VOLUME I

RESEARCH COMPONENT

NEUROLOGICAL AND COGNITIVE SYMPTOMS AND WELLBEING OUTCOMES IN ADULTS WITH COELIAC DISEASE

by
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A THESIS SUBMITTED TO THE UNIVERSITY OF BIRMINGHAM FOR THE DEGREE OF DOCTOR OF CLINICAL PSYCHOLOGY

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OVERVIEW

This thesis is submitted as part of the requirements for the degree of Doctorate in Clinical Psychology at The University of Birmingham. This thesis consists of two volumes which demonstrate clinical (Volume II) and research (Volume I) ability.

Volume I

The first volume consists of three chapters. The first is a systematic literature review examining what the evidence is for neurological and cognitive symptoms of coeliac disease and non-coeliac gluten sensitivity in adults. The second chapter presents a piece of research investigating whether illness perceptions are moderated and mediated through self-efficacy for the gluten free diet and coping for the outcomes of psychological wellbeing and quality of life. The final chapter is a brief public dissemination document that provides an overview of the research carried for this thesis.

Volume II

The second volume demonstrates clinical ability by presenting four clinical practice reports (CPR) and one CPR abstract for a report that was presented orally. CPR 1 describes assessment and formulation of 10-year-old boy referred to Child and Adolescent Mental Health Service (CAMHS) due to lifelong food neophobia and limited diet. CPR 2 is a service evaluation on how well a West Midlands CAMHS service follows the local anorexia nervosa pathway and how this pathway compares to the NICE guidelines for eating disorders (NICE, 2004). The third CPR is a single case experimental design (SCED) aimed at reducing obsessive compulsive (OCD) checking behaviours in an 82-year-old woman who had been experiencing symptoms for around 60 years. CPR 4 is a case study of a 35-year-old male British military veteran with anxiety and post-traumatic stress disorder. The final CPR is the abstract of an oral presentation outlining a case study of a 29-year-old woman with borderline personality disorder using a dialectical behaviour therapy (DBT) framework.

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CONTENTS

VOLUME I: RESEARCH COMPONENT

SYSTEMATIC REVIEW

What is the Evidence for Neurological and Cognitive Symptoms Associated with Coeliac Disease and Non-Coeliac Gluten Sensitivity in Adults?

ABSTRACT 2

INTRODUCTION 4

METHODOLOGY 11

THEMES IDENTIFIED 29

CLINICAL AND RESEARCH IMPLICATIONS 40

GLOSSARY 43

REFEjRENCES 45

EMPIRICAL PAPER

Adult Coeliac Disease: Illness Perceptions, Psychological Wellbeing, Quality of Life and the Moderating and Mediating Roles of Coping and Self-Efficacy

ABSTRACT 53

INTRODUCTION 54

METHOD 63

RESULTS 70

DISCUSSION 93

CONCLUSION 102

REFERENCES 104

PUBLIC DISSEMINATION DOCUMENT

PUBLIC DISSEMINATION DOCUMENT 114

VOLUME I: APPENDICES

SYSTEMATIC REVIEW

Appendix A - Reason articles rejected.....120
Appendix B - Full text articles not available 121

EMPIRICAL PAPER

Appendix A – Questionnaire Pack.....122
Appendix B – Ethics approval letter.....135
Appendix C - Illustrations of significant x~m pathways for DASS and CDQ.....136
Appendix D - Illustrations of significant xw~m pathways for DASS and CDQ.....139

PUBLIC DISSEMINATION DOCUMENT

None

VOLUME I: LIST OF FIGURES

SYSTEMATIC REVIEW

Figure 1: Search terms for review……..……..11
Figure 2: Flowchart of article selection……..……..13
Figure 3: Questions included in Caldwell, Taylor & Henshaw (2005)..……..23

EMPIRICAL PAPER

Figure 1: Participant marrital status and educational level……..……..60
Figure 2.1: Conceptual illustration of mediation with multiple mediators..…….....79
Figure 2.2: Statistical illustration of mediation with multiple mediators…….....79
Figure 3.3: Conceptual illustration of moderated mediation with multiple mediators..…84
Figure 3.2: Statistical illustration of moderated mediation with multiple mediators……84

PUBLIC DISSEMINATION DOCUMENT

None

VOLUME I: LIST OF TABLES

SYSTEMATIC REVIEW

Table 1: Inclusion criteria……..12
Table 2: Summary of studies reviewed……14
Table 3: Quality assessment framework scores……25
Table 4: Neurological symptoms……...29
Table 5: Cognitive symptoms……33

EMPIRICAL PAPER

Table 1: Missing data patterns……...66
Table 2: Internal consistency……68
Table 3: Standard errors and means for IPQ-R subscales..……...69
Table 4: Correlations for IPQ-R subscales……70
Table 5: Correlations for DASS and years since diagnosis by gender...……...71
Table 6: Standard errors and means for CDQ subscales……...71
Table 7: Correlations for CDQ subscales……..72
Table 8: Correlations for CDQ and years since diagnosis……72
Table 9: Standard errors and means for Brief COPE subscales……73
Table 10: Correlations for Brief COPE subscales……74
Table 11: Correlations for ASES, DASS, CDQ and Brief COPE……74
Table 12: Correlations for IPQ-R and CDQ……76
Table 13: Correlations for IPQ-R and Brief COPE……..77
Table 14: Correlations for Brief COPE, DASS and CDQ……78
Table 15: Significant x~m routes for DASS……80
Table 16: Significant m~y routes for DASS……80
Table 17: Significant x~m routes for CDQ……...81
Table 18: Significant m~y routes for CDQ……...82
Table 19: Significant xw~m routes for DASS……..85
Table 20: Significant xw~m routes for CDQ……86

PUBLIC DISSEMINATION DOCUMENT

None

VOLUME II: CLINICAL COMPONENT

CLINICAL PRACTICE REPORT 1

A 10-year-old boy referred to Child and Adolescent Mental Health Services due to lifelong food neophobia and limited diet: Formulation from cognitive-behavioural model and psychodynamic models

ABSTRACT 2
CONSENT 3
ASSESSMENT 4
FORMULATIONS 11
CRITIQUE AND REFLECTIONS 22
REFERENCES 26

CLINICAL PRACTICE REPORT 2

A service evaluation on how well a West Midlands CAMHS service follows the local anorexia nervosa pathway and how this pathway compares to the NICE (2004) guidelines for eating disorders

ABSTRACT 30
CONSENT 31
INTRODUCTION 32
DISCUSSION 52
RECOMMENDATIONS 55
CONCLUSION 56
REFERENCES 58

CLINICAL PRACTICE REPORT 3

A single case experimental design (SCED) aimed at reducing obsessive compulsive (OCD) checking behaviours in an 82-year-old woman who had been experiencing symptoms for around 60 years

ABSTRACT 62
INTRODUCTION 63
ASSESSMENT 64
FORMULATION 68

INTERVENTION 76
METHOD 78
RESULTS 80
DISCUSSION 84
REFLECTIONS 87
REFERENCES 88

CLINICAL PRACTICE REPORT 4

A case study of a 35-year-old male British military veteran with anxiety and post-traumatic stress disorder

ABSTRACT 95
CONSENT 96
INTRODUCTION 97
ASSESSMENT 99
FORMULATION 106
INTERVENTION 113
EVALUATION 117
REFLECTIONS 118
REFERENCES 120

CLINICAL PRACTICE REPORT 5

Clinical Case Presentation of a 29-year-old Woman with Borderline Personality Disorder Using a Dialectical Behaviour Therapy (DBT) Framework

ABSTRACT 126

VOLUME II: APPENDICES

CLINICAL PRACTICE REPORT 1

Appendix A – The SCARED Child 128
Appendix B – The Food Neophobia Scale (FNS) 130

CLINICAL PRACTICE REPORT 2

Appendix A – Audit Tool 132

Appendix B – Service User Questionnaire 133
Appendix C - Flow chart of the CAMHS annorexia pathway.....134
Appendix D – NRES Guidance 135

CLINICAL PRACTICE REPORT 3

Appendix A - Core 10.....136
Appendix B - Obsessive Compulsive Inventory (OCI) 137
Appendix C - Examples of British propaganda circa 1939-1945 139
Appendix D - OCD Ritual Diary 140

CLINICAL PRACTICE REPORT 4

Appendix A - Self-administered Admission Outcome Measures.....141
Appendix B - CBT “hot cross bun” maintenance cycle (Dudley & Kuyken, 2006) 151

