current study need to be replicated in future prospective studies and extended to cross-sectional studies of those who have experienced IBS for some time. Longitudinal studies may give some indication of the changes that occur in behaviour over the course of a condition like IBS. In the

meantime, it is clear that the impact of behaviour on the development of IBS warrants more attention than has previously been afforded it.

The analyses conducted in this part of the study also gave an opportunity to investigate other variables relevant to the development of IBS, including gender, symptom severity and the prevalence rate of post-infectious IBS in a New Zealand sample. Gender was a consistently significant predictor in almost all analyses undertaken, with females twice as likely to go on to develop IBS as males. This result is consistent with that found in primary care and community samples (Muller-Lissner et al., 2001) and again highlights the gender imbalance associated with this condition. A higher *Campylobacter* symptom total was also found to be significantly associated with IBS at both three and six months post-*Campylobacter*. Although this measure does not provide the same objectivity as clinical measures of severity, it does however support findings from previous studies regarding the influence of acute illness severity in the development of post-infectious IBS.

This study also provided an opportunity to replicate findings from previous research regarding the prevalence of IBS following gastroenteritis. As presented in Chapter 6, previous studies indicated that between 9 and 17% of gastroenteritis cases go on to develop IBS. Prevalence rates in the current study were largely consistent with these findings; with 16% of the *Campylobacter* sample categorised as new cases of IBS at three months, and 11% at six months. Direct comparison with other studies, however, indicated that this six month rate was considerably lower than the original hospital in-patient studies which reported rates around 20-30% (Gwee et al., 1999; McKendrick & Read, 1994), and slightly lower than the 17% of new onset cases reported by a recent prospective study carried out in the community (Parry, Stansfield et al., 2003). Only one study reported a much lower rate of IBS of 4.4% (Rodriguez & Ruigomez, 1999), but this relied on general practitioner diagnosis of IBS and it has been estimated that only around 45% of patients who meet criteria for IBS present to their doctors (Drossman et al., 1993).

Two factors may have contributed to the lower prevalence rates in the current study. The studies with the highest prevalence rates were conducted with hospital inpatients. Such samples are likely to have been experiencing a greater severity of illness, a factor previously associated with the development of IBS. It is also possible that the conservative method of determining exclusion criteria in this study impacted on prevalence rates. Patients were excluded based on self-reported bowel-related illnesses or a prior diagnosis

of IBS, meaning that new cases of IBS may have been inadvertently excluded due to participants mislabelling their symptoms. In contrast, Parry and colleagues (2003) used a more thorough self-report questionnaire of FGID symptoms experienced prior to acute illness, which may have more accurately reflected the numbers of prior IBS cases than the method employed in this study.

The prevalence rates for IBS in this study, however, are consistent with a study conducted using hospital employees following a gastroenteritis outbreak (Ji et al., 2005). At three months the rate of IBS in this study was 20%, at six months it was 11%, and at 12 months, 15%. This study also provided information about the developmental course of IBS for the 12 months of the study. Of the 15 IBS cases at 12 months post-infection, only 5 had met criteria at all three time points, with the remainder experiencing a fluctuating course. In the current study, of the 65 cases of IBS at six months, only 49 had been cases at three months, meaning that only 8% of the total number of *Campylobacter* cases met IBS criteria at both time points. The results of the current study and that of Ji and colleagues, confirm the fluctuating course associated with IBS.

Hypothesis 2:

Psychological variables operationalised from the cognitive-behavioural model of CFS will be significantly associated with the development of CFS following glandular fever.

The second hypothesis in this study was developed in order to confirm the role of particular psychological variables in the predisposition to, precipitation of and early perpetuation of CFS. An acute illness sample already established as being at risk for the development of CFS (glandular fever) was used as a means of prospectively investigating these aspects of the cognitive-behavioural model of this condition. The results provided strong support for this model, with a large number of individual cognitive, emotional and behavioural variables found to be significant risk factors for the development of post-infectious CFS.

Predisposing variables identified as significant risk factors included anxiety, depression and somatisation. Interestingly, perfectionism was not a significant predisposing variable in any of the analyses. Similarly, perceived stress, a variable proposed to be an important

precipitant of CFS in the cognitive-behavioural model of this condition, was not significantly associated with the development of CFS in this study. With regard to potential early perpetuators of the condition, a range of negative illness beliefs including timeline, illness coherence and emotional representations were all significantly related to the development of CFS. The only behavioural measure to be identified as a risk factor for CFS, however, was all-or-nothing behaviour, which was significant at three months post glandular fever only. Neither limiting behaviour nor support seeking were significantly associated with CFS at either time.

The multivariate analysis using the groups of variables identified during factor analysis provided an insight into the relative importance of these variables. Three months following glandular fever, somatisation, psychological distress and illness perceptions were all significant predictors of CFS, supporting the findings of the individual analyses. These findings indicate that in the very early stages of CFS, a range of variables are implicated in the development of this condition, and that together they provide a good assessment of risk. The influence of the behavioural variables at this point, however, appeared to be outweighed by these other psychological factors, indicating that behaviour associated with an acute illness may be less important in the development of CFS than are other cognitive and emotional factors.

By six months, however, the impact of illness perceptions outweighed all other factors. These results indicate that negative illness beliefs may be one of the most important psychological variables in the cognitive-behavioural model of CFS. They confirm previous findings from a prospective study that found illness perceptions to be important predictors of CFS (Candy et al., 2003), and support those studies that have found illness beliefs to be associated with the perpetuation of CFS (Moss-Morris, 1997). Taken together, these results suggest that although the attention given to emotional states in the development of CFS is more warranted for this group than it is for IBS, cognitive variables in the form of illness perceptions may be of equal or greater importance.

The result that perceived stress was not a significant predictor in any analysis using the post glandular fever sample was unexpected, and was in contrast to its strong effect in the IBS sample. Earlier in this thesis (see Chapter 5) it was hypothesised that the failure of previous studies to find a clear relationship between stress and the development of CFS was due to retrospective designs and the measurement of life events rather than perceptions

of stress (Bruce-Jones et al., 1994; Candy et al., 2003; Lewis et al., 1994). However, the current results instead supported these earlier findings and suggest that the emphasis on stress as a precipitating variable in the cognitive-behavioural model of CFS could now be challenged. It is possible that this result may be specifically related to the use of a post–infectious sample or again related to the type of measure; however, it would appear that the evidence for life events and perceived stress as risk factors for the development of CFS is not as strong as the model would suggest.

Negative perfectionism, another important feature of the cognitive-behavioural model of CFS, was not found to be a significant predisposing variable in this study either. This is the first study to prospectively examine the role of perfectionism in CFS. Previous studies that have measured this concept in relation to fatigue have done so retrospectively and in non-clinical fatigued samples (e.g. Magnusson et al., 1996). Despite limited evidence regarding this concept, perfectionism has been considered both anecdotally and theoretically as an important aspect of CFS (Surawy et al., 1995). Based on the results from this study, it would appear that perceived stress and negative perfectionism may have been overemphasised in the cognitive-behavioural model of CFS. However it does not rule out the possibility that they may be important as perpetuating factors in CFS, and further research should aim to clarify this. It is also possible that the choice of measure (i.e. the focus on negative perfectionism) in this study may have influenced this result and future prospective studies using other measures may clarify the role of perfectionism further.

The evidence was stronger for other variables thought to predispose individuals to this condition. In accordance with earlier prospective studies of chronic fatigue and CFS (Wessely et al., 1995; White et al., 2001), somatisation, depression and anxiety were all found to be significant risk factors for the development of CFS, although these factors were most significant in the three month analyses. Only depression was a significant risk factor for CFS at both three and six months post-infection. As was found in the IBS sample, however, many of the patients who went on to develop CFS were not cases of anxiety or depressive disorders. This was despite the CFS cases' mean score being much closer to the levels that would indicate a subthreshold or diagnosable clinical condition. At both three and six months, the CFS group scored just under 9 for anxiety and approximately 7 for depression on the HADS.

In accordance with the findings for IBS these results suggest that using strict cut off levels on the HADS or the existence of categorical disorder may not necessarily identify those at risk of IBS or CFS. What may be more important as a risk factor for these conditions is the presence of distress or depressed mood rather than psychopathology per se. These findings provide further support for a recent study examining the use of depression rating scales in CFS, which advocated for a cut off of 8 on the HADS to determine clinically relevant levels of depressed mood in this population (Henderson & Tannock, 2005). Similarly, those who scored higher on somatisation in this sample may not necessarily meet criteria for somatisation disorder.

Finally, the results regarding behavioural factors identified as key perpetuators in the cognitive-behavioural model of CFS were also mixed. Despite the theoretical attention given to the role of behaviour in this model, few studies have looked carefully at actual behaviour in the development of CFS. Results from this study indicate that such influences in the development of CFS may not be as relevant as might have been expected based on the theoretical model. Although higher levels of all-or-nothing behaviour at the time of acute illness were found to be significantly associated with the development of CFS three months post illness, no other behavioural measures were significant.

The lack of association between limiting behaviour in the development of CFS in particular was unexpected, as this was the strongest risk factor identified in a recent review of post-infectious CFS (Candy et al., 2002). The current study used a self-report measure of this behaviour, in contrast to other studies which have used more objective indicators such as the number of days of bed rest or days off work, and this may account for the differing result. However, it may also reflect the fact that previous studies have looked at limiting behaviour in isolation, rather than as a component of the oscillating pattern encompassed by the all-or-nothing measure developed for this study. It is possible that limiting behaviour on its own may not be as relevant in the early stages of the development of CFS, as it is when found in conjunction with an overactive pattern. Taken together, these results suggest that the role of behaviour at the time of acute illness may not be as relevant to the development of CFS as previously assumed.

As was the case with the gastroenteritis sample, the glandular fever sample also provided an opportunity to investigate other variables relevant to the development of CFS, including gender, symptom severity and the prevalence rate of post-infectious CFS in a New Zealand

sample. Of particular interest were the results for the influence of gender. Whilst there were significantly more women developing CFS at six months than men, this difference was not evident at three months. In addition, gender was not a significant risk factor for CFS in any of the univariate analyses, a finding that was in direct contrast to the IBS results where gender was consistently important. Unfortunately, gender had to be removed from the six month multivariate analysis due to the very small number of male cases, meaning that it was impossible to be sure that it was not a significant risk factor at this point. Overall, however, these results indicate that the impact of gender may be less important than the impact of psychological variables in the development of CFS.

Previous studies that have looked at the influence of gender on post-infectious fatigue have also had mixed results. One study that used both the British and the Fukuda criteria found that gender was not a significant predictor of fatigue (White et al., 2001). However, two other studies using less strict definitions of CFS demonstrated that there was indeed an association between the development of fatigue and female gender six months following infection (Buchwald et al., 2000; Candy et al., 2003). Candy and colleagues (2003) found that females had almost four times the risk than that for males for the development of fatigue as defined by the Chalder fatigue scale. Buchwald and colleagues (2000) found that those who reported a failure to recover from glandular fever after six months, were more than three times more likely to be female than those who had recovered. Together with the results of the current study, the findings from these studies suggest that gender influences in CFS may be related to varying definitions of fatigue. Whilst the association with gender is significant in a wider group of fatigue cases, this association is not so robust in the group defined by current CFS criteria.

Severity of illness, as indicated by the number of glandular fever symptoms and the prescription of antibiotics, was not significantly different between CFS cases and non-cases. In contrast to this result, however, the number of glandular fever symptoms was a risk factor for the development of CFS at three months when analysed in conjunction with the psychological variables in the multivariate analysis. This suggests that illness severity may be important in the early stages of CFS development after all, but only in conjunction with certain psychological risk factors. Alternatively, participants' ratings of their glandular fever symptoms may reflect an underlying somatising factor, a possibility that is supported by the factor analysis, which grouped together the number of glandular fever symptoms with that of non-glandular fever symptoms.

Prevalence rates were also able to be compared with those from previous studies. The rates of CFS in this study (9.4% at three months, and 8% at six months) are comparable to the only other prospective study to use the Fukuda criteria, who found a rate of 9% six months following infection (White et al., 1998). As expected, the rate was much higher than the 1.3% to 4.4% found in those studies which examined the development of CFS following an upper respiratory tract infection (Wessely et al., 1995; White et al., 1998). The use of different measurement methods and criteria in other post-infectious studies, however, make further direct comparisons difficult.