CLINICAL PRACTICE REPORT 5

None

VOLUME II: LIST OF FIGURES

CLINICAL PRACTICE REPORT 1

Figure 1: Bobby’s Genogram...……...……..10
Figure 2: Longitudinal formulation of Bobby’s difficulties...……...……14
Figure 3: Maintenance Cycle of Bobby’s Avoidance of Anxiety……...…...……...16
Figure 4: Maintenance Cycle of Bobby’s Avoidance of New Foods……...…….20
Figure 5: Bobby’s Triangle of Conflict...……...……...……21
Figure 6: Bobby’s Triangle of Person...……...…….21

CLINICAL PRACTICE REPORT 2

Figure 1: A flow chart illustrating the CAPA model…….36
Figure 2: An example of a matching theme in NICE guidelines and local pathway…….50

CLINICAL PRACTICE REPORT 3

Figure 1: Genogram of Emily's family…….…….65
Figure 2: "Vicious Flower"…….……...71
Figure 3: A possible downwards chain to Emily's Core Beliefs…….……..73
Figure 4: "Vicious Flower"……..…….…….……76

CLINICAL PRACTICE REPORT 4

Figure 1: Paul's Genogram……....97
Figure 2: Timeline of life events……...104
Figure 3: Ehlers and Clark (2000) Cognitive Model of PTSD…… 107
Figure 4: Illustration of Paul's longitudinal formulation……..113

CLINICAL PRACTICE REPORT 5

None

VOLUME II: LIST OF GRAPHS

CLINICAL PRACTICE REPORT 1

None

CLINICAL PRACTICE REPORT 2

Graph 1: Age of referral shown in years...…….39
Graph 2: Self-reported ethnicity…….39
Graph 3: Reason for referral……...40
Graph 4: Was height information was present at referral……...41
Graph 5: How often BMI information was present at referral……42
Graph 6: How frequently rate of weight loss was gathered by referral officer…….. 43
Graph 7: How frequently medical information were requested by the referral officer….. 44
Graph 8: How frequently the gender specific centile charts were completed…….45
Graph 9: How frequently referrals were made to a dietician for consultation……46
Graph 10: How frequently referrals were made for urgent medic appointments……48

CLINICAL PRACTICE REPORT 3

Graph 1: The daily frequency of Emily's checking behaviour……..82
Graph 2: The median trendline for baseline data……...83

CLINICAL PRACTICE REPORT 4

None

CLINICAL PRACTICE REPORT 5

None

VOLUME II: LIST OF TABLES

CLINICAL PRACTICE REPORT 1

None

CLINICAL PRACTICE REPORT 2

Table 1: Items against which clinical notes will be audited...……38
Table 2: NICE (2004) guideline relating to AN……...……..51

CLINICAL PRACTICE REPORT 3

Table 1: List of items checked and rituals……..75
Table 2: Table to show timeline of events……..81

CLINICAL PRACTICE REPORT 4

Table 1: Psychometric assessments completed at assessment……..100
Table 2: List of groups offered during 2-week residential program…….115
Table 3: Topics covered in individual therapy session…….117
Table 4: Pre- and post- intervention outcome measures……...124

CLINICAL PRACTICE REPORT 5

None

VOLUME I: SYSTEMATIC REVIEW

What is the Evidence for Neurological and Cognitive Symptoms Associated with Coeliac Disease and Non-Coeliac Gluten Sensitivity in Adults?

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ABSTRACT

Introduction

Coeliac disease (CD) and non-coeliac gluten sensitivity (NCGS) are generally identified by their gastro-intestinal symptoms. However, more recently there has been an increasing focus on the extra-intestinal symptoms of such conditions. Within the literature, these symptoms remain up to now somewhat under-explored and the data that does exist are reported across various disciplines. This review aims to combine data on the neurological and cognitive symptoms experienced by adults with untreated CD or NCGS from multiple disciplines and to assess the quality of this research using an established research quality framework.

Method

Six databases were searched (Medline, PsychARTICLES, PsychINFO, EMBASE, CINHAL and ProQuest), these results were combined with backwards and forwards reference searches and resulted in 114 articles. After application of the inclusion criteria, 21 studies were included for review; five qualitative and 16 quantitative. Studies including CD and NCGS, neurological e.g. slowed nerve function or altered sensation and cognitive symptoms e.g. memory difficulties or word-finding problems were included. These were assessed against Caldwell, Taylor and Henshaw's (2005) quality framework.

Results

The literature gives the clearest picture of the neurological symptoms found in adults with CD and to a lesser extent NCGS, these studies are generally more robust. There is consensus as to what the symptoms are (slowed nerve conduction, neurological pain and altered sensation in hands and feet). The cognitive symptoms are less clear; there is no over-all agreement as to whether there are cognitive symptoms and certainly not which cognitive abilities are affected. This review tentatively suggests there is some evidence for short-term memory problems and fatigue, however, to accept these results with confidence further research focussing on this area would need to be conducted.

Discussion

The literature is complex and there are a number of issues that make it more difficult to be confident in the neurological and cognitive symptoms found in adults with untreated CD and

NCGS. Further high-quality research would help to clarify the picture. Studies varied in their designs and the methods used by different studies to assess cognitive symptoms were less consistent than those used to assess neurological symptoms. Neurological tests such as transcranial magnetic stimulation (TMS) were able to identify neurological symptoms before individuals were aware of them. This was not possible for cognitive symptoms, which mainly relied on self-report methods of identification. Response to a gluten free diet (GFD) varies depending on duration of gluten exposure, symptoms and GFD. The importance of early diagnosis and treatment in both CD and NCGS to prevent potentially permanent neurological damage is discussed.

INTRODUCTION

Gluten is the collective name for the proteins found in wheat (Biesiekiersk, 2017) and other cereals such as barley, rye, oats and spelt (Kupper, 2005). There are a number of conditions related to gluten ingestion, these include, but are not limited to coeliac disease (CD) and non-coeliac gluten sensitivity (NCGS) – which will be discussed in detail below - wheat allergy (Coeliac UK, 2017), dermatitis herpetiformis (DH) (Coeliac UK, 2017), and gluten ataxia (Baizabal-Carvallo & Jankovic, 2012) are all related to gluten ingestion. DH has no known cognitive or neurological symptoms associated with it (Coeliac UK, 2017; NICE, 2011). In contrast, gluten ataxia (GA), which is a relatively newly identified auto-immune mediated response to gluten (Hadjivassiliou et al., 2015), is wholly defined by neurological symptoms, such as poor balance and unusual sensations in the hands and feet (Hadjivassiliou et al., 2003). Removal of gluten from the diet halts and even reverses symptoms in GA (Hadjivassiliou et al., 2008), which suggests gluten has a direct effect on symptoms. In terms of wheat allergy, ingestion of gluten leads to an allergic response, which includes the cognitive symptom of fatigue. These gluten-mediated conditions contain neurological and/or cognitive symptoms. If these symptoms are directly related to gluten, other gluten-mediated conditions may have similar extra-intestinal symptoms.

In addition to wheat allergy, GA and DH, autoimmune conditions frequently co-occur with CD (Gujral et al., 2012; NICE, 2015) such as type 1 diabetes and autoimmune thyroid disease. Brands et al. (2005) and Dore et al. (2015) reported cognitive dysfunction in adults with type 1 diabetes in the areas of attention, psychomotor speed and visual perception even when control of diabetes is taken into account. Further to this, in 2005 Brands et al. concluded that processing speed and cognitive flexibility were mildly impaired in individuals with type 1 diabetes and McCrimmon et al. (2012) found memory and learning were affected by type 1 diabetes. Untreated hypothyroidism has an established link with cognitive

symptoms such as attention, concentration, language and memory difficulties (Cordes et al., 2015; Davis & Tremont, 2007) and sub-clinical and/or untreated hypothyroidism can cause symptoms of dementia (Pasqualetti et al., 2015) in older adults. It is difficult to establish whether these neurological and cognitive effects are disease-specific or, instead, due to more general autoimmune processes, in which case similar symptoms in adults with CD could be expected.