One final aspect of the post-infectious CFS sample is worth comment. Preliminary analyses indicated that cases of CFS, like the IBS cases, had higher mean scores in comparison to non-cases on almost all variables. However, a simple comparison of mean scores between IBS cases, CFS cases and non-cases in each group indicated that, with only a few exceptions, non-cases in the glandular fever group had similar or higher levels on almost all psychological variables than the IBS cases. CFS cases had generally higher levels than all other groups. As mentioned in the results section, these differences in mean scores across the two illness samples may reflect the differential impact of the two acute illnesses, with glandular fever having a greater psychological impact than *Campylobacter*. An alternative explanation, however, is that psychological factors may play more of a role in the development of glandular fever itself than it does in the development of an illness such as *Campylobacter*. That is, those experiencing the clinical illness of glandular fever may be more vulnerable to the development of that illness following infection with the Epstein Barr virus (EBV) **as a result of** these psychological factors, even prior to the development of CFS.

An early study of the seroconversion of EBV in military cadets lends weight to this possibility (Kasl et al., 1979). Kasl and colleagues monitored when cadets became infected with EBV for the first time and found that those who had a high level of motivation combined with poor academic achievement were significantly more likely to develop clinical glandular fever than those who did not. Taken in the context of the findings from the current study, these results suggest that the development of clinical signs following infection with EBV is indeed influenced by psychological factors and may explain why the non-cases in the glandular fever group had higher levels of psychological variables than would be expected in comparison to non-cases in the *Campylobacter* sample.

Hypothesis 3:

The type of acute illness will be significantly associated with the development of specific functional somatic syndromes; however the impact of this physiological risk factor will lessen over time in favour of the psychological risk factors.

The first two hypotheses concentrated on the psychological aspects of the cognitive-behavioural model with regard to the development of IBS and CFS. However, the cognitive-behavioural model also incorporates the influence of physiological variables, and this hypothesis aimed to consider the impact of one such variable; acute infection. As expected, almost twice as many *Campylobacter* cases at three months developed IBS compared to glandular fever cases, whereas twice as many glandular fever cases developed CFS compared to *Campylobacter* cases. Whilst these differences were less striking at six months, a similar pattern continued.

Multinomial logistic regression indicated that acute illness type was a significant risk factor for IBS at both time points, with *Campylobacter* cases 2-3 times more likely to have developed IBS than glandular fever cases. With regard to CFS, however, glandular fever illness type was a significant predictor of the development of CFS at three months only. In other words, *Campylobacter* infection placed an individual at greater risk of IBS six months post-infection than glandular fever did, whereas glandular fever was no more of a risk factor for CFS at six months post-infection than was *Campylobacter*. These results indicate that physiological factors in the form of infection may be more important in IBS than in CFS, and that the influence of *Campylobacter* remains significant to the development of IBS well past the acute phase of the initial illness.

An even more interesting pattern emerged when the psychological predictors were added to the regression analyses. Results of multinomial analyses comparing CFS cases with non-cases found that the influence of the acute illness type was overshadowed at both three and six months post-infection by the same psychological factors found significant when the acute illness type was not considered. Higher levels of somatisation, psychological distress, and illness perceptions at the time of acute illness were more important risk factors for CFS following infection than was the type of acute illness. These psychological variables were also more important than the influence of gender. These findings suggest

that the existence of glandular fever prior to the development of CFS adds little to the risk associated with the psychological variables, particularly at six months post illness.

The results for IBS suggested a different pattern. Comparing cases of IBS with non-cases in the total sample indicated that both *Campylobacter* infection type and gender remained significant predictors of IBS at both three and six months post-infection. Comparison with previous analyses looking at the relevance of psychological factors and illness type separately indicated that the inclusion of psychological variables actually strengthened the predictive ability of the *Campylobacter* infection type, rather than diluted it. This finding was in direct contrast to the results for the impact of glandular fever on CFS. Odds ratios indicated that the risk associated with *Campylobacter* increased when measured in conjunction with the psychological variables, at both three and six months following illness. For example, when analysed without the psychological variables the risk of developing IBS following *Campylobacter* was 2-3 times that of glandular fever. Following the inclusion of the psychological variables the risk associated with *Campylobacter* jumped to 3-5 times that of glandular fever.

The inclusion of *Campylobacter* infection in the analysis also strengthened the association between negative illness beliefs and the development of IBS six months post-infection. The relationship between the two behavioural factors, somatisation and psychological distress remained unchanged, with all four factors significant predictors of IBS at both three and six months post-infection. The differences between the two regression analyses with and without infection type provide preliminary support for the proposal in the cognitive-behavioural model that psychological and biological variables can influence each other in the development of IBS. These results indicate that not only is *Campylobacter* an important risk factor for the development of IBS, but that when considered in conjunction with psychological factors, the risk is increased.

Campylobacter gastroenteritis and glandular fever are two very different illnesses, with very different physiological processes and symptom profiles. They do bear some similarities, however. They are both moderate to severe infections which have no standard medical treatment and generally necessitate a longer period of convalescence than would be expected for more minor viral and bacterial infections. Both illnesses are generally left to self-resolve and have no specific treatment. In this sense, the two illnesses provided an excellent opportunity to investigate whether the development of post-infectious IBS and

CFS is specific to the distinct infectious illness, related to a general illness factor such as severity, or instead influenced primarily by psychological variables. The results presented in this section suggest that there is a complex interplay of psychological and physiological risk factors for each of these conditions, with particular individual risk factors and combination of risk factors important at different times across the two conditions.

The role of infection has previously been investigated in a range of studies looking at IBS and CFS (e.g. Candy et al., 2003; Mearin et al., 2005; Parry, Stansfield et al., 2003; White et al., 1995). These studies had confirmed the importance of specific infectious precipitants such as glandular fever and gastroenteritis in the development of CFS and IBS respectively. A small number of studies had also used these samples to prospectively examine the influence of both psychological and infectious variables in the development of these conditions. Two studies examining post-infectious IBS reported that both psychological factors (such as anxiety and depression) and physiological factors (chronic inflammation and mucosal changes) were able to predict the development of IBS three months post-infection (Dunlop, Jenkins, Neal et al., 2003; Gwee et al., 1999). The current study supports and expands on these findings in several ways. First, it seems likely that the predictive power of both physiological and psychological variables in IBS continue to six months following infection. Second, rather than one set of risk factors being more influential than others, it appears that the existence of both physiological and psychological risk factors can combine to increase that risk.

More specifically, with regard to CFS, the current findings were largely consistent with previous studies. Two studies examined baseline physiological variables (such as temperature, clinical examination and cortisol levels) and psychological measures (such as anxiety, depression, life events) as risk factors for the development of fatigue (Buchwald et al., 2000; Candy et al., 2003). Both found that of the few physiological factors that predicted ongoing fatigue, their effect was only significant at 2 or 3 months post-infection. By six months post-infection, psychological predictors were more important indicators of fatigue in each of these studies. The use of standardised diagnostic criteria to determine fatigue caseness in the current study can now confirm the relevance of these findings to a more traditional CFS population.

No previous study, however, has examined the same psychological measures in two separate illness samples that were already established as known risk factors for the

development of two distinct functional somatic syndromes. In this respect, it is worth noting that 5% of the total sample in this study developed CFS following *Campylobacter*, a rate much higher than would be expected given the population prevalence for CFS in the community, which is less than 1% (Ranjith, 2005). Similarly, 8% of those with glandular fever went on to develop IBS six months after their illness. This compares with the previously reported 0.3% general population rate of IBS (Rodriguez & Ruigomez, 1999) and the 1.9% of community controls developing IBS that has been reported in one other prospective study (Parry, Stansfield et al., 2003). These same studies have reported relative risks or odds ratios of 11.9 and 10.1, in contrast to the 2.2 odds ratio found in the current study for the development of IBS following *Campylobacter* as opposed to glandular fever.

These results indicate that, contrary to expectations, glandular fever cannot be ruled out as a risk factor for the development of IBS, whereas *Campylobacter* may also be a risk factor for CFS. The lower odds ratios in this study may reflect the common impact across all participants of having a moderate to severe infection. In this context, the finding that the specific risk associated with glandular fever in the development of CFS lessens over time, whilst the association between *Campylobacter* and IBS does not, becomes all the more significant. Without a community control group to compare the relative odds, however, it is difficult to explore this notion further. Future research should include a community based healthy control group, in addition to the two illness groups. Despite the possibility that glandular fever may put people at risk of developing IBS, however, it is important to place this risk into context; that is, the risk associated is still significantly less than that related to *Campylobacter*.

In summary, the results of analyses investigating the first three hypotheses of the study indicate that a range of infectious, demographic and psychological variables are important in the development of IBS and CFS. Examining the results as a whole, it is clear that there is good evidence for the overall concept proposed by the cognitive-behavioural models of these two conditions. Risk factors for the development of both IBS and CFS were found in each of the domains of cognition, behaviour, emotion and physiology. In many cases, these factors bore similarities across the two conditions studied. However, there were also some important differences in both the nature and relative importance of those variables. There was also evidence to suggest that the importance of various predictors changed over time, in accordance with the cognitive-behavioural model's premise that the variables that

predispose an individual to a condition, or those that precipitate it, may vary from that which perpetuate the condition.

Hypotheses 4 and 5:

IBS and CFS will differ with respect to prevalence, disability, health care utilisation and psychological risk factors; and these differences will be the result of the differential emphasis on disability in the criteria for each condition.

The remaining hypotheses in this study aimed to build on the comparative aspects of the research conducted so far, by further investigating features relevant to the classification of the functional somatic syndromes. The fourth and fifth of these hypotheses aimed to shed further light on the 'one or many' debate discussed in Chapter 2. Differences between non cases, IBS and CFS with regard to prevalence, disability, health care utilisation and the previously identified psychological risk factors were analysed first; followed by a consideration of whether these differences were the result of variations in the development of their definitions.

It was hypothesised that there would be fewer CFS cases and that they would have higher levels of disability and health care utilisation than IBS cases. In effect, it was hypothesised that the CFS group would represent a more severely affected group due to the requirements regarding disability that are included in the CFS criteria but are absent for IBS. As expected, at six months post-infection, there were twice as many IBS cases than CFS cases. With regard to demographic variables, the only significant difference was that IBS cases were more likely to be female compared to non-cases. There were no significant differences between any other group comparison with regard to gender, and there were no significant differences in age between the three groups.

When comparing disability levels across the three groups, a clear pattern emerged from all measures; as expected, CFS cases were significantly more disabled than IBS cases. IBS cases, however, were also significantly more disabled than non-cases in this sample, although the extent of that disability did not reach the levels found in cases of CFS. A similar pattern occurred with levels of health care utilisation. Although there appeared to be a trend in the data, there was no significant difference across groups, indicating that the

IBS group was just as likely to seek help from a health professional as the more disabled CFS group, and those with neither of these conditions. This result suggests that health care utilisation may not be associated with levels of disability alone and that other factors may be more important in the decision to seek help for these particular conditions.

The relative importance of psychological risk factors in the development of IBS and CFS was compared using binary logistic regression. Results demonstrated that with regard to most risk factors the two groups were very similar. There were some relevant differences, however. At both three and six months post-infection, IBS cases could be distinguished from CFS cases according to their baseline levels of all-or-nothing behaviour, with IBS cases having higher levels of this risk factor. In contrast, cases of CFS at three months had experienced significantly higher baseline levels of somatisation than the IBS cases, and CFS cases at six months had experienced significantly higher baseline levels of psychological distress than the IBS cases. It would appear that although the two conditions share some similarities with regard to the importance of psychological risk factors, there are also some key differences that need to be taken into account.

It was important to identify whether these differences in disability levels and psychological risk factors were simply the result of the presence or absence of disability criteria as set by the definitions of IBS and CFS. Because the IBS criteria resulted in a group that included cases with and without associated disability, a new group of fatigue cases was created that included participants who were not reporting significant disability. This group had the same number of cases as the IBS group and there were no age or gender differences between them, indicating that with regard to prevalence and demographics, they were more comparable groups. It was anticipated that the two groups would also be more comparable with regard to disability levels and psychological risk factors. In contrast to expectations, however, the distinctions found in previous analyses were retained, with the chronic fatigue group having significantly higher levels of disability than the IBS group on every measure. Comparison of the importance of psychological risk factors for each group at six months also replicated the findings of the previous analysis comparing IBS and CFS, with psychological distress more strongly related to chronic fatigue, and all-or-nothing behaviour more strongly associated with IBS.