Inflammation is currently one of the leading theories for the cause of damage seen in a number of diseases including gastro-intestinal cancers (Eiro & Viscozo, 2012), Alzheimer's disease (Tansey et al., 2017), diabetes (Weir & Bonner-Weir, 2017) and thyroid disease (Khan et al., 2015). The processes behind inflammation are complex, but in an autoimmune condition such as CD, gluten molecules trigger a cellular response that includes the production and release of pro-inflammation cytokines. These cells then attract others to combat the intruding molecules, causing inflammation. Diet has also been found to increase inflammation in healthy individuals that leads to cognitive decline (Ozawa et al., 2017) so an autoimmune condition is not required for cognitive abilities to be affected (Lionetti et al., 2015). The most inflammatory dietary pattern is one high in red and processed meats, legumes and some vegetables, but low in whole grains. Individuals who cannot eat gluten will not be eating whole grains and may be more susceptible to the role of inflammation. Inflammation is likely to be strongest in the areas where gluten is most highly concentrated, namely the gut and brain.

Coeliac Disease

CD is an autoimmune condition triggered by the ingestion of gluten in genetically susceptible individuals. It was previously thought to be a disease of childhood (Hallert & Astrom, 1983), however, individuals are most frequently diagnosed between 40 – 60 years of age (Coeliac

UK, 2017). Gluten elicits an immune response and damage occurs to the villi of the small intestine. These hair-like structures (villi) absorb nutrients from food and villous atrophy is the term used to describe the flattening of the villi as a result of this auto-immune assault. Flattened villi significantly reduce the surface area of the small intestine, which results in a significant reduction in absorption, and nutritional deficiencies (Kupfer, 2009).

Prevalence of CD correlates with the amount of gluten containing foods typically consumed in the national diet and global rates vary (Hischenhuber et al., 2005; Koning, 2012). The UK reports around 1% of the population have CD (NICE, 2015), although CD is thought to be underdiagnosed (NICE QS134, 2016; Coeliac UK, 2017).

Stepkiak & Koning (2003) outline three factors that are required for the onset of CD, namely (1) a genetic predisposition, (2) a gluten containing diet and (3) a trigger (also Sollid & Jabri, 2013). Gastrointestinal infections are commonly reported as occurring before the onset of CD (Evans et al., 2012). Although there are some conflicting findings (Troncone et al., 2007) the most widely accepted explanation for the development of CD is that an appropriate immune response to an invading pathogen continues to respond to gluten after the initial infection is removed (Troncone et al., 2007).

Symptoms

Symptoms described by individuals with CD most commonly include gastrointestinal problems such as diarrhoea or constipation, bloating, pain and discomfort (Coeliac UK, 2017). There are also extra-intestinal symptoms, such as fatigue, weight loss and headaches (Bushara, 2005; NICE, 2015).

More recently, research literature is starting to emerge on the topic of CD “brain fog” (Yelland, 2017; Campagna et al., 2017), which up to this point has been a term frequently

used by the “CD community” - in forums and support groups - to describe what may be transient, mild, cognitive impairment. Anecdotally, people with CD have reported cognitive symptoms as the first indication of gluten exposure. However, there has been little empirical investigation of “brain fog” in CD to date, but Yelland (2017) identified memory, attention, executive function and processing speed as reported symptoms of “brain fog”. Cognitive impairment or “brain fog” is not exclusive to CD and has been examined in more detail in other conditions such as chronic fatigue syndrome (CFS: Jorgenson, 2008; Ocon, 2013) and postural tachycardia syndrome (Ross et al., 2013). Within CFS “brain fog” has been conceptualised as involving cognitive symptoms of poor attention, concentration and difficulty focussing on tasks (Ocon, 2013), as well as neurological symptoms of slowed reaction times (Cockshell & Mathias, 2010). Ross et al. (2013) reported similar findings of memory problems, attention and concentration difficulties and finding it hard to focus on tasks in their investigation of participants with postural tachycardia syndrome and “brain fog”.

Diagnosis and Management

Diagnosis is made via blood test and confirmatory biopsy if CD-specific antibodies are found or if symptoms persist in the absence of antibodies (NICE NG20, 2015; NICE QS134, 2016). There is no cure for CD and treatment involves removing the immune response-triggering molecule from the diet by following a lifelong gluten free diet (GFD) (NICE, 2015). This diet allows the villi to recover and within 12 months of a GFD commencing 27-66% of individuals’ intestines show no damage (rate of recovery is related to severity of disease; Corbett et al., 2012; Galli et al., 2014), and levels of CD-specific antibodies have reduced to a normal range in 43% of individuals (Corbett et al., 2012). Patients with CD typically report improvement in gastro-intestinal symptoms immediately after starting a GFD, whereas for

some the improvement is more gradual (Coeliac UK). Gastro-intestinal symptoms may reduce rapidly after the start of a GFD, but extra-intestinal symptoms can take longer to resolve (www.celiac.com).

Research using adult samples has found long-term, undiagnosed CD can result in several nutritional deficiencies and conditions related to malabsorption, which need to be treated alongside a GFD (American College of Gastroenterology, 2013; Urban-Kowalczyk et al. 2014). The most common of these conditions tends to be iron deficiency with or without anaemia (Carroccio et al., 1998), vitamin B12 deficiency, folic acid deficiency (Hu et al., 2006) and calcium deficiency.

Non-Coeliac Gluten Sensitivity

NCGS has previously been known as gluten sensitivity (Sapone et al., 2010). Despite the considerable overlap of symptoms of NCGS and CD reported below, the conditions are separate; the defining characteristic of NCGS is the presence of healthy villi cells in the small intestine (Lundin & Aleadini, 2012). The history of NCGS in the literature suggests that prior to the 1970s there was some investigation into gluten sensitivity, however the condition became lost and individuals with NCGS were either diagnosed as having CD or not diagnosed, but treated with a GFD (Catassi, 2015). NCGS is believed to affect more individuals than CD (Volta et al., 2014), however, due to the lack of a consistent definition the true rates are hard to establish. Sapone et al. (2012) reported an incidence rate of 6% whereas the Continuous National Health and Nutrition Examination Survey (CNHANES) a year later reported 0.55% of the population of the United States suffered from NCGS (Di Giacomo et al., 2013).

Symptoms

Due to the relative neglect of this condition there remains poor universally recognised symptomatology of NCGS (Di Sabatino et al., 2015) and cases are often self-reported (Rostami & Hogg-Kollars, 2012). Commonly reported symptoms of NCGS are similar to those of CD (Sapone et al, 2012; Sapone et al., 2015; Volta et al., 2012). As with CD, extra-intestinal complaints are also recognised (Yelland, 2017), the most frequently reported of which are fatigue and headaches (Volta et al., 2012). Numbness or altered perception in the extremities, such as pins and needles sensations, are also reported (Catassi et al., 2015).

Diagnosis and Management

For NCGS, no serological markers are known, however, this may change as the condition benefits from more attention, discussion and publication (Catassi et al., 2012; Volta et al., 2015). Within the literature diagnostic criteria are being developed for clinical use (Catassi et al., 2015; Catassi et al., 2013).

As with CD, the only effective treatment for NCGS is lifelong adherence to a GFD (Holmes, 2013). For some, gastro-intestinal symptoms remain even on a GFD, possibly due to other food intolerances (Catassi, 2015).

Aims

As discussed above, some of the conditions that occur as a result of gluten ingestion have neurological symptoms associated with them; in fact, GA is wholly defined by neurological symptoms. Other autoimmune conditions that frequently occur with CD (e.g., Type 1 diabetes) have been shown to be associated with neurological and cognitive symptoms. The defining characteristic of CD is that it is a gluten-mediated autoimmune response and, as

such, it is likely that there are neurological and cognitive symptoms associated with the condition, as have been found in other autoimmune conditions and as have been reported by patients with CD. Published literature on CD has focussed more on the medical and biological symptoms of the condition and response(s) to a GFD, while extra-intestinal symptoms (including cognitive and neurological symptoms) have been relatively neglected.

In contrast NCGS has suffered from under-investigation across all areas - little is known about the extra-intestinal symptoms related to this condition. It was decided therefore to include NCGS in this review partly to add to what is known about the condition. However, most significantly, including NCGS (with its symptomology that matches CD to such a degree, without it being an autoimmune condition) would help in identifying whether the neurological and cognitive symptoms seen in CD are related to gluten itself rather than an autoimmune process.

A complication of the extant literature is that evidence for cognitive and neurological symptoms is spread across a number of discipline areas; no review exists that has collated data to explore the evidence and quality of evidence for cognitive and neurological symptoms in CD and NCGS.