Taken together, these results suggest that even when the disability criteria are removed from the CFS criteria, the chronic fatigue group were still more disabled than those with

IBS and were also able to be distinguished with regard to the importance of psychological risk factors associated with their development. Therefore, differences on these measures are not simply due to the inclusion of disability in the criteria for CFS and its absence in IBS. In the context of the 'one or many' debate, these differences between the two conditions become important. The overall conceptualisation that the individual functional somatic syndromes are different manifestations of the same underlying condition leads to the expectation that IBS and CFS cases would be affected by similar levels of disability and by the same risk factors in their development. Based on this assumption, the results from these comparative analyses were expected to be non-significant once variations in definition were taken into account. Instead, some clear differences with regard to disability levels remained, and a number of psychological risk factors were clearly associated with one condition over the other. When added to the results indicating that biological factors may be more important in the development of IBS than CFS, it would seem that the differences between the two conditions cannot be disregarded.

Hypothesis 6:

Subthreshold fatigue and bowel disturbance will be comparable to CFS and IBS with regard to psychological risk factors, but differ in the relative importance of those variables and levels of associated disability.

The final hypothesis considered the practical utility of the current thresholds associated with the IBS and CFS definitions. In this part of the study, comparisons were made between each condition and a subthreshold group for each condition, in order to determine the utility of the current cut-off levels. It was expected that similar baseline psychological factors would be associated with each subthreshold condition as found for its diagnosable counterpart, but that the relative importance of those variables would differ. Similarly, the subthreshold groups were expected to be less disabled than their diagnosed counterparts, as measured by the psychological wellbeing and general disability measures gathered at six month follow-up.

Results comparing cases of IBS with a disturbed bowel function subthreshold group indicated that almost twice as many participants met criteria for this subthreshold group than that for IBS six months following infection. However, there were no age or gender

differences between these two groups, and there were no significant differences on the disability or psychological wellbeing measures. In addition, neither group was any more likely than the other to seek help from a health professional. Comparisons of the predictive ability of the psychological factor scores also produced a similar pattern. There was no single factor that could differentially predict the development of a subthreshold case over an IBS case, indicating that these two groups have common psychological risk factors as well as similar levels of associated disability. These results indicate that on these psychological measures at least, the group with subthreshold bowel disturbance were identical to diagnosable cases of IBS, lending weight to the proposal that the criteria for IBS can be greatly simplified (Agreus, 2000).

When the fatigue symptom groupings were compared, a similar pattern emerged with a few minor differences. The prevalence rates of CFS and the subthreshold fatigue group were very similar, with only slightly more CFS cases than that found in the subthreshold group. Once again there were no significant differences between the two groups with regard to age, gender, or disability. The lack of significant difference in disability levels between these two groups is particularly surprising given that a moderate to severe degree of disability is an essential component of the criteria for CFS and was specifically avoided when determining the subthreshold group. This result suggests that those with subthreshold fatigue may also be moderately to severely disabled and warrants further investigation.

The only difference found between the two groups was that of psychological wellbeing, as measured by the MHI-5. On this measure, CFS cases were experiencing lower levels of psychological wellbeing than the subthreshold fatigue group. With regard to the psychological risk factors, the only factor that could differentiate between the two groups was the psychological distress factor, with higher levels found in the CFS group: a result consistent with the lower levels of psychological wellbeing on the MHI-5 found at follow-up. These results indicate that subthreshold chronic fatigue and CFS have many common psychological risk factors as well as similar levels of associated disability, but that the CFS cases are distinguishable from the subthreshold group with regard to their higher levels of psychological distress at both baseline and follow-up.

Also relevant to the issue of subthreshold groups, were the inconsistencies found in group membership of IBS and CFS cases across the two follow-up time points. The fluctuating

course of IBS was mentioned earlier in the context of the intermittent nature of this complaint. When viewed alongside the information regarding CFS, however, it is possible that this variation represents more than just a fluctuating course. CFS is generally thought to have a more stable course than IBS; however, more than two thirds of CFS cases at three months did not meet criteria at six months, whereas less than half of the CFS cases at six months had met criteria at three months. Only seven people (3% of the total glandular fever sample) met criteria for CFS at both three and six months. The instability between cases at three and six months post-infection in both groups may indicate a classification issue, with those cases who are near the threshold for diagnostic criteria slipping between the groups. With regard to the CFS cases, it is possible that the 14 participants who met criteria at three months but not six months were still in a sub-acute phase of their illness. However, this does not account for the fact that 10 participants, who did not meet criteria for CFS at three months, did so by six months. It is possible that these 10 participants may represent a subthreshold group of participants who were experiencing significant fatigue at three months that was not severe enough to warrant a diagnosis of CFS.

As outlined in the introduction, there has been considerable debate about the practical utility of the various revisions of the IBS criteria. Similarly, the utility of criteria for CFS that sees incidence in the community lower than one percent in many studies has also been questioned. Primary care physicians see many more people with disturbed bowel function and significant ongoing fatigue than they do with IBS and CFS, yet these individuals are rarely studied due to their failure to meet diagnostic criteria. The results from this study suggest that the subthreshold bowel and fatigue groups share many similarities with their respective diagnosable conditions. They are not generally distinguishable with regard to levels of disability, and psychological risk factors were largely consistent between subthreshold and threshold groups. Only one psychological variable (higher levels psychological distress both at the time of initial illness and at six month follow-up) could differentiate between subthreshold fatigue and cases of CFS, as a predictor and an outcome variable. Viewed in conjunction with the variability in group membership across the two time points, the lack of differences between these subthreshold and diagnosable conditions suggests that the current criteria for IBS and CFS may be too conservative, and that the consideration of subthreshold symptoms soon after acute infection may be warranted.

Chapter 12.

General discussion.

> *"The substantial army of patients with functional somatic complaints constitute a large, clinically important, and costly force who will hold the health care system under siege until it develops a better understanding of and response to their needs" (Michael Sharpe, 2000)*

This study was designed to prospectively evaluate the existence of key variables proposed by the cognitive-behavioural models of IBS and CFS. The aggregation of two separate post-infectious samples enabled an investigation of the relative importance of both psychological and physiological risk factors defined by these models. In each case commonalities and differences between the two conditions were assessed in order to shed light on the classification of the functional somatic syndromes and the 'one-or-many' debate in particular. Finally, due to the large sample size, it was possible to determine the effect of classification anomalies. In particular, the emphasis on disability criteria in CFS and its absence in the IBS criteria were examined, as was the utility of the current thresholds associated with each. The results from each individual hypothesis have been presented and discussed in the previous chapter. These findings will now be discussed more generally with regard to their implications in three broad areas: the application of the cognitive-behavioural model to IBS and CFS, the utility of an overall conceptualisation of these syndromes, and the value of taking into consideration subthreshold conditions. The theoretical and practical implications of this study regarding each of these areas will be outlined, followed by a discussion of the study's limitations and directions for future research.

Theoretical and clinical implications.

The cognitive-behavioural model.

This study has added considerably to the theoretical understanding of the functional somatic syndromes and the practical application of that knowledge to IBS and CFS. The

introductory chapters of this thesis concluded that the investigation of the role of psychological factors in the development of IBS and CFS have been somewhat piecemeal in its approach. Empirical studies have often focused on global indicators of distress such as major depressive disorder, number of life events and history of abuse in the development of these conditions. In contrast, cognitive-behavioural models of the functional somatic syndromes propose very specific mechanisms based on anecdotal evidence, clinical experience and retrospective reporting of those individuals in chronic stages of these conditions. By utilising the conceptual framework of the cognitive-behavioural model to guide the current study, the results were able to determine the significance of psychological risk factors in a more integrated way.

This study has provided clear support for the importance of psychological factors in the development of IBS and CFS, and has supported the application of the cognitive-behavioural model to the functional somatic syndromes. Overall a range of cognitive, behavioural, emotional and physiological variables were found to be significant in the development of these conditions. The key psychological risk factors for IBS appeared to be perceived stress, anxiety, all-or-nothing behaviour and illness perceptions. For CFS, depression, anxiety and illness perceptions appeared to be the most important variables. Many of the variables incorporated within the cognitive-behavioural models were found to be associated with the development of these conditions. However, several other variables that have been assumed to be important risk factors were not significant when examined in a prospective manner in an early onset population. In particular, there was no evidence for the role of depression and somatisation in the development of IBS, nor was there any confirmation of the role of perceived stress and limiting behaviour in the development of CFS.

The finding that key variables were perhaps not as relevant as previously assumed, lends weight to Aaron Beck's (1991) stated concern that the adaptation of the cognitive-behavioural model to new conditions should not be without evidence of the specific mechanisms relevant to that condition. More focused investigation of specific cognitions, emotions and behaviours relevant to each individual condition is therefore essential to clarify the unique contribution each makes. In this respect, the contribution this study makes is an important one. Few studies have used such a large post-infectious sample to prospectively test these hypotheses. No other study has combined the investigation of two

distinct conditions in order to determine the relative importance of these variables. In doing so, the significance of many of these variables was able to be clarified.

In addition, the results confirmed the importance of considering predisposing, precipitating and perpetuating variables separately. The cognitive behavioural model has always considered that different factors may precipitate and maintain these disorders, however, this study has also demonstrated that the influence of the same variable may change over time. For example, limiting behaviour has been considered an important precipitant and perpetuator of CFS (Candy et al., 2002). In the current study, limiting behaviour was investigated both on its own and in combination with overdoing things (in the form of all-or-nothing behaviour). In this way, it was established that the effects of limiting behaviour alone in response to acute illness was not associated with the development of CFS. The more complex all-or-nothing response, however, placed an individual at greater risk in the early stages of the development of this condition. In this context, it appears that limiting behaviour may be more important as a chronic perpetuator rather than as a predictor of CFS, where all-or-nothing behaviour may be more relevant. This study suggests that the role of specific behaviours over time in the development of IBS and CFS clearly warrant additional exploration. The behavioural measure designed for this study has gone some way toward clarifying the impact of distinct behavioural responses in the development of IBS and CFS. However, further validation of this instrument in other acute and chronic illness samples is required in order to fully determine these influences across conditions, and over time.

Finally with regard to theoretical implications, the results supported the use of multifactorial conceptualisations such as that provided by the cognitive-behavioural model. This was most clearly evidenced by the discovery that the existence of physiological factors in the form of an infectious precipitant can increase the relevance of psychological factors in the development of IBS and vice versa. The influence of mind-body dualism has seen swings of focus from the biological to the psychological, with very little integration of research efforts in each of these areas. With the advent of new technologies and the burgeoning interest in genetic vulnerabilities in recent years, increased effort has once again gone into the investigation of possible physiological mechanisms of these conditions. It is important that this surge of interest does not take place at the expense of research integrating other perspectives. Single physiological mechanisms will almost certainly be

uncovered for subsections of these populations over time, however, it will be many years before they will become 'medically explained' as a group.

The results also have important practical implications for the treatment of IBS and CFS. The finding that some mechanisms are more relevant than others for each condition and that their relative importance may change over time, are important considerations in the development of cognitive-behavioural treatment programmes for these conditions. For example, the results for IBS suggest that anxiety and stress should be particularly targeted in the early stages of treatment, whereas depression may be less important. Similarly, the consideration of emotional variables in the form of subthreshold levels of anxiety and depression are likely to be more relevant clinically in the treatment of these conditions than the existence of categorical diagnoses. The distinction between limiting and all-or-nothing behaviour also has implications for treatment. Previous authors have pointed out that these two patterns of behaviour warrant quite different treatment planning; those patients with a limiting style require immediate attention on promoting the gradual increase in activity, whereas patients with an all-or-nothing style must first achieve a balance of rest and activity (Moss-Morris, 2005).

One of the most clinically relevant findings from this study in terms of prevention is the finding that negative illness beliefs regarding an episode of acute illness are one of the most robust indicators of the development of both IBS and CFS. This result suggests that illness perceptions may be relevant in the development of other functional somatic syndromes that have an acute onset associated with them, and should be investigated further. It also indicates that these beliefs may be pertinent with regard to barriers to recovery in any acute illness, a hypotheses that deserves further exploration. It is possible that illness beliefs, such as expectations of illness duration and the negative consequences of an acute illness, can be readily modified by GPs with the provision of basic information. For example, a local study demonstrated that the most important determinant of return to work following surgery for appendicitis was the advice given by the doctor regarding the length of time expected for recovery, and that this variable was more important than the kind of surgery, extent of pathology, number of complications and age of the patient (Wagener & Windsor, 2003). By incorporating an understanding of the importance of illness beliefs into the initial consultation, GPs may go some way toward the prevention of disabling conditions like CFS and IBS.

The 'one or many' debate.

As discussed in Chapter 2 of the introduction, part of the case for an overriding classification of the functional somatic syndromes was that they share similar psychological processes and responses to psychological treatment. The considerable overlap presented in the literature regarding predisposing, precipitating and perpetuating variables indicated that an overall conceptualisation was likely to be supported. In many cases, the differing emphases on some variables at the expense of others between the two conditions appeared to be more a function of historical influence, rather than being related to actual differences between the two conditions. For example, the bulk of research on CFS has been conducted by psychiatrists and psychologists, in contrast to IBS where most research is still conducted by gastroenterologists. This has resulted in a greater emphasis on physiological factors and broader psychological constructs in IBS than in CFS, which has tended to focus in more detail on the psychological variables. Enough parallels existed, however, that those psychological mechanisms found to be significant in one area also warranted investigation in the other.

This study set out to determine whether the same risk factors existed for both IBS and CFS, and whether the relative importance of those factors was also similar. Based on the evidence put forward supporting an overriding conceptualisation, it was hypothesised that the risk factors measured in this study would be similar for both IBS and CFS. The results did demonstrate similarities between these two conditions with regard to the risk factors measured. Despite these similarities, however, it was clear that there were also some key differences in the relative importance of these risk factors in their association with the development of IBS and CFS.

The nature of the precipitating acute infection was a strong influence in the development of IBS, but its importance faded over time for CFS. Certain psychological factors also helped to differentiate between the two conditions. The two conditions differed in their levels of disability, with the CFS group significantly more disabled than the IBS group, regardless of the inclusion of disability criteria. In addition, results indicated that there was minimal diagnostic overlap between CFS and IBS within the samples, a finding at odds with that expected given the high rates of comorbidity of these two conditions found in other studies (Aaron & Buchwald, 2001; Whitehead et al., 2002). At 3 months post-infection, only 14 participants in the combined sample (1.7%) were diagnosed with both conditions. This

number had halved by 6 months, indicating that there was little overlap in the symptom presentation of patients with relatively new onset IBS and CFS.

Whilst they may share some risk factors in their development, including the role of psychological distress and illness perceptions, the data support the need to distinguish between IBS and CFS, particularly early on in the presentation. The two conditions appear to have some distinct differences that warrant further consideration and caution against the wholesale adoption of an overall conceptualisation. Taken together, the results provide evidence that the two conditions, at least in their early stages, are relatively distinct and that there are clear distinctions between post-infectious IBS and CFS in primary care patients.

On a theoretical level, the similarities between these conditions are important to recognise, as they are able to guide research and support investigation of new avenues for one disorder based on findings in another. In this study, for example, the protective effect of limiting behaviour at the time of acute illness with regard to the development of IBS would never have been discovered had it not been included in the study as a proposed risk factor for CFS. The generic focus of the cognitive-behavioural model, however, must now be supplemented by the exploration of more specific psychological variables found to be important in the development of each individual condition. These results also add weight to the caution that findings from secondary care studies may reflect a group of patients at the far end of the spectrum who have a wider range of symptoms and greater levels of distress.

These findings indicate that a careful consideration of the differences between the disorders is also required in the clinical setting. Whilst it may be useful to have a broad conceptualisation of the functional somatic syndromes to guide non-specific aspects of treatment, it is essential that differences are taken into account. For example, focusing on the role of stress in the treatment of CFS is likely to be less important than considering low mood, whereas the converse is likely to be the case for those with IBS. Similarly, a greater emphasis on illness perceptions may increase the effectiveness of cognitive-behavioural treatment for CFS, whilst a more targeted focus on specific behavioural responses to illness such as all-or-nothing behaviour may prove beneficial in the treatment of IBS. Failure to consider such differences with the application of a ‘one size fits all’ approach to treatment is likely to be at best inefficient, and at worst, harmful.

Classification issues.

As set out in the introduction, the classification of conditions such as CFS and IBS has been fraught with difficulty. Defined criteria has led to increased research output, however, these criteria have become increasingly complex for each condition and are infrequently used by clinicians as a result. The applicability of that knowledge to those with subthreshold conditions has also been problematic. Results from this study support the argument that these criteria could be less complex than is currently the case (Agreus, 2000). In this study, a self-report questionnaire determining standard criteria was able to identify a similar number of cases to that found in previous studies using clinician assessment and/or more detailed questionnaires. In addition, use of the same data was able to define a second group of individuals who, whilst not meeting standard criteria, were nonetheless experiencing significant bowel or fatigue-related symptoms. Comparison of these subthreshold groups with those who did meet criteria found little to distinguish them. With regard to psychological risk factors, disability levels and health care utilisation, these subthreshold groups differed little from their diagnosable counterparts.

These findings are preliminary and warrant further investigation, however, they have important theoretical and practical implications for these conditions. It is clear from these results that large numbers of patients exist in the community experiencing a considerable level of symptomatology and associated disability that are not currently recognised by the existing criteria. In this respect, the somewhat arbitrary nature of many of these diagnoses was confirmed. This result indicates two possibilities, the first of which is that the thresholds for the diagnosis of IBS and CFS have been set too high. If the differences that exist between subthreshold and threshold groups of these patients are minimal, as was found in this study, our classification systems may be able to be greatly simplified. Clinically, it is possible that this subthreshold group may benefit from some of the cognitive-behavioural treatments developed for those who meet criteria for these conditions. The alternative is that these groups differ qualitatively or quantitatively in ways that are yet to be identified. Future research needs to consider this possibility.

Limitations and future directions.

When interpreting the findings of this study, there are a number of limitations that need to be taken into account. This study aimed to address some of the methodological problems that have been associated with the study of the functional somatic syndromes by the use of a prospective, community-based design. Such a design was essential in order to determine the prior existence of psychological vulnerabilities for IBS and CFS in the general population. However, the use of a post-infectious population raised its own methodological difficulties that need to be considered. Given the limited resources available, the use of a postal survey and follow-up were necessary in order to obtain a post-infectious sample large enough to provide sufficient power to test the study's hypotheses. Although this maximised participation, it limited the amount and type of material that could be gathered from participants. This section will highlight a number of aspects of the design of this study that warrant consideration with regard to their potential impact on the results, and suggestions for future research will be made accordingly.

As discussed in the introduction, IBS and CFS are known to be heterogeneous disorders, with multiple presumed aetiological pathways. Not all cases of IBS and CFS will have experienced a prior infection, and because of this, individuals with a post-infectious onset in both conditions have been set apart as belonging to specific subsets of each wider group. Those with post-infectious CFS have been difficult to distinguish from those without an infectious onset (Buchwald et al., 1996). However, one study of post-infectious IBS has indicated that this group can be distinguished from those with no history of infection with regard to the type of prominent symptoms, lower levels of psychiatric illness, and histological changes (Dunlop, Jenkins, & Spiller, 2003). Because of potential differences like these, therefore, the results from this study apply specifically to post-infectious IBS and CFS, and the generalisability of these findings to the wider groups remains to be determined. The finding that psychological factors are an important aetiological influence in groups with a known biological precipitant, however, suggests that such factors will be relevant to the same conditions without such an infectious precipitant. Future prospective studies, using other at risk samples (such as victims of psychological trauma or patients undergoing surgery), may help to clarify the role of these variables.

The use of a post-infectious sample led to another sampling issue. Diagnostic laboratory test results were used to determine eligibility for this study in order to obtain two homogeneous and verified illness samples. An unavoidable result of such an approach, however, is that it considerably reduces the number of participants eligible for a study of this type. For example, in the case of gastroenteritis it has been estimated that of those experiencing such an infection, the group who consult a doctor may be as small as 17%, of whom only 27% will go on to supply a stool sample, and of whom only 24% will be a positive case of gastroenteritis (Spiller, 2003). This final sample then, represents a small minority of the original illness population. A myriad of factors, both physiological and psychological may impact on this process, all of which may have compromised the representativeness of the sample eligible to enter this study. Future studies of outbreaks of gastroenteritis such as that conducted by Ji and colleagues (2005) represent a way around this problem, and are needed to replicate these results.

In addition, of those eligible to enter the study, not all had the opportunity to participate. The two stage recruitment procedure required by the ethics approval for this study meant that an accurate response rate was difficult to determine. It was clear that a number of general practitioners had not sent the information on to their patients, as evidenced by a nil response rate from patients of certain GPs. Using this as an indicator of non-cooperation by GPs, it was estimated that the response rate was around 52%, which is consistent with the rate found in another large community survey (Wilson et al., 2004). The lack of access to patient data without consent, however, meant it was not possible to compare responders and non-responders. Despite these difficulties, by recruiting through the diagnostic laboratory, the study had access to a large sample of patients attending a wide range of general practitioners. The sample size obtained as a result meant that the study was well powered to test the hypotheses. In addition, the follow-up rate was over 90% at both time-points, so few patients were lost over time.

A healthy control group was not included in this study as the acute illness specific risk factors were considered to be well established, with a number of studies determining relative risks (see Chapters 5:2 and 6:2). Because of this, the current study focused attention on the comparison of cases and non-cases at three and six months following infection. However, it was not anticipated that participants with *Campylobacter* would develop CFS in any greater numbers than that found in the general population, nor that participants with glandular fever would go on to develop IBS in a similar way. The fact

that they did, along with lower than expected odds ratios, indicates that there may be some non-illness specific factors at play here. The inclusion of a healthy control group in future studies is now needed to clarify the relative risks associated with these conditions. Future studies comparing these two groups should include a non-illness control group in order to explore this issue further. The investigation of other moderate to severe acute illnesses may also help to determine how non-specific illness effects may generalise.

With regard to procedure, this study relied entirely on self-report data to identify both prior and new-onset cases of IBS and CFS, rather than clinical examination. This approach ensured that the maximum number of participants could be included in the study; however, it may have introduced a number of confounding factors. It is possible that a number of participants may have experienced IBS or CFS prior to their infections, but had never been diagnosed by their doctor, and were therefore not excluded as prior cases. In order to account for this, the study employed conservative exclusion criteria, excluding any patient disclosing a related condition (such as spastic colon or fibromyalgia) or one of a wide range of medical conditions which could cause either chronic fatigue or bowel problems. In addition, in many analyses, two functional somatic syndromes were being considered rather than one, necessitating the exclusion of all participants with a bowel or a fatigue condition, rather than one or the other. As a result, these broad exclusion criteria would most likely have reduced rates of IBS and CFS in the study, rather than inflated them.

The use of self-report data in the absence of a clinical examination to determine caseness at follow-up must also be carefully considered. Whilst there is evidence to suggest that it is possible to identify these conditions more simply by the use of self-report questionnaires (Agreus, 2000), there was still a risk that a number of participants would be included in the study as false positives; that is, classified as cases of IBS or CFS when they do not have the condition. Conversely, some participants may have been false negatives, or classified as not having the condition when in fact they do. Should there have been a large number of cases like this included in the study, the quality of the results could have been compromised. Several procedures were included in the study to reduce the likelihood of this. Firstly, published diagnostic criteria were used to determine IBS and CFS caseness at follow-up. Secondly, controversies surrounding the utility of various definitions led to the inclusion of all participants who met either of the two best known criteria for each condition (Rome I modified or Rome II criteria for IBS, and both the British and Fukuda criteria for CFS). Thirdly, as mentioned above, the exclusion criteria were conservative so

as to reduce the number of false positives. The resulting prevalence rates reported in the results section are comparable, if slightly lower, than those found in previous studies, indicating that these procedures had the desired effect.

A final limitation of this study that warrants consideration is the choice of measures used. Environmental influences, a key component of the cognitive-behavioural model, were not included in the initial questionnaire as it would have unreasonably increased its length for participants. In this sense, the study was not a complete examination of the cognitive-behavioural model, and these variables remain to be examined. Of those measures that were included, some performed better than others. Many measures such as the HADS, the PSS, and the newly created BRIQ worked well to clarify aspects of the models, however, others such as the causal beliefs and illness attributions questions were less easily interpreted in an acute illness population. In particular, the measures used to determine illness severity could have been more influenced by psychological variables such as somatisation, than by actual symptom severity. In this respect, clinical examination, physiological measures such as inflammation following *Campylobacter,* or specific questions regarding the duration of symptoms, may have provided more objective markers of severity than simply the overall number of symptoms. Although the results regarding severity were largely consistent with previous findings, more objective measures would have improved the veracity of this finding.