This review aims to combine data on the neurological and cognitive symptoms of adults with untreated CD or NCGS from multiple disciplines by:

1. Reviewing the literature on the cognitive and neurological symptoms of adults with untreated CD and NCGS, and
2. Assessing the quality of this research using an established research quality framework

METHODOLOGY

Search strategy

Six databases were originally searched in November 2016: Medline (1946-2016), PsychARTICLES, PsychINFO (1967-2016), EMBASE (1947-2016), CINHAL and ProQuest. The same search process was repeated in October 2017 to identify any new, additional, articles relevant for inclusion. Search terms were defined for the purpose of this review taking the key terms from the title (Figure 1).

Childhood CD can be related to complex conditions such as epilepsy (Mavroudi et al., 2005) and emotional disturbances (Da Silva Kotze et al., 2000) and identifying the symptoms related to CD or NCGS, but excluding those relating to other conditions, would be beyond the scope of this review. Similarly, in the elderly there is some cross-over between symptoms of dementia and the cognitive and neurological symptoms of CD and NCGS. Given the complexities of these two age-related samples in allowing a differentiation of CD neurological and cognitive symptoms from other associated conditions, childhood CD and CD in the elderly were excluded from the present review. As the majority of diagnoses of CD occur in adulthood (Coeliac UK) literature was restricted to studies relating to adult participants (18-65 years).

GA was not included as a search term as it is recognised as a separate autoimmune condition that can occur with or without CD. Research investigating GA has been included in the review as long as participants had CD or NCGS and met the requirements of the other inclusion criteria.

Search terms (Figure 1) were combined, as follows: neuro* OR cognitive* AND adult* or working age AND celiac or coeliac or gluten free diet AND gluten intol* or gluten sensi*

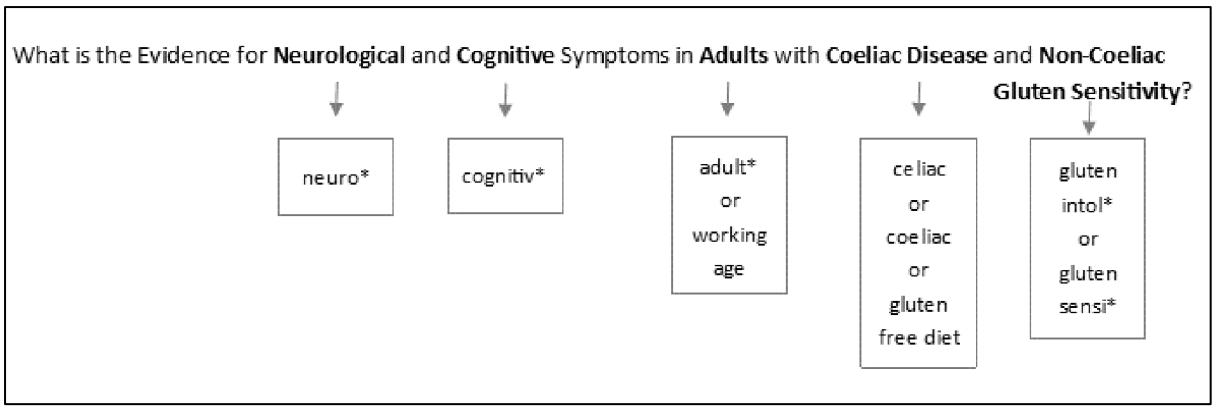

Figure 1: *Search terms derived from title of review*

The terms 'cognitive' and 'neurological' were searched separately before results were combined to ensure all articles were captured by the search.

Combining the above terms resulted in 156 articles. Four further articles were identified from backwards and forwards reference searches of the final articles. Duplicate articles (46) were removed and the remaining 114 abstracts reviewed to establish eligibility in relation to the inclusion criteria (Table 1). To identify cognitive and neurological symptoms the following definitions were used:

Cognitive - Relating to mental processes e.g. perception, memory, judgment, knowing, learning and reasoning - based on the definition provided by Collins English Dictionary (2016).

Neurological - Of or relating to the nervous system e.g. structural, biochemical or electrical abnormalities in the brain, spinal cord or other nerves - based on the definition provided by Collins English Dictionary (2016).

Following the application of the inclusion criteria, 88 articles were removed (Appendix A) leaving 26 for full article review; five articles were not available (Appendix B). A total of 21 articles met inclusion and were reviewed (Figure 2).

Table 1: *Inclusion criteria applied to retrieved abstracts*

Inclusion criteria
1. Cognitive and/or neurological symptoms[1] measured and reported 2. Studies including participants with formally diagnosed CD 3. Studies including participants with self-reported NCGS[2] 4. Participants not on a GFD when neurological and cognitive symptoms were assessed or reported 5. Studies reporting on original data 6. Participants primarily between 18-65 years of age[3] 7. Quantitative and/or qualitative study 8. Case study[4] 9. Full text English language available

In total, five articles were qualitative and the remaining 16 were quantitative. Eighteen used participants with CD, two with NCGS, and one with both. Twelve studies measured and reported neurological symptoms, three only cognitive symptoms, and six included both neurological and cognitive symptoms.

[1] Research must include measurement and reporting of cognitive and/or neurological symptoms

[2] As no standardised diagnostic criteria is currently in use for NCGS, studies including participants who self-reported NCGS were included

[3] If data from participants outside of this age range could be differentiated in the results this was done by the author and not reported. If this was not possible the study was included if mean age was between 18-65 years and all other inclusion criteria were met

[4] Case studies can be the first type of published research and in some areas, for example, in neuropsychology this is customary. Case studies were included so as not to lose valuable data on emerging areas across disciplines

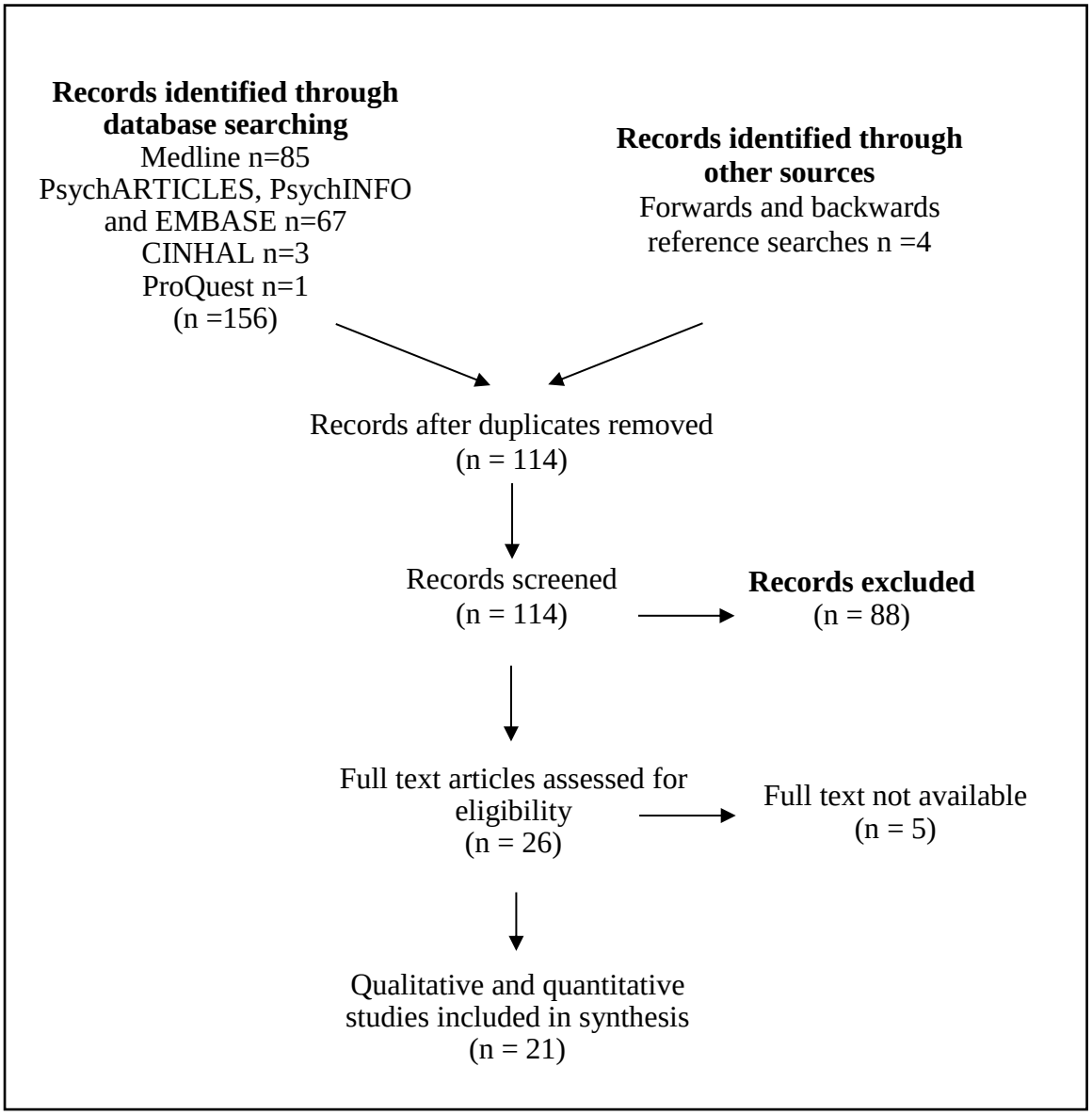

Figure 2: *Flowchart of article selection*

Search Results

For each included study, a data extraction form was used to capture the details of the papers relevant to this review, and an overall summary of each of the papers is shown in Table 2, studies are presented alphabetically.