There are some final considerations for future research. The distinction between what perpetuates a disorder in its early stages and whether the influence of these variables change over time needs clarification with longer term prospective studies. For example, the previous emphasis in the cognitive-behavioural models on variables that did not have a significant association in this study may simply indicate that they are more important as perpetuators of these conditions, rather than as predisposing or precipitating variables. One other study that followed a post-infective sample up to 12 months following infection, found that the utility of predictive measures continued to vary over time (Candy et al., 2003). Further studies of this nature will help to clarify the way in which these variables influence the development of conditions like CFS and IBS.

With regard to classification issues, this study provides some evidence to suggest that an overall conceptualisation of the functional somatic syndromes may not be appropriate when considering the differential impact of variables across individual conditions. Future

studies must determine whether these differences are important with regard to treatment in order to establish if they are clinically relevant. Future studies of this type will most likely continue to discover ways in which the conditions can be distinguished. In addition, subthreshold conditions clearly warrant further investigation and their inclusion alongside current diagnostic criteria may be a way to ensure this. The findings of this study with regard to the similarities between threshold and subthreshold cases may only be relevant in post-infectious or early onset populations; however they are striking enough to warrant cross-sectional comparison of subthreshold conditions with diagnosed cases at any stage of their development to further determine whether the current thresholds are meaningful.

Conclusion.

Functional somatic syndromes have existed within the human race for at least as long as the written word has been able to describe them. Despite this long history, researchers have struggled to provide evidence of clearly identifiable causal pathways for these syndromes. This dearth of aetiological understanding has created problems in the classification, assessment and treatment of these conditions. In response to these problems, symptom-based classification systems were established and biopsychosocial models proposed. As a result of these initiatives, there has been an increased level of interest in these syndromes and researchers have made significant advances in the understanding of these syndromes and the identification of potential treatment processes.

Standardised diagnostic criteria focused research attention and provided a means by which researchers could compare their findings. However, regular changes to these criteria, and methodological problems associated with studies that used them, have made their practical utility questionable. Meanwhile, the adaptation and development of cognitive-behavioural models to IBS and CFS encouraged a multifactorial approach to the understanding of these conditions. These models provided promising explanatory frameworks and facilitated the development of specific treatment approaches. Despite the popularity of these models, however, very few studies have prospectively investigated the core premises of these models in their application to specific conditions. As a result, only limited empirical evidence was available to support the proposal that cognitive, behavioural, emotional and physiological factors did indeed influence the development of these syndromes.

This study has provided clear evidence for the cognitive-behavioural model in its application to IBS and CFS. The use of a prospective design in a newly diagnosed general practice-based sample allowed the investigation of risk factors relevant to this model. Results demonstrated that this model is capable of providing valuable insights into the theory, classification and treatment of these syndromes. This study has begun to evaluate the more intricate aspects of the cognitive-behavioural model with regard to the predisposition, precipitants and early perpetuators relevant to these syndromes. The results are of theoretical importance and have important implications for the prevention, early intervention and treatment of these conditions. The multifactorial approach provided by the cognitive-behavioural model will continue to be of theoretical and clinical utility, both as an explanatory model and a guide for treatment.

The design of this study also made comparative analysis of the two conditions possible with regard to classification issues. In this respect, the results give rise to a cautionary note against the adoption of an overall conceptualisation of the functional somatic syndromes. While grouping these conditions together theoretically may help to highlight commonalities, it is clear that the differences that exist are significant and should not be forgotten. Careful comparative work such as that carried out in this study to clarify key differences also has the potential to enhance treatment effectiveness for these conditions. In addition, this study has raised some important issues with respect to the utility of the current diagnostic criteria. Based on the results, the presence or absence of disability criteria and the current thresholds that exist, appear somewhat arbitrary. It is possible that the current criteria for both IBS and CFS are unnecessarily restrictive and that these components may be adding little to the diagnostic process.

There is no doubt that the functional somatic syndromes represent a complex group of disorders that will continue to challenge researchers and clinicians alike. The numbers of individuals who present with these conditions are considerable, their problems significant, and the current methods of treatment are still far from adequate. Despite these difficulties, the disparate group of researchers investigating these syndromes are slowly piecing the puzzle together. Much work remains before the whole picture will become apparent, however this study has added some important pieces that will help to guide future developments in this area.

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Appendices.

Appendix 1. The Behavioural Responses to Illness Questionnaire - Pilot study.

COPING WITH INFECTION

Listed below are a number of statements that people use to describe what they do when they are experiencing a moderately severe infection. Imagine that you are **currently experiencing** an illness such as a **really bad flu**. Consider the following statements and tick the box that best describes **how often** you would do the following**, during this period of illness.**

	Not at all	**Once or twice**	**Some days**	**Most days**	**Every day**
1. I would avoid physical exercise					
2. I would go to the chemist for advice					
3. I would overdo things, then need to rest up for a while					
4. I would rely on my family or friends to look after me					
5. I would talk to others about how bad I feel					
6. I would pace myself in what I need to do					
7. I would continue to work and play as I do normally					
8. I would ask for help from my family or friends					
9. I would take time off even if my work or other responsibilities suffered					
10. I would ring people close to me for sympathy					
11. I would put parts of my life on hold					
12. I would take some medicine to make me feel better					
13. I would carry on with some of my daily activities but take more time to rest					
14. I would keep up my normal level of exercise					
15. I would make sure I had someone to look after me					

	Not at all	Once or twice	Some days	Most days	Every day
16. I would push myself as hard as ever until I could not push myself any more					
17. I would avoid my usual activities					
18. I would tell people around me how miserable I feel in the hope that they feel sorry for me					
19. I would carry on with things as normal until my body could not cope any longer					
20. I would use herbal remedies					
21. I would go to bed during the day					
22. I would carry on with my usual daily activities but at a slower pace					
23. I would try to find someone to help me out					
24. I would want people to acknowledge how sick I am					
25. I would look for information about my illness					
26. I would feel obliged to carry out all my responsibilities, no matter how bad I feel					
27. I would know just what needs to be done and what can wait until I am feeling better					
28. I would try to do too much and feel even worse as a result					
29. I would ask my family and friends to carry out my usual responsibilities					
30. I would not be able to carry on with my usual level of activities					
31. I would want people to understand how awful I feel					
32. I wouldn't slow down, I would just carry on as normal					
33. I would speak to my doctor or practice nurse about my illness					
34. I would take time out from my usual activities so that I can get back to normal quicker					
35. I would find myself rushing to get everything done before I crashed					

How old were you at your last birthday? _____ Are you: Male ☐ Female ☐

Thank you for your time

Appendix 2. Ethics approval.

Auckland
Ethics Committees

Delivery Address:
C/O Ministry of Health
3rd Floor, Unisys Building
650 Great South Road, Penrose
Private Bag 92522
Wellesley Street
Auckland
Phone (09) 580 9105
Fax (09) 580 9001
Email: pat_chainey@moh.govt.nz

Please include the reference no. and study title in all correspondence/telephone calls.

14 December 2001

Ms Meagan Spence
Health Psychology & Practitioner Development
Faculty of Medical & Health Science
The University of Auckland
PB 92019
Auckland

Dear Meagan,

2001/303 Psychological predictors of delayed recovery and the development of somatic syndromes following acute infection.

Thank you for your amendments received 18 January 2002.

We are pleased to inform you that this study has received ethical approval until 31 December 2003, at which time a final summarised report/ abstract is required to be presented to the committee for consideration. It is certified as not being conducted principally for the benefit of the manufacturer and will be considered for coverage under ACC.

Please note that the Committee grants ethical approval only. If management approval from the institution/organisation is required, it is your responsibility to obtain this.

A yearly progress report is required by 25 January 2003. Approximately two months prior to the end of this period you should receive a progress report form off our data base that needs to be completed and submitted to the Ethics Committee one month before the expiry date. However, it is your responsibility to ensure that a yearly progress report is submitted to the Ethics Committee.

Please ensure you advise us when this study is completed. The Committee wishes you well with your research.

Yours sincerely,

Pat Chainey
Administrator

Cc: Auckland DHB

Appendix 3. Letter to individual General Practitioners.

RECOVERY FROM ACUTE INFECTION

We need your help

Dear <insert GP name>

Re: Your patient: <insert patient name> D.O.B: <insertDOB>

The above named patient of yours has recently tested positive for either infectious mononucleosis or *Campylobacter* infection. As you may be aware from recent publicity, a group of researchers at the University of Auckland are currently undertaking a major prospective study looking at predictors of delayed recovery from acute infection. Diagnostic Medlab is supporting this research by forwarding information to GPs as patients receive positive test results for these illnesses. The researchers would like every patient to have the opportunity to be involved in this study; however, they need your help to enable this to occur.

Enclosed is a post paid envelope for your patient, which includes an information pamphlet, consent form and questionnaire for your patient to fill out, should they choose to participate in the study. We ask you to address this envelope to your patient and post as soon as is practical for you. It is important that patients receive their questionnaire as close to the date of microbiological confirmation of their illness as possible to increase the validity of the results.

We realize that you have many demands on your time and have endeavoured to make this task as simple as possible. Should you have any questions about the study please feel free to contact the principal investigator, Meagan Spence, whose contact details are included below. The research team would like to thank you in advance for your support of the study and look forward to informing you of the results in due course.

Yours sincerely,

Dr Susan Taylor, Microbiologist

Diagnostic Medlab

In association with

Meagan Spence MA(Hons),Dip.Clin.Psyc. (Principal Investigator)
Dr Rona Moss-Morris, Senior Lecturer
Dr Keith Petrie, Assoc. Professor

The University of Auckland
Private Bag 92019
Auckland
Telephone: 09 373 7599 extn 6757
Facsimile: 09 373 7013
Email: m.spence@auckland.ac.nz

Appendix 4. Publicity information.

Recovery from acute infection –

Why do some people take longer than others?

A group of investigators at the University of Auckland, have recently begun a major prospective study looking at recovery following the acute illnesses of glandular fever and *Campylobacter* gastroenteritis. They propose that psychological factors will interact with medical factors to determine which patients fail to recover within the expected time frame. The researchers also propose that these factors will determine a subgroup of patients who go on to develop the more chronic somatic conditions of chronic fatigue syndrome and irritable bowel syndrome. In this way it is hoped to identify risk factors for delayed recovery in these populations.

Diagnostic Medlab is supporting this study by recruiting patients with a confirmed lab result for these acute illnesses. Due to the privacy of health information we are unable to contact patients directly. Questionnaires will instead be sent to patients via their referring practitioners, who can expect to receive a letter from DML containing a post-paid envelope for each of their patients. The patient envelope contains an information pamphlet, consent form and questionnaire for your patient should they choose to be involved in the study. The researchers ask you to simply address this envelope, and send it on to your patient. The data collection period is due to run for 18 months, including two follow-up questionnaires at 3 and 6 months post-infection, which will be sent directly to patients.

The researchers would like to thank you in advance for your assistance with this project and look forward to sharing the results with you in due course. If you would like to know more about the study, please feel free to contact the principal investigator, Meagan Spence, on 09 373 7599 ext 6757, or alternatively e-mail her at m.spence@auckland.ac.nz. Similarly, if your patients have questions, please ask them to contact Meagan Spence directly.

DML Mini-newsletter

Since July last year, DML has been involved in the development of a major prospective study looking at recovery following the acute infectious illnesses of glandular fever and *Campylobacter* gastroenteritis. Investigators at the Faculty of Medical and Health Sciences, University of Auckland, hypothesise that psychological factors such as perceived stress, emotional state, illness-related behaviours, and patient's beliefs about their illness will be predictive of those who fail to recover within the expected time frame. They also hypothesise that these factors will determine a subgroup of patients who go on to develop the more chronic somatic conditions of chronic fatigue syndrome and irritable bowel syndrome.

DML is supporting this study by helping to recruit patients following a confirmed lab result for either of the acute illnesses. From Friday the 1st of March, questionnaires and information packs will be sent to patients via their referring practitioner. Practitioners can expect to receive a letter from DML containing a post paid envelope for each patient. The researchers ask that you simply address the envelope and send it on to your patient as soon as possible. Due to the privacy of health information and ethical considerations, we are unable to send the information directly to patients. The data collection period is due to run for 18 months, including two follow-up questionnaires at 3 and 6 months post-infection. These questionnaires will be sent directly to patients.

The researchers and DML would like to thank you in advance for your assistance with this project and hope that it does not inconvenience you in any way. Should you have any queries about the study or would like to know more about the study please feel free to contact the principal investigator, Meagan Spence, on 09 373 7599 ext 6757, or alternatively e-mail her at m.spence@auckland.ac.nz

GP Update

Health Psychology

THE UNIVERSITY OF AUCKLAND
FACULTY OF MEDICAL AND HEALTH SCIENCES

The University of Auckland
Private Bag 92019
Auckland
New Zealand,

85 Park Road, Grafton
www.health.auckland.ac.nz

Telephone: 64 9 373 7599 extn 6757
Facsimile: 64 9 373 7013
Email: m.spence@auckland.ac.nz

RECOVERY FROM ACUTE INFECTION STUDY: UPDATE

Dear……..,

We would like to take this opportunity to sincerely thank all those practice managers, GPs and practice nurses who have been sending on the *Recovery from Acute Infection* questionnaire packs to their patients. We realise that you have many demands on your time and appreciate the time taken to help us to recruit patients.

The study has been running for just over 30 weeks and DML have sent out 2,100 questionnaires to general practices Auckland-wide for us. We have received approximately 660 replies, a response rate of just over 30%. We are currently receiving both three and six month follow-up data and are pleased to report that our response rate for this part of the study is approximately 90%. Preliminary analysis indicates that 12% of patients meet criteria for irritable bowel syndrome at 3 months, and 1.5% have symptoms consistent with the development of chronic fatigue.

By the end of the year, we hope to have recruited sufficient numbers of *Campylobacter* patients to discontinue recruitment for this group. However, we will continue to recruit from the infectious mononucleosis group for at least another 8 months, as our numbers in this group are much smaller, and we urge you to continue sending on any packages you receive for your patients. We would greatly value your ongoing participation in this study and may give you a call from time to time to maintain contact.

We would also like to take this opportunity to inform you of an intervention study that we will be undertaking in the New Year. All patients from this current study who meet criteria for irritable bowel syndrome and/or chronic fatigue syndrome at six month follow-up will be offered the opportunity to participate in a randomised controlled trial evaluating a four week self-help intervention. The intervention is designed to work alongside the standard care the patient is receiving from their general practitioner and should in no way interfere with any other treatments. The purpose of the intervention is to significantly reduce and prevent ongoing disability and distress associated with these syndromes.

We have had some GPs requesting the opportunity to view the contents of the envelopes before they are passed on to their patients. We are more than happy for you to open the envelopes for this purpose. We have also enclosed a copy of the patient information pamphlet that is in all envelopes you send on.

Once again thank you for all your help, and we wish you a Merry Christmas and a Happy New Year.
Kind regards,

Meagan Spence MA(Hons),Dip.Clin.Psyc.
(Principal Investigator)

Dr Rona Moss-Morris, Senior Lecturer
Dr Keith Petrie, Associate Professor

Appendix 5. Participant information sheet.

Recovery from acute infection:

How long does it take?

This is your invitation to take part in a study that will help health professionals understand more about the process of recovery from a moderately severe infection.

This information sheet provides an overview of the study so that you can decide whether you would like to participate.

How did we get in touch with you?

You have recently had a positive test result for glandular fever or *Campylobacter* gastroenteritis sent to your GP. We have asked all GPs in the Auckland area to forward this information pack to their patients who receive these test results.

Why is this study important?

Thousands of people in Auckland, like you, fall ill each year with acute infections. While doctors know a lot about the acute phase of these illnesses, they know much less about the process of recovery. With the help of people such as you, we hope to gain a better understanding of what may speed up this recovery process.

What are we asking you to do?

We ask you to complete the enclosed questionnaire and consent form, which should take you approximately 20 minutes to fill out. We need you to fill it in as soon as possible, and send it back to us in the reply paid envelope enclosed. It is also important that you fill out the consent form so that we can make use of the information you give us. We will then send you two further questionnaires, one at 2 months and one 6 months from now. These questionnaires will ask you about your general wellbeing and any ongoing symptoms you may be having at those times.

Why should you participate?

Your involvement in this study is vital to broaden our understanding of the process of recovery. We will be looking at the symptoms you experience, factors which may have caused your illness and the things you have done to manage this illness. By adding your answers to those of others

we hope to find patterns that will help doctors recognise what may speed up or slow down recovery. What if you don't want to be involved?

The decision is entirely yours. If you agree to take part initially, but then change your mind later, you can withdraw from the study without having to give a reason.

What will happen to the information you give us?

Your answers will remain confidential and will only be seen by those directly involved in this research project. The questionnaires will be coded and locked away, so that you cannot be identified during the data analysis process, or in any reports on this study. If you have a chronic medical condition that could impact on your recovery, your questionnaire will not be used in this study. It is your choice whether you want to tell your GP that you are involved in this study.

When will the results be available?

Because this study will be contacting people over a 12 month period, it may be more than a year after you fill out your questionnaire before we can start to analyze the results. Once we have all the questionnaires back a summary of the results will be sent to all participants.

Are there any risks?

There are no known risks associated with being involved in a study of this type. However, the study is covered by the accident compensation legislation with its limitations, in the unlikely event of any injury. This study has received ethical approval from the Auckland Health Ethics Committee.

Where can I get more information about the study?

Please feel free to call the principal investigator, Meagan Spence, whose details are below, if you have any questions about the study. If you have any queries or concerns regarding your rights as a participant in this research you may contact the Health Advocates Trust, phone 09 623 5799 or toll free 0800 555 050.

Principal investigator:
Meagan Spence
The University of Auckland
Faculty of Medical and Health Sciences
Private Bag 92019,
Auckland

Phone: 09 373 7599 extn 6757
Fax: 09 373 7013
Email: m.spence@auckland.ac.nz

Co-investigators:
Dr Rona Moss-Morris
Assoc Prof Keith Petrie
Dr Susan Taylor

Appendix 6. Consent form.

THE UNIVERSITY OF AUCKLAND
FACULTY OF MEDICAL AND HEALTH SCIENCES

The University of Auckland
Private Bag 92019
Auckland
New Zealand,

Telephone: 64 9 373 7599 extn 6757
Facsimile: 64 9 373 7013
Email: m.spence@auckland.ac.nz

CONSENT FORM

Title of Project: **Study on Recovery from Acute Infection**

Principal Investigator: Meagan Spence Ph. 09 373 7599 ext 6757

Participant's Name: _____

Postal Address: _____

_____

_____

Telephone Number: _____

E-mail address: _____

I have read and understood the information sheet for volunteers taking part in the study designed to investigate recovery from acute infection. I am aware I will be contacted at 3 and 6 months from now with regard to this study. I am aware that I have the opportunity to discuss this study with the principal investigator should I choose to do so. I understand that taking part in this study is my choice and I may withdraw from the study at any time without it affecting my future health care. I understand that my participation in this study is confidential and that no material that could identify me will be used in reports on this study. I understand the compensation provision for this study. I have had time to consider whether to take part and I know whom to contact if I have any questions about the study.

I _____ (full name) hereby consent to take part in this study.

Signed:_____ Date: _____

Appendix 7. Welcome letter.

THE UNIVERSITY OF AUCKLAND
FACULTY OF MEDICAL AND HEALTH SCIENCES

The University of Auckland
Private Bag 92019
Auckland
New Zealand,

85 Park Road, Grafton
www.health.auckland.ac.nz

Telephone: 64 9 373 7599 extn 6757
Facsimile: 64 9 373 7013
Email: m.spence@auckland.ac.nz

Dear

Thank you for returning the questionnaire that was sent to you regarding your recovery from your recent infection. We hope that you are feeling much better and would like to take this opportunity to welcome you to the study. We appreciate the time and effort that went into filling the questionnaire out, particularly if you were still unwell at the time.

We would also like to remind you that we will be sending you two further questionnaires, 3 months and 6 months from now. Should you have any questions about the study, please feel free to contact me at the above address.

Yours sincerely,

Meagan Spence

Dr Rona Moss-Morris

Assoc. Prof Keith Petrie

Appendix 8. Follow-up covering letter.

«Letter_no»

THE UNIVERSITY OF AUCKLAND
FACULTY OF MEDICAL AND HEALTH SCIENCES

The University of Auckland
Private Bag 92019
Auckland
New Zealand,

Telephone: 64 9 373 7599 extn 6757
Facsimile: 64 9 373 7013
Email: m.spence@auckland.ac.nz

«Title» «FirstName» «Surname»
«Street»
«Suburb»
«City», «PostalCode»

Dear «FirstName»

As you will remember, you received a questionnaire in the mail several months ago, which you kindly filled out and returned to us. Along with that questionnaire was an information pamphlet that stated you would be contacted at 3 and 6 months. It is now 3 months since you were ill and we would very much appreciate your ongoing participation in the study. We hope that you have recovered fully, but realize that some people will only have recovered partially. Either way, we have enclosed a further questionnaire that asks some similar questions to before and some new questions.

Please work your way through the questionnaire answering all questions that are relevant to you. You will notice that some questions do not need to be answered if you are not experiencing the symptoms described. We estimate that it will take approximately 5-15 minutes to fill out depending on how many questions you need to answer. Once you have completed the questionnaire please put it in the post paid envelope that is enclosed and post as soon as you are able.

If you choose not to participate any further in the study, please call or return the questionnaire with your details, so that we know not to send you a reminder note. Once again if you have any queries or concerns about the study please feel free to call Meagan Spence 09 373 7599 extn 6757. Thank you for your participation so far, and we look forward to informing you of the results in due course.

Yours sincerely,

Meagan Spence,
Principal investigator

In association with
Dr Rona Moss-Morris, Senior Lecturer
Dr Keith Petrie, Associate Professor

Appendix 9. Reminder letter.

28 June 2007

«Title» «FirstName» «Surname»,

«Street»,

«Suburb»,

«City», «PostalCode».

Dear «FirstName»,

Two weeks ago we wrote to you requesting your ongoing participation in the recovery from acute infection study. If you have already completed and returned the questionnaire, please accept our sincere thanks. If by some chance you did not receive this letter or have misplaced your copy of the questionnaire, I have enclosed another and would very much appreciate it if you could complete and return to me as soon as possible. If you no longer wish to have contact with us, please call me at 09 373 7599 extn 86757, and we will not send you any further reminders. Thank you for your ongoing support of this study.

Kind regards,

Meagan Spence

Principal Investigator

In association with:
Dr Rona Moss-Morris
Assoc. Prof. Keith Petrie

Appendix 10. Baseline questionnaire.

Code				

THE UNIVERSITY OF AUCKLAND
FACULTY OF MEDICAL AND HEALTH SCIENCES

Recovery from Acute Infection

- We are interested in finding out about your recovery from the *Campylobacter* gastroenteritis you have recently been diagnosed with, which we will refer to as "your current illness".

- This questionnaire will ask you questions about your symptoms, stress, exercise levels and emotions so that we may determine whether or not these factors influence how quickly you recover.

- If you have already recovered we are still very keen to hear from you as we want to know what may speed up recovery as well as what may slow it down.

- There are no right or wrong answers to these questions. Try and answer them all but do not spend too long on each question. Remember that all answers are kept totally **CONFIDENTIAL** and you will not be identified in any way.

When you have finished,
please place this questionnaire and your
consent form in the envelope provided,
and post as soon as possible.

If you have any queries about this study or questionnaire, please do not hesitate to call Meagan Spence at the following number:-

373 7599 ext. 6757

Thank you for your time!

Section 1: Symptoms you have been experiencing

We would like to know what kind of symptoms you have been experiencing **since your illness began.** Please indicate on the chart below whether or not you have experienced any of these symptoms, and if so, whether you believe that these symptoms are **related** to your illness.

SYMPTOM	Have you experienced this symptom *since your current illness began?*				If yes, is this symptom *related to your current illness?*	
	No		Yes		Yes	No
Sore throat						
Loss of appetite						
Weight loss						
Nausea						
Headache						
Sore eyes						
Loss of strength						
Feeling off colour				☞		
Breathlessness						
Joint pain						
Dizziness						
Fever				If Yes		
Unrefreshing sleep						
Swollen glands						
Fatigue/tiredness				☞		
Vomiting						
Rash						
Diarrhoea						
Racing heartbeat						
Feeling worse after exertion						
Stomach pain						
Blood in faeces						
Aching muscles						

Section 2: How you have managed your illness

The statements below refer to things that you may or may not have done to manage your symptoms. Please indicate how often you have done the following **since your current illness began**.