Table 2: *Summary of studies included in review*

Study Type/ Aims	Sample	Intervention or Investigation	Neurological and Cognitive Symptoms	Key Findings	Limitations
1. Alaedini, Green, Sander, Hays, Gamboa, Fasano, Sonnenberg, Lewis & Latov (2002)					
Investigation of anti-ganglioside antibodies as an explanation of neuropathy in CD patients.	- 27 participants with CD (42-53 years) - 6 patients with Motor Neuron Disease - 20 patients with Multiple Sclerosis - 40 healthy controls (negative control) - Patients with Guillian-Barre syndrome (positive controls)	- Individuals who had increased anti-ganglioside antibodies were given a detailed neurological examination	- Numbness and pins and needles in hands and feet - Pain	- The body's autoimmune response to gluten has a role to play in the neurological symptoms seen in CD	- Only 6 participants were examined neurologically - It is not known how many individuals without CD would also show these symptoms - Study cannot establish cause and effect
2. Cervio, Volta, Verri, Boschi, Pastoris, Granito, Barbara, Parisi, Felicani, Tonini & De Giorgio (2007)					
Investigation into the mechanism underlying neurological impairment in CD. Aims to investigate whether the sera of patients with CD cause apoptosis of neuronal cells.	- 9 participants (3 male) with CD, neurological symptoms and anti-neuronal antibodies (21-61years) - 6 participants (1 male) with CD, no neurological symptoms and without anti-neuronal antibodies - 4 participants (2 male) without CD, but with neurological disorders - 10 healthy controls - Animal subjects	N/A	- Cerebellar ataxia (unsteady gait and poor muscle coordination) - Poor memory - Poor attention Other neurological conditions present: - Multiple sclerosis - Epilepsy - Moyamoya disease	- The study concluded that specific damage occurs to neuronal cells via an immune-mediated pathway in adults who show anti-neuronal antibodies - The presence of anti-neuronal antibodies alone are not enough to cause neurological symptoms	- Results are too general to be specific to CD - Small sample - Sample "selected" (page 196) and selection not defined
3. Cicarelli, Della Rocca, Amboni, Ciacci, Mazzacca, Filla & Barone (2003)					
Comparison between 2 groups with CD (classical and subclinical) and age matched controls	- 127 participants with classic CD (16-76 years) - 49 participants with subclinical CD (19-67 years) - 52 healthy controls	N/A	- Migraine - Tension headache - Mixed type headache - Pins and needles - Muscle weakness - Reduction of vibratory response	- No difference between classic or subclinical CD - No signs of nutritional deficiencies - Correlation between length of untreated	- Compared separate groups - Correlations can't establish cause and effect

To identify the occurrence and frequency of subtle neurological symptoms in adults with CD			- Poor reflexes Other neurological conditions present: - Epilepsy	disease and number of neurological symptoms - No ataxia found	
4. Collin, Kaukinen, Mattila & Joukamaa (2009)					
Between subjects study Aiming to compare the levels of alexithymia in adults with CD with non-CD controls	- 20 participants (5 male) with CD (16-72 years) - Data for controls was taken from previous population studies	- GFD - The Crown and Crisp Experiential Inventory (CCEI) - The Toronto Alexithymia Scale (TAS-20)	- No difference in alexithymia Other neurological conditions present: - Epilepsy	- Coeliac patients did not show more psychoneurotic symptoms than the controls - There was an insignificant trend towards improvement in scores - Only 2 participants showed alexithymia	- Reliance on subjective accuracy is a limitation of all self-report measures - Small sample size - Control data from previous studies used, not matched to this study and participants
5. Di Sabatino, Volta, Salvatore, Biancheri, Caio, De Giorgio, Di Stefano & Corazza (2015)					
A randomized, double-blind, placebo-controlled, cross-over trial. To investigate the intestinal and extra-intestinal effects of low levels of gluten ingestion on adults who have self-diagnosed NCGS	- 59 participants with self-diagnosed NCGS	**Week 1** GFD **Week 2** 4.375g of gluten or 4.375g of rice starch as a placebo **Week 3** GFD **Week 4** alternate arm of study **Week 5** GFD Self-reported questionnaires of symptoms	- Headache - Fatigue - Malaise - Foggy mind - Joint pain - Other pain - Pins and needles in hands and feet (most common at the top)	- Gluten ingestion led to significantly more symptom severity than placebo -3 patients identified as having NCGS -Depression was among the top 5 symptoms reported	- Nocebo effects - Relatively short wash out period and ingestion period for gluten - Only 3 participants did have NCGS - Presence or absence of CD not explained
6. Gao, Dhiren Varma, Patel, Lee & Chen (2015)					
Case study	- A 58-year-old male with permanent, but partial sight loss and CD	N/A	- Partial sight loss and 20 years CD - Bilateral occipital calcifications (deposits of calcium in the brain, in this	- Male with 40 years sight loss and 20 years CD - CD now well controlled	- Case study - Unable to determine cause - Unable to generalise

			case on the areas that control the eyes)		
7. Hadjivassiliou, Davies-Jones, Sanders & Grunewald (2003)					
A longitudinal between and within subjects' design To (1) establish any therapeutic effect of GFD on the treatment of gluten ataxia (GA) and (2) establish whether the nervous system can be the sole target organ of an immune mediated disease triggered by gluten	- 26 participants with GA who adhered to a GFD (8 had CD) (28-84 years) - 14 participants with GA who did not follow the GFD (1 had CD) (38-82 years)	- GFD	- Ataxia - Slowed fine motor control	- GFD group showed reduction in GA symptoms - Inflammation plays a role in GA - Those with the shortest history of GA returned to normal functioning	- No randomisation - Bias due to one investigator doing all testing - Identical "clinical picture" (p 1222) for those with and without CD, however improvement in outcomes only "apparent" (p 1222) after removing participants with CD
8. Hadjivassiliou, Kander, Chattopadhyay, Davies-Jones, Jarratt, Sanders, Sharrack & Grunewald (2006)					
With and between subjects repeated measures cohort study To assess the effect of a GFD on gluten neuropathy	- 25 participants with gluten neuropathy who followed a GFD (7 had CD) (63-65 years) - 10 participants with gluten neuropathy who did not follow a GFD (control)	- GFD	- Tingling in hands and feet - Numbness - Pain - Unusual sensation e.g. sharp stabbing pains - Slowed nerve response to stimulus - Reduced nerve response to stimulus	- 64% of GFD group reported symptoms improved compared to only 12% in the non-GFD group - Symptoms worsened with time and exposure to gluten as did outcomes for recovery - Partial adherence to GFD partially improves neurological symptoms	- Follow-up over a brief period, may not allow all improvements to be identified - Patients without CD included - Presence of antibodies may not be a reliable measure of GFD adherence - No randomisation
9. Hadjivassiliou, Rao, Grunewald, Aeschlimann, Sarrigiannis, Hoggard, Aeschlimann, Mooney & Sanders (2015)					
Between subject design Aim to compare and identify differences in neurological	- Group 1 (with CD) 228 participants - Group 2 (NCGS) 334 participants	- Retrospective analysis of case notes	**Group 1** - Ataxia (severe) - Weakness, numbness and pain in hands, feet, arms and legs	- Encephalopathy more common in Group 1 and neuropathy more common in Group 2 - Neuropathy more severe in Group 1	- Retrospective review of notes – not all tests/assessments available for all participants

dysfunction in individuals with CD and NCGS			- Encephalopathy (changes to the brain) **Group 2** - Weakness, numbness and pain in hands, feet, arms and legs - Ataxia (mild) - Encephalopathy (changes to the brain)	- No difference in ataxia - Both groups equally benefitted from GFD	
10. Hallert & Astrom (1983)					
Between subjects design Aims to identify whether intellectual impairment is a feature of untreated CD	- 19 newly diagnosed adults with CD (37-59 years)	- The synonyms reasoning block test - Thurnstone's memory test - Reaction time (simple and 3-choice stimulation) - Figure identification - Figure rotation - Finger dexterity - Benton's visual retention test	- No cognitive impairment	- No signs of intellectual impairment in adults with newly diagnosed CD - Irrespective of whether CD was developed in adulthood or childhood	- Unclear whether any participants were on a GFD at any point in the study - Small sample size
11. Hu, Murray, Greenaway, Parisi & Josephs (2006)					
Retrospective case series from existing clinical notes Describes profiles of patients who reported cognitive symptoms 2 years prior to CD diagnosis	- 13 participants with CD who had reported neurological symptoms within 2 years of diagnosis	- Neurological and cognitive assessment data, EEG and MRI scans where data were available	- Amnesia - Acalculia - Confusion - Disorientation - Dysgraphia	- 10 patients deteriorated cognitively Other common symptoms: - Personality change - 2 improved following GFD - No pattern to EEG findings - CJD initially diagnosed in 1/3 of patients	- Consistent data for analysis between individuals not present - Not able to establish cause and effect - Very small sample sizes - Not able to generalise results
12. Ihara, Makino, Sawada, Mezaki, Mizutani, Nakase, Matsui, Tomimoto & Shimohama (2005)					
Case series and a case report	- 14 participants with idiopathic cerebellar ataxia	N/A	- Cerebellar atrophy - Slowed cerebral blood flow - Mild cognitive impairment	- MRI showed cerebellar atrophy in 10 participants	- Small sample size - Unable to identify cause and effect

To investigate whether gluten sensitivity (NCGS) is present in adults who are experiencing sporadic cerebellar ataxia	with extra-cerebellar symptoms (44-84 years) - 9 individuals with Parkinson's disease - 18 participants with ALS - 47 healthy controls			and slowed blood flow in all but one participant - In the experimental group, participants were more likely to be AGA IgG or IgA positive - Mild cognitive impairment was more prevalent in the AGA positive group - Ataxic patients are more likely to have NCGS	- Unclear whether participants had CD or what would now be termed NCGS
13. Lichtwark, Newnham, Robinson, Shepherd, Hosking, Gibson & Yelland (2014)					
A longitudinal study to investigate mucosal healing and cognitive function in adults with CD	- 11 participants (8 female) with CD (22-39 years)	- GFD	Improved scores following GFD found in: - Verbal fluency - Attention - Motoric function	Alongside cognitive improvement GFD correlated with: - Improved mucosal healing - Reduction of CD antibodies	- Small sample size - Can't be generalised
14. Millington, James-Galton, Barbur, Plant & Bridge (2015)					
Case study	- A 54-year-old woman with CD. She has visual disturbance that is stable and permanent - 12 control subjects who have visual disturbance resulting from stroke	N/A	- Extensive damage to the occipital lobe - Evidence of calcification - Visual problems	- Treatment for CD did not improve visual problems, but may have stabilised it - Importance of early diagnosis and treatment to prevent visual damage	- Case study - Can't be generalised - Complex history, causal link between CD and visual problems not clear - Implications of study not clear
15. Pennisi, Lanza, Giuffrida, Vinciguerra, Puglisi, Cantone, Pennisi, D'Agate, Naso, Aprile, Malaguarnera, Ferri & Bella (2014)					
Between subjects design Aim to identify if there is a pattern of excitability of the	- 20 CD patients (4 male) not on a GFD (24-45 years) - 20 age-matched controls (8 male)	- Mini Mental State Examination (MMSE) - Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I)	- Tiredness/Fatigue - Normal cognitive function - Different electrophysiological changes in the motor cortex of participants with CD	- All participants had normal MMSE CD participants scored more highly on depression scale	- MMSE may not be sensitive enough to capture mild cognitive change - TMS does not provide cause for change

motor cortex found in CD individuals		- Hamilton Depression Rating Scale - EEG - CT scan - Single and paired TMS (transcranial magnetic stimulation)	Other autoimmune conditions: - Hypothyroidism - Asthma - Vitiligo	- 5 CD participants had dysthymic disorder (SCID-I)	- Small sample - Can't be generalised
16. Poloni, Vender, Bolla, Bortolaso, Constantini & Callegari (2009)					
Case study	- A 38-year-old Italian male with a neurological and psychiatric presentation of CD initially without signs of malabsorption	N/A	- Mild, non-specific, non-focal abnormalities on EEG - Muscle rigidity - Psychomotor slowing - Progressive frontal cognitive deficit (affective and behavioural lability) - Loss of language	- Patient showed improvement of all symptoms following diagnosis of CD and commencing a GFD	- Single case - Can't be generalised - Can't establish cause and effect
17. Rigamonti, Magi, Venturini, Morandi, Ciano & Lauria (2007)					
Two case reports	- A 26-year-old woman with sporadic gastro-discomfort after eating carbohydrate since childhood - A 62-year-old woman with no gastrointestinal complaints	N/A	- Lower and upper limb weakness - Lower reflexes absent - Poor nerve conduction in extremities - Progressive hand and leg weakness - Slowing of nerve conduction	- Both patients showed improvement of muscle strength and other neurological symptoms following commencement of a GFD - A direct pathogenic effect of gluten suggested	- Single cases described - Can't be generalised - Can't establish cause and effect
18. Somay, Cevik, Halac, Arbut & Erenoglu (2004)					
Case report	- 32-year-old woman with CD	N/A	- Ataxia - Pain - Leg weakness - Tingling in legs - Pinprick and temperature sensation reduced in hands and feet	- Ataxia and neuropathy symptoms improved at 2-month follow-up - Oral pigmentation remained	- Unable to establish cause due to multiple interventions - Single case described - Can't be generalised

19. Souayah, Chin, Brannagan, Latov, Green, Kokoszka & Sander (2008)					
Multiple case series Investigating the effect of intravenous immunoglobulin (IVIG) on ataxia and neuropathic pain in adults with CD	- (1) A 32-year-old woman with CD - (2) A 41-year-old woman with CD - (3) A 42-year-old woman with CD	All treated with initial high dose of IVIG followed by a maintenance dose	- Dysarthria (inability to produce clear speech) - Ataxia - Progressive numbness - Tingling or stabbing pains in fingers, face and legs - Neuropathic pain - Impaired fine motor control - Reduced pinprick and light touch sensation in legs - Poor balance - Absent vibratory response in feet	- Within 1 month ataxia and neuropathy improved	- Single cases described - Can't be generalised - No statistical information reported - Not noted how adherence to GFD was evaluated
20. Stipic, Perkovic, Crnek-Kunstelj, Relja, Stipic-Markovic & Skreb (2002)					
Case study	- A 47-year-old woman with CD	N/A	- Paraparesis (partial loss of movement in all limbs) - Urine incontinence - Fatigue - Headache - Pain in legs and back	- At 3 months clinical and haematological symptoms improved	- Single case studied - Complexity of treatment makes it impossible to identify what caused the improvements - IQ at baseline, no follow-up or pre-morbid measure taken
21. Tursi, Giorgetti, Iani, Arciprete, Brandimarte, Capria & Fontana (2005)					
Between subjects design Aim to neurologically evaluate adults with untreated CD	- 32 (7 male) participants newly diagnosed with CD and not on a GFD	- Neurological investigation - Electroneuromyo-graphy (ENMG) - CT scanning - GFD	- Tingling or numbness in hands and feet - Muscle weakness - Recurrent feinting - Motor slowing - Touch insensitivity	- 12 patients did not improve during GFD - Bowel atrophy improved - CD antibodies still present in 2 participants - No cerebral alterations	- No control group - Small sample - Self-report measure of adherence to GFD may not be reliable - Not all the participants had neurological symptoms - Unable to establish cause and effect

Description of Studies

Eighteen of the 21 studies (86%) included participants with CD (studies 1-4, 6-8, 10, 11 & 13-21); of the remaining three studies, 2 (67%) focused on NCGS (5 & 12) and one included participant groups with CD and NCGS (9).