	Not at all	Rarely	Some days	Most days	Every day
I have avoided physical exercise					
I have overdone things, then needed to rest up for a while					
I have relied on my family or friends to look after me					
I have talked to others about how bad I feel					
I have asked for help from my family or friends					
I have rung people close to me for sympathy					
I have put parts of my life on hold					
I have made sure I have someone to look after me					
I have pushed myself as hard as ever until I can not push myself any more					
I have avoided my usual activities					
I have told people around me how miserable I feel, in the hope that they feel sorry for me					
I have carried on with things as normal until my body can not cope any longer					
I have gone to bed during the day					
I have tried to find someone to help me out					
I have wanted people to acknowledge how sick I am					
I have felt obliged to carry out all my responsibilities, no matter how bad I feel					
I have tried to do too much and felt even worse as a result					
I have not been able to carry on with my usual level of activity					
I want people to understand how awful I feel					
I haven't slowed down, I've just carried on as normal					
I have taken time out from my usual activities so that I can get back to normal quicker					
I find myself rushing to get everything done before I crash					

Section 3: Details about your recent illness

1. How many days ago did you experience the first symptoms of your illness?__ **days.**
2. What is the date today? _ _ / _ _ / _ _
3. If you are working or studying, how much time off have you had with this illness?__ **days.**
4. How many more days do you think your illness will last? _____ **days.**
5. Has your doctor given you an antibiotic for this illness?**Yes** ☐ **No** ☐ **Don't know** ☐
6. When the doctor told you what illness you had, what advice were you given? Please tick one or more of the boxes below according to the advice you were given.

Advice given	Tick if appropriate
None	
Information about what to eat and drink	
Take medication to cope with symptoms	
Rest	
Avoid vigorous activities or sport	
Other (please specify) ……	

Section 4: Causes of your illness

We are interested in what **<u>you</u>** consider may have been the **cause** of your illness. We are most interested in your own ideas rather than what others including doctors or family may have suggested to you. Please list in rank-order the most important factors that **you** believe caused **your** illness:

1._____

2._____

3._____

Section 5: Your views about your illness

We are interested in your own personal views of how you see the illness you are experiencing. Please indicate how much you agree or disagree with the following statements about your illness by ticking the appropriate box.

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
My illness does not have much effect on my life					
This illness will pass quickly					
What I do can determine whether my illness gets better or worse					
The symptoms of my condition are puzzling to me					
My illness makes me feel angry					
My illness is a serious condition					
My illness will last a short time					
There is a lot which I can do to control my symptoms					
My illness doesn't make any sense to me					
Having this illness makes me feel anxious					
My illness has major consequences on my life					
My illness will last for a long time					
The course of my illness depends on me					
I get depressed when I think about my illness					
My illness strongly affects the way others see me					
My illness is likely to be permanent rather than temporary					
My illness will improve in time					
Nothing I do will affect my illness					
I have a clear picture or understanding of my condition					
My illness makes me feel afraid					
My illness has serious financial consequences					
I have the power to influence my illness					
When I think about my illness I get upset					
My illness causes difficulties for those who are close to me					
My actions will have no affect on the outcome of my illness					
My illness does not worry me					

Section 6: Details about other health problems

1. Has a doctor ever diagnosed you with either of the following medical conditions:

   Chronic fatigue syndrome **Yes** ☐ **No** ☐ **Don't know** ☐

   Irritable bowel syndrome **Yes** ☐ **No** ☐ **Don't know** ☐

2. If yes, are you currently experiencing symptoms of this condition? **Yes** ☐ **No** ☐

3. Are you aware of any other major medical problem you have that may affect your recovery?

   Yes ☐ **No** ☐

   If yes, what is this problem or illness? _____

Section 7: Recent stress levels

Stress is known to be an important factor in our ability to fight infection. The questions in this section ask about your feelings and thoughts in the ***month before you became ill***. In each case you will be asked to indicate how often you have felt or thought a certain way by ticking the box that best applies.

	Never	**Almost never**	**Some-times**	**Fairly often**	**Very often**
How often have you been upset because of something that happened unexpectedly?					
How often have you felt that you were unable to control the important things in your life?					
How often have you felt nervous and stressed?					
How often have you felt confident about your ability to handle your personal problems?					
How often have you felt that things were going your way?					
How often have you found that you could not cope with all the things you had to do?					
How often have you been able to control irritations in your life?					
How often have you felt that you were on top of things?					
How often have you been angered because of things that happened that were outside of your control?					
How often have you felt difficulties were piling up so high that you could not overcome them?					

Section 8: Questions about how you have been feeling

Emotions play an important part in most illnesses. This section is designed to help us know how you are currently feeling. Read each statement and *circle* the one answer below it that comes closest to how you have been feeling **during the past week**.

1. I feel tense or 'wound-up':

1. Most of the time
2. A lot of the time
3. From time to time, occasionally
4. Not at all

2. I still enjoy the things I used to enjoy:

1. Definitely as much
2. Not quite as much
3. Only a little
4. Hardly at all

3. I get a sort of frightening feeling as if something awful is about to happen:

1. Very definitely and quite badly
2. Yes, but not too badly
3. A little, but it doesn't worry me
4. Not at all

4. I can laugh and see the funny side of things:

1. As much as I always could
2. Not quite as much now
3. Definitely not so much now
4. Not at all

5. Worrying thoughts go through my mind:

1. A great deal of the time
2. A lot of the time
3. From time to time but not too often
4. Only occasionally

6. I feel cheerful:

1. Not at all
2. Not often
3. Sometimes
4. Most of the time

7. I can sit at ease and feel relaxed:

1. Definitely
2. Usually
3. Not often
4. Not at all

8. I feel as if I am slowed down:

1. Nearly all the time
2. Very often
3. Sometimes
4. Not at all

9. I get a sort of frightened feeling like 'butterflies' in the stomach:

1. Not at all
2. Occasionally
3. Quite often
4. Very often

10. I have lost interest in my appearance:

1. Definitely
2. I don't take as much care as I should
3. I may not take quite as much care as ever
4. I take just as much care as ever

11. I feel restless as if I have to be on the move:

1. Very much indeed
2. Quite a lot
3. Not very much
4. Not at all

12. I look forward with enjoyment to things:

1. As much as I ever did
2. Rather less than I used to
3. Definitely less than I used to
4. Hardly at all

13. I get sudden feelings of panic:

1. Very often indeed
2. Quite often
3. Not very often
4. Not at all

14. I can enjoy a good book or radio or TV programme:

1. Often
2. Sometimes
3. Not often
4. Very seldom

Section 9: Details about your usual exercise levels

1. Before you became ill, did you do any **regular** form of exercise for more than 15 minutes? If yes, please write in the table below the kind of exercise you **usually** do, and how many times a week on average you would do this exercise.

Type of exercise	Times per week
Strenuous exercise (heart beats rapidly) eg: running, rugby, aerobics. ……	……
Moderate exercise (not exhausting) eg: fast walking, dancing, easy cycling. ……..	……
Mild exercise (minimal effort) eg: yoga, bowls, golf, easy walking. ……..	…….....

2. During a normal week, how often do you engage in **any** regular activity long enough to work up a sweat (heart beats rapidly)? (Please tick one)

Often ☐ **Sometimes** ☐ **Never/Rarely** ☐

Section 10: Expectations you have of yourself

We are interested to know about your general expectations of yourself. Please read the following statements and tick the box that best describes how true the statement is for you.

	Strongly agree	Agree	Don't know	Disagree	Strongly disagree
When I start something I feel anxious that I might fail					
It feels as though my best is never good enough for other people					
If I make a mistake, I feel that the whole thing is ruined					
If I fail people, I fear they will cease to respect or care for me					
I feel guilty or ashamed if I do less than perfectly					
No matter how well I do, I never feel satisfied with my performance					
I feel I have to be perfect to gain people's approval					
I worry what others think if I make mistakes					
I would rather not start something than risk doing it less than perfectly					
When I do things, I feel others will judge critically the standard of my work					

Section 11: Questions about you:

1. Are you: Male ☐ Female ☐

2. What is your age? _____

3. With which ethnic group do you identify? _____

4. Where do you live? Suburb _____

5. Are you:

Single	Married/de facto	Divorced/separated	Widowed

6. Do you have any children? **Yes** ☐ **No** ☐

*If you answered 'Yes', how many:*_____

7. What is the highest educational qualification you received?

None	Secondary School	Polytechnic or similar	University

8. Do you have paid work outside the home? **Yes** ☐ **No** ☐

If yes, please describe what you do for paid work:

_____

_____

Thank you for your valuable time

We appreciate your participation in this study

Please place this questionnaire with your consent form in the envelope provided, and post it as soon as possible

Appendix 11. Three month follow-up questionnaire.

Code				
Date				

THE UNIVERSITY OF AUCKLAND
FACULTY OF MEDICAL AND HEALTH SCIENCES

Recovery from Acute Infection

Follow-up questionnaire

- We are interested to find out about your recovery from the illness you experienced 3 months ago.
- This questionnaire is important even if you are not experiencing any further symptoms as we want to know what may speed up recovery as well as what may slow it down.
- Remember that all answers are kept totally **CONFIDENTIAL** and you will not be identified in any way.
- There are no right or wrong answers to these questions. Try to answer them all and do not think too long about each question.

When you have finished,
please place the questionnaire in the envelope provided,
and post as soon as possible.

If you have any queries about this study or questionnaire, please do not hesitate to call Meagan Spence at the following number:-

3737 599 ext. 6757

Thank you for your time!

Section 1: Details about general symptoms

Please indicate whether or not you have experienced any of these symptoms **in the last month**, and whether or not you believe that these symptoms are **related** to your illness three months ago.

SYMPTOM	I have experienced this symptom in the last month				If yes, is this symptom *related to your illness 3 months ago?*	
	No		Yes		Yes	No
Sore throat						
Loss of appetite						
Weight loss						
Nausea						
Headache						
Sore eyes						
Loss of strength						
Feeling off colour				☞		
Breathlessness						
Joint pain						
Dizziness						
Fever				If Yes		
Unrefreshing sleep						
Swollen glands						
Fatigue/tiredness				☞		
Vomiting						
Rash						
Diarrhoea						
Racing heartbeat						
Feeling worse after exertion						
Stomach pain						
Blood in faeces						
Aching muscles						

Section 2: Fatigue-related symptoms

1. Do you suffer from fatigue or excessive tiredness?

Yes ☐ **No** ☐ **(If no please go to section 3 on the next page)**

2. How severe is the fatigue you are experiencing?

Mild ☐ **Moderate** ☐ **Severe** ☐

3. Please answer the following questions, yes or no, as they apply to you.

	Yes	No
Do you suffer from physical fatigue?		
Do you suffer from mental fatigue?		
Do you feel tired 50% of the time or more?		
Have you been experiencing this fatigue for 6 months or more?		
Is this fatigue disabling?		
Does the fatigue disappear or get significantly better if you rest?		
Was there a definite start to this fatigue?		
Does this fatigue occur only after excessive exercise?		
Does this fatigue stop you from doing things you would like to do?		
Can you ignore this fatigue?		

4. Does this fatigue significantly impair any of the following areas of your life? (please tick all that apply)

- ☐ Work
- ☐ Study
- ☐ Physical exercise
- ☐ Leisure activities
- ☐ Self care (dressing, bathing, preparing meals)
- ☐ Housework and home management
- ☐ Family life/childcare

5. Do you suffer from any of the following symptoms? (please tick all that apply)

- ☐ Muscle pain
- ☐ Joint pain
- ☐ Headaches
- ☐ Sore throat
- ☐ Tender neck/armpit glands
- ☐ Unrefreshing sleep
- ☐ Poor memory
- ☐ Poor concentration
- ☐ Feeling off colour for 24 hours after exertion

Section 3: Bowel-related symptoms

1. Certain infections can affect the bowel. Even if this is not the case for you we would like you to answer the following questions by ticking the appropriate boxes.

	Yes	No
Do you have more than 3 bowel movements each day?		
Do you have less than 3 bowel movements each week?		
Do you have loose or watery stools more than 25% of the time?		
Do you have hard or lumpy stools more than 25% of the time?		
Do have an urgent need to have a bowel movement more than 25% of the time?		
Do you have to strain to have a bowel motion more than 25% of the time?		
Do you feel that your bowel movement is incomplete more than 25% of the time?		
Do you feel that your abdominal area is bloated more than 25% of the time?		
Do you notice mucous in your stools more than 25% of the time?		

2. Do you often experience abdominal pain?

Yes ☐ **No** ☐ **(If no please go to question 3 below)**

	Yes	No
Does this pain get better after having a bowel movement?		
Do you have more frequent bowel movements when you have this pain?		
Do you have less frequent bowel movements when you have this pain?		
Is this pain related to your stools being looser/watery?		
Is this pain related to your stools being harder/lumpier?		

3. If yes to any of the above bowel symptoms in question 1 or 2, please answer the following:

	Yes	No
Have you had these symptoms for 3 months or more?		
Can you ignore these symptoms?		

Do these bowel symptoms significantly impair any of the following areas of your life? (please tick all that apply)

- ☐ Work
- ☐ Study
- ☐ Physical exercise
- ☐ Leisure activities
- ☐ Self care (dressing, bathing, preparing simple meals)
- ☐ Housework and home management
- ☐ Family life/childcare

Section 5: Your general health and wellbeing

1. Please answer the following questions about whether or not the illness you experienced three months ago has had any ongoing impact on your daily life. Circle the number that best describes your current situation.

(a) Because of my illness three months ago, my ability to **go to work** or **attend school/university** is impaired.

0	1	2	3	4	5	6	7	8
Not at all	Slightly		Definitely		Markedly		Very severely impaired / Cannot work	

(b) Because of my illness three months ago, my **home management** is impaired (e.g. cleaning, shopping, cooking, child care, paying bills, etc).

0	1	2	3	4	5	6	7	8
Not at all	Slightly		Definitely		Markedly		Very severely impaired	

(c) Because of my illness three months ago, my **social & leisure** activities are impaired (with other people, e.g. outings, visitors, parties, etc).

0	1	2	3	4	5	6	7	8
Not at all	Slightly		Definitely		Markedly		Very severely impaired	

(d) Because of my illness three months ago, my **private** leisure activities are impaired (those things done alone, e.g. reading, gardening, walking alone, sewing, etc).

0	1	2	3	4	5	6	7	8
Not at all	Slightly		Definitely		Markedly		Very severely impaired	

(e) Because of my illness three months ago, my ability to form and maintain **relationships** is impaired.

0	1	2	3	4	5	6	7	8
Not at all	Slightly		Definitely		Markedly		Very severely impaired	

2. Please write in the boxes below the number of times you have sought help from each of the following health professionals in **the last three months** for any complaint or problem.

Doctor	_____ times
Naturopath	_____ times
Medical Specialist	_____ times
Acupuncturist	_____ times
Other (please specify)……..……..	_____ times

3. These questions are about how you have been feeling *during the past 4 weeks*. For each question please tick the box that comes closest to the way you have been feeling.

How much of the time *during the past 4 weeks…*	**All of the time**	**Most of the time**	**A good bit of the time**	**Some of the time**	**A little of the time**	**None of the time**
Have you been a nervous person?						
Have you felt so down in the dumps that nothing could cheer you up?						
Have you felt calm and peaceful?						
Have you felt downhearted and blue?						
Have you been a happy person?						

4. Over the last month, did you do any **regular** form of exercise for more than 15 minutes?

Yes ☐ **No** ☐

If yes, please write in the table below the kind of exercise you did, and how many times a week you did this exercise.

Type of exercise	**Times per week**
Strenuous exercise (heart beats rapidly) eg: running, rugby, aerobics. …….…….	……
Moderate exercise (not exhausting) eg: fast walking, dancing, easy cycling. ……..	……
Mild exercise (minimal effort) eg: yoga, bowls, golf, easy walking. ……..	…….....

5. During a normal week, how often do you engage in **any** regular activity long enough to work up a sweat (heart beats rapidly)? (Please tick one)

Often ☐ **Sometimes** ☐ **Never/Rarely** ☐

Please answer these last two questions only if you have been experiencing ongoing symptoms of <u>any</u> kind.

6. Do you have a name or diagnosis to explain your current symptoms?

   Yes ☐ **No** ☐

   If yes, what is that name or diagnosis?

   _____

7. Which of the following best applies to how you see your current symptoms (please tick one):

My symptoms are physical	My symptoms are mainly physical	Both physical and psychological factors are involved in my symptoms	My symptoms are mainly psychological	My symptoms are psychological in nature

Thank you for your valuable time

We appreciate your participation in this study

Please place this questionnaire in the envelope provided,
and post as soon as possible

Appendix 12. Six month follow-up questionnaire.

Code				
Date				

Recovery from Acute Infection

Six month follow-up questionnaire

- Thank you for your ongoing willingness to participate in this study. We are still interested to find out about your recovery from the illness you experienced 6 months ago.

- This questionnaire is important **even if you are not experiencing any further symptoms** as we want to know what may speed up recovery as well as what may slow it down.

- Remember that all answers are kept totally **CONFIDENTIAL** and you will not be identified in any way.

- There are no right or wrong answers to these questions. Try to answer them all and do not think too long about each question.

When you have finished,
please place the questionnaire in the envelope provided,
and post as soon as possible.

If you have any queries about this study or questionnaire, please do not hesitate to call Meagan Spence at the following number:-

3737 599 ext. 6757

Thank you for your time!

Section 1: Details about general symptoms

1. Please indicate whether or not you have experienced any of these symptoms **in the last month**, and whether or not you believe that these symptoms are **related** to your illness six months ago

SYMPTOM	I have experienced this symptom in the last month				If yes, is this symptom *related to your illness 6 months ago?*	
	No		Yes		Yes	No
Sore throat						
Loss of appetite						
Weight loss						
Nausea						
Headache						
Sore eyes						
Loss of strength				☞		
Feeling off colour						
Breathlessness						
Joint pain						
Dizziness				**If Yes**		
Fever						
Unrefreshing sleep						
Swollen glands						
Fatigue/tiredness						
Vomiting				☞		
Rash						
Diarrhoea						
Racing heartbeat						
Feeling worse after exertion						
Stomach pain						
Blood in faeces						
Aching muscles						

2. Are you currently experiencing any other symptoms not listed in this table?
   Yes ☐ **No** ☐ If yes, what are they?

_____

3. Are you currently experiencing an illness that explains these symptoms?
   Yes ☐ **No** ☐ If yes, what is that illness?

_____

Section 2: Fatigue-related symptoms

1. Do you suffer from fatigue or tiredness?

Yes ☐ **No** ☐ **(If no please go to section 3 on the next page)**

2. How severe is the fatigue you are experiencing?

Mild ☐ **Moderate** ☐ **Severe** ☐

3. Please answer the following questions, yes or no, as they apply to you.

	Yes	No
Do you suffer from physical fatigue?		
Do you suffer from mental fatigue?		
Do you feel tired 50% of the time or more?		
Have you been experiencing this fatigue for 6 months or more?		
Is this fatigue disabling?		
Does the fatigue disappear or get significantly better if you rest?		
Was there a definite start to this fatigue?		
Does this fatigue occur only after excessive exercise?		
Does this fatigue stop you from doing things you would like to do?		
Can you ignore this fatigue?		

4. Do you suffer from any of the following symptoms?

- ☐ Muscle pain
- ☐ Joint pain
- ☐ Headaches
- ☐ Sore throat
- ☐ Tender neck/armpit glands
- ☐ Unrefreshing sleep
- ☐ Poor memory
- ☐ Poor concentration
- ☐ Feeling off colour for 24 hours after exertion

5. Do you have a name or diagnosis to explain your fatigue-related symptoms?

Yes ☐ **No** ☐ If yes, what is that name or diagnosis?_____

6. Have you sought help for these symptoms from a doctor or other health professional in the last 6 months?

Yes ☐ **No** ☐ If yes, how many times have you seen them? ____ times

Section 3: Bowel-related symptoms

1. Certain infections can affect the bowel. Even if this is not the case for you we would like you to answer the following questions by ticking the appropriate boxes.

	Yes	No
Do you have more than 3 bowel movements each day?		
Do you have less than 3 bowel movements each week?		
Do you have loose or watery stools more than 25% of the time?		
Do you have hard or lumpy stools more than 25% of the time?		
Do have an urgent need to have a bowel movement more than 25% of the time?		
Do you have to strain to have a bowel motion more than 25% of the time?		
Do you feel that your bowel movement is incomplete more than 25% of the time?		
Do you feel that your abdominal area is bloated more than 25% of the time?		
Do you notice mucous in your stools more than 25% of the time?		

2. Do you often experience abdominal pain?

Yes ☐ **No** ☐ (If no please go to question 3 below)

	Yes	No
Does this pain get better after having a bowel movement?		
Do you have more frequent bowel movements when you have this pain?		
Do you have less frequent bowel movements when you have this pain?		
Is this pain related to your stools being looser/watery?		
Is this pain related to your stools being harder/lumpier?		

3. If yes to **any of the above bowel symptoms** in question 1 or 2, please answer the following:

	Yes	No
Have you had these symptoms for 3 months or more?		
Can you ignore these symptoms?		
Do you have a name or diagnosis to explain these symptoms? If yes, what is that name or diagnosis? _____		
Have you sought help for these symptoms from a doctor or other health professional in the last 6 months? If yes, how many times have you seen them? _____ times		

Section 4: Your general health and wellbeing:

	No. of days
1. Thinking about your physical health, which includes physical illness or injury, for how many days during the past 30 days was your physical health not good?	……..
2. Thinking about your mental health, which includes stress, depression, and problems with emotions, for how many days during the past 30 days was your mental health not good?	……..
3. During the past 30 days, approximately how many days did poor physical or mental health keep you from doing your usual activities, such as self care, work or recreation?	……..

4. Please write in the boxes below the number of times you have sought help from each of the following health professionals in the last three months for any complaint or problem.

Doctor	_____ times
Naturopath	_____ times
Medical Specialist	_____ times
Acupuncturist	_____ times
Other (please specify)……..……..	_____ times

5. Over the last month, did you do any **regular** form of exercise for more than 15 minutes?

Yes ☐ **No** ☐

If yes, please write in the table below the kind of exercise you did,and how many times a week you did this exercise.

Type of exercise	Times per week
Strenuous exercise (heart beats rapidly) eg: running, rugby, aerobics. …….…….	……
Moderate exercise (not exhausting) eg: fast walking, dancing, easy cycling. ……..	……
Mild exercise (minimal effort) eg: yoga, bowls, golf, easy walking. ……..	……...

6. During a normal week, how often do you engage in **any** regular activity long enough to work up a sweat (heart beats rapidly)? (Please tick one)

Often ☐ **Sometimes** ☐ **Never/Rarely** ☐

7. These questions are about how you have been feeling ***during the past 4 weeks.*** For each question please tick the box that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks…	**All of the time**	**Most of the time**	**A good bit of the time**	**Some of the time**	**A little of the time**	**None of the time**
Have you been a nervous person?						
Have you felt so down in the dumps that nothing could cheer you up?						
Have you felt calm and peaceful?						
Have you felt downhearted and blue?						
Have you been a happy person?						

8. Please answer the following questions about whether or not the illness you experienced six months ago has had any ongoing impact on your daily life. Circle the number that best describes your current situation.

(a) Because of my illness six months ago, my ability to **go to work** or **attend school/university** is impaired.

0	1	2	3	4	5	6	7	8
Not at all	Slightly		Definitely		Markedly		Very severely impaired / Cannot work	

(b) Because of my illness six months ago, my **home management** is impaired (e.g. cleaning, shopping, cooking, child care, paying bills, etc).

0	1	2	3	4	5	6	7	8
Not at all	Slightly		Definitely		Markedly		Very severely impaired	

(c) Because of my illness six months ago, my **social & leisure** activities are impaired (with other people, e.g. outings, visitors, parties, etc).

0	1	2	3	4	5	6	7	8
Not at all	Slightly		Definitely		Markedly		Very severely impaired	

(d) Because of my illness six months ago, my **private** leisure activities are impaired (those things done alone, e.g. reading, gardening, walking alone, sewing, etc).

0	1	2	3	4	5	6	7	8
Not at all	Slightly		Definitely		Markedly		Very severely impaired	

(e) Because of my illness six months ago, my ability to form and maintain **relationships** is impaired.

0	1	2	3	4	5	6	7	8
Not at all	Slightly		Definitely		Markedly		Very severely impaired	

If you have any further comments to make about your illness six months ago, how you have managed it and/or recovered from it please feel free to write them below.

……

……

……

……

……

……

……

……

……

Thank you for your valuable time

We appreciate your participation in this study

Please place this questionnaire in the
envelope provided,
and post as soon as possible