Publication dates for the studies identified above ranged from 1976 – 2017. Articles were included from across the globe with the majority being published in Italy (2, 3, 5, 16, 17 & 21), followed by the UK (7-9 & 14), the USA (1, 11 & 19), and Australia (6 & 13). One article each from Canada (15), Croatia (20), Finland (4), Japan (12), Turkey (18) and Sweden (10) made up the remaining studies.

There was variation in the methodological designs used across studies: nine case studies or multiple case series (6, 11, 12, 14 & 16-20); seven used a within-subjects design with follow-up over 12 months (4, 10, 13 & 21) or data collected at one time-point only (1, 2 & 15); four used between groups methods with controls (3, 7 & 8) or different groups based on CD or NCGS (9); and one study utilised a randomised, double-blind, placebo-controlled cross over trial (5).

The number of participants in each study ranged from one (6, 16 & 20) to 562 (9), with 81% of the 21 articles (n=17) having between 1 – 35 participants. Only nine studies (43%) included control groups, three exclusively used healthy controls who were fit and well (2, 3 & 14), while the majority included controls with other conditions (4, 6 & 11) such as motor neurone disease (1), other neurological conditions (11) or used a control group with CD that refused a GFD while the treatment group complied (7).

Demographic information on age of participants was not provided by two studies (9 & 11). Where ages were published, they ranged from 26– 84 years. Studies reported different demographics in terms of the duration of difficulties or symptoms, with some reporting age of diagnosis and age of symptoms onset (9 & 11) and others reporting the duration of relevant

symptoms (6 & 11). Due to the variation across the studies it was not always possible to record the duration of CD, NCGS, cognitive or neurological symptoms; however, where these data were provided, duration of untreated symptoms ranged between < 1 – 20 years.

When reported, methods of diagnosis for CD did not vary. Some studies accepted formal diagnosis from participant case notes (13), or because participants were receiving care from the relevant service (8) and a diagnosis had already been formally established. However, when diagnosis of CD had not already been acquired, all studies required confirmation by biopsy (6, 7, 8 & 14). Response to a GFD was viewed as confirmatory of CD or NCGS, but not diagnostic; in one study, inclusion was withdrawn from participants with CD who did not respond to a GFD (2).

Quality Assessment Framework

Due to the variation in methodology across the included studies, it was important to assess the quality of each using a published quality assessment framework. Even well-designed studies can include bias and applying a framework to studies allows the level of bias to be measured and the results from less biased studies to be given greater weight in the reporting of the results. The framework used here is that from Caldwell, Taylor and Henshaw (2005), which was developed specifically for use in health research and provides the framework for "a detailed critique of a piece of published research" (Caldwell et al., 2005: pg 45) to inform practice. This quality framework allows qualitative and quantitative studies to be considered side by side using matched criteria (Figure 3). It was developed after the authors evaluated several quantitative, qualitative and mixed (Caldwell et al, 2005) frameworks and assesses both internal and external validity.

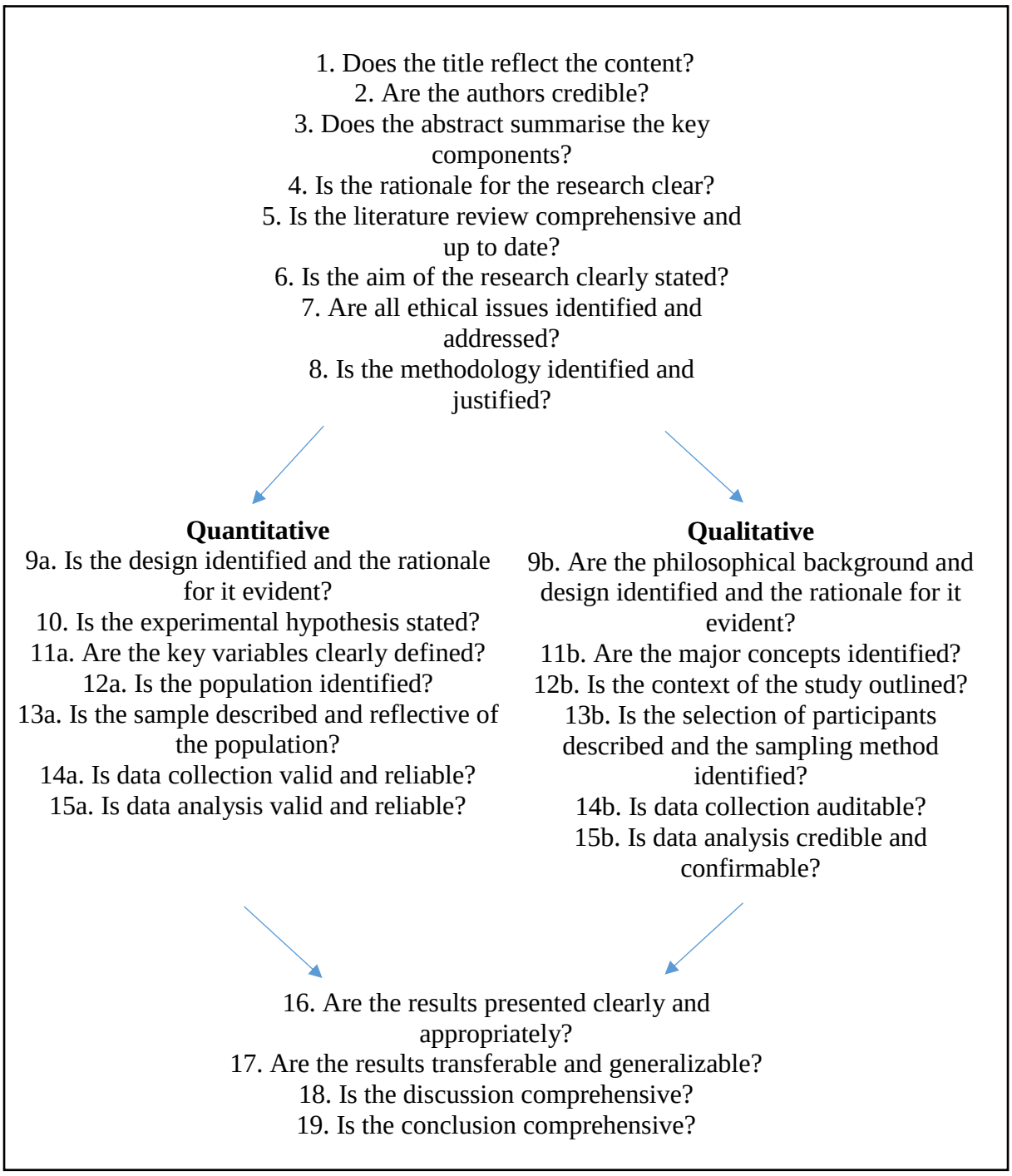

Figure 3: *Questions included in Caldwell, Taylor and Henshaw's (2005) quality assessment framework*

Caldwell, Taylor and Henshaw's (2005) quality framework provided the questions to enable analysis of studies, but did not provide guidance of how to score studies against these questions. The Cochrane Handbook (Higgins & Green, 2011) advises the use of 3 levels to

assess studies for bias and this guidance was applied here for each of the 19 quantitative and 18 qualitative items of Caldwell, Taylor and Henshaw's (2005) framework:

0 = Criteria not met/ Unable to determine (Low)	1 = Criteria partially met (Medium)	2 = Criteria fully met (High)	N/A=Quantitative only questions

A total score was calculated for each study, with a total potential score of 36 being available for qualitative studies and a total potential score of 38 for quantitative studies. All qualitative studies were case studies and so were not assessed against the framework for reasons discussed in detail below.

A random sample of four quantitative studies, generated by computerised random number selection, was reviewed by a colleague from another discipline (nursing) who was familiar with the quality framework. The resulting disagreement level was 14% across items 9b, 11b, 15b and 16. Upon discussion it became clear that these were the more subjective questions and appeared to be more influenced by previous experience and professional discipline than subjective judgment of the studies. A final score was allocated following discussion.

Separating total scores into groups (e.g. high, medium or low) to identify levels of potential bias was considered, however no quality assessment framework or guidance could be found that supported this action and so studies are discussed in terms of level of quality on a continuous scale from the most to the least robust relative to one another (Table 3).

Table 3: *Quality Assessment Framework in order of score*

	1	2	3	4	5	6	7	8	9a 9b	10	11a 11b	12a 12b	13a 13b	14a 14b	15a 15b	16	17	18	19	**Total**
Quantitative Studies																				
7. Hadjivassiliou et al. (2003)	2	2	2	2	2	2	2	2	2	1	2	2	1	2	2	2	2	2	2	**36**
9. Hadjivassiliou et al. (2015)	2	2	2	2	2	2	1	2	2	1	2	2	1	2	2	2	2	2	2	**35**
12. Ihara et al. (2005)	2	2	2	2	2	1	1	2	2	2	2	1	2	2	2	2	2	2	2	**35**
8. Hadjivassiliou et al. (2006)	2	2	2	2	2	2	2	2	2	0	1	2	2	2	2	2	1	2	2	**34**
15. Pennisi et al. (2014)	2	2	2	2	2	2	1	2	2	2	2	2	1	2	2	2	1	2	1	**34**
2. Cervio et al. (2007)	2	2	2	2	2	2	0	2	1	0	2	2	1	2	2	2	2	2	2	**32**
3. Cicarelli et al. (2003)	2	2	2	2	2	2	1	2	2	0	2	2	1	2	2	2	1	2	1	**32**
1. Alaedini et al. (2002)	2	2	2	2	2	1	0	2	2	0	2	2	1	2	2	2	2	1	2	**31**
21. Tursi et al. (2006)	2	2	2	1	2	2	0	2	2	0	2	2	1	2	2	2	1	2	2	**31**
5. Di Sabatino et al. (2015)	2	2	2	2	1	1	0	2	2	2	2	1	1	2	1	2	2	2	1	**30**
13. Lichtwark, et al. (2014)	2	2	2	2	2	2	0	2	1	0	1	2	1	2	2	2	0	2	2	**29**
4. Collin et al. (2008)	2	2	2	1	1	2	1	1	2	0	2	2	1	2	2	2	1	1	1	**28**
10. Hallert & Alstrom (1983)	2	2	2	1	1	2	0	1	2	0	1	2	1	2	2	2	1	1	1	**26**

19. Souayah et al. (2008)	2	2	2	1	1	2	0	0	1	0	2	1	0	1	0	2	0	2	2	**21**
11. Hu et al. (2006)	1	2	2	1	2	2	0	1	1	0	1	1	1	0	1	1	0	2	1	**20**

Note: Colour coding: High (green), Medium (yellow) and Low (red)

The quality of the studies varied and according to the results from the quality assessment framework scores ranged from 20 to 36. In terms of patterns or aspects of quality, the majority of studies provided high quality introductions, abstracts and summaries to their content. There were two areas where there was a difference between the higher and lower quality studies, these were identification and justification of the methodology and the results being transferable and generalizable; studies achieving relatively lower scores consistently performed poorly against these criteria.

Case studies were not interrogated against the quality assessment framework as they would necessarily perform poorly in measures of ability to generalise findings as well as others such as sampling method. Inclusion of these studies in the framework unfairly disadvantages case studies and so there is no advantage to including them. The framework was developed with the intention to provide a framework that evaluated health research that could then be put into practice and so it is correct that case studies perform poorly as they should not be used to develop clinical changes, certainly not on their own. The value of case studies is in the depth of information that they provide and as this is an exploratory review they provide further information that is valuable to discuss. Results of case studies will be discussed below with these considerations in mind.

Areas where there were consistently lower scores on the quality framework were around ethical considerations and lack of experimental hypothesis. Where there was a mention of ethical factors, details were scarce or included only that research had been granted ethical approval and the name of the institution that had granted it. Given the symptomology associated with CD, NCGS and the nature of some participants' symptoms this lack of consideration of, or at least reporting of, ethical issues was disappointing.

Poorer quality studies increase the chance of bias in the results and caution needs to be taken when reporting such results. Two studies (11 & 19) performed poorly across all areas of bias

(Pannucci & Wilkins, 2010) and particularly poorly in terms of internal validity (Higgins et al, 2011) which is most likely to cause unreliable results. The risk of bias in the above two papers is so high and the likelihood of false results so probable they will not be discussed further in this review. Excluding the poorest quality studies ensures minimal data is lost, but also that the results reported are robust enough to inform the area of neurological and cognitive symptoms in adults with CD and NCGS.

THEMES IDENTIFIED

Neurological

The neurological symptoms reported by adults with CD or NCGS are shown below (Table 4). The highest quality studies (7, 9 & 12) reported neurological symptoms of ataxia, slowed motor function, pain, poor balance, weakness, numbness and altered sensation in extremities and changes to the brain. Hadjivassiliou et al.'s (2003) participants had severe ataxia that required diagnoses or treatment by specialist services. This degree of severity was also found by Hadjivassiliou et al. (2006), which has comparable quality to the above studies. However, Pennisi et al. (2014) reported neurological examinations for all participants to be normal and Aleadini et al. (2002) reported only mild impairment (e.g. of nerve conduction). As all these studies performed highly on the quality assessment framework these differences are unlikely to be the result of bias. Indeed, this variation likely reflects the methods of recruitment in the above studies; Hadjivassiliou et al. (2003) and Hadjivassiliou et al. (2006) recruited from ataxia or neurology clinics, whereas Pennisi et al. (2014) and Aleadini et al. (2002) recruited from gastrointestinal or CD clinics, respectively. Being under the care of a neurology or ataxia clinic indicates more severe neurological symptoms are likely to be present at the point

of recruitment and would explain why these studies reported more significant levels of neurological symptoms.

Table 4: *Neurological symptoms in adults with CD and NCGS*

Study	NCGS or CD	Symptoms
Reporting only Neurological results:		- Cerebellar ataxia (unsteady gait and poor muscle coordination) - Slowed fine motor control - Pain - Dizziness and feinting - Poor balance - Numbness and pins and needles in hands and feet - Tingling in hands and feet - Muscle weakness - Encephalopathy (changes to the brain) - Slowed nerve response to stimulus - Reduced nerve response to stimulus - Electrophysiological changes in the motor cortex of participants with CD - Poor reflexes - Muscle rigidity - Visual problems - Paraparesis (partial loss of movement in all limbs) - Urine incontinence - Dysarthria (inability to produce clear speech)
Hadjivassiliou et al. (2003)	CD	
Hadjivassiliou et al. (2015)	Both	
Hadjivassiliou et al. (2006)	CD	
Cicarelli et al. (2003)	CD	
Alaedini et al. (2002)	CD	
Tursi et al. (2006)	CD	
Millington et al. (2015)	CD	
Rigamonti et al. (2007)	CD	
Souayah et al. (2008)	CD	
Reporting Neurological and Cognitive results:		
Ihara et al. (2005)	NCGS	
Pennisi et al. (2014)	CD	
Cervio et al. (2007)	CD	
Di Sabatino et al. (2015)	NCGS	
Poloni et al. (2009)	CD	
Stipic et al. (2002)	CD	

Note: Studies and symptoms ordered by quality; light grey indicates poorest studies and so potentially less reliable symptoms

High quality studies (1, 2, 3, 8, 15 & 21) additionally reported symptoms of slowed and reduced nerve response to stimuli, muscle weakness and poor reflexes. The central and peripheral nervous systems were both found to be affected (Cicarelli et al., 2003; Tursi et al., 2006). Tursi et al. (2006) report that 38% of their adult CD participants reported signs of peripheral neurological damage and autonomic dysfunction (e.g. altered perception in extremities and recurrent fainting). Brain changes that would account for neurological

symptoms were not seen on CT (computerised tomography), but were shown by more sensitive nerve conduction tests. Comparable results were found in another study (Pennisi et al., 2014), where neurological examination was normal, however transcranial magnetic stimulation (TMS) found a pattern of brain activity that was unique to individuals with CD when compared to healthy controls. It is not clear whether the participants in this study reported any neurological concerns, however they were recruited consecutively as individuals with recent diagnoses of CD with no mention of experiencing neurological symptoms and so it is unlikely to have been an issue at the time of recruitment. Ihara et al. (2005) also identified the presence of motor neuropathy via nerve conduction studies.

Studies that performed less well against Caldwell, Taylor and Henshaw's (2005) quality assessment framework (4, 5, 10, 13 & 16) reported similar symptoms to those above. In fact, the only additional symptom reported is that of muscle rigidity (16); slowed motor function, pain and unusual sensations in hands and feet were all present in these studies, which makes them consistent with those symptoms reported in the higher quality studies. The case studies reported all previous symptoms, but also visual problems (14), paraparesis and urine incontinence (20), and dysarthria (19). The additional symptoms may be a result of the level of detail allowed in this methodological design that was not possible in other types of study. Also, case studies are more likely to be written (and published) when they are exploring new or unusual cases and so it follows that they may report symptoms that larger studies have not yet considered, for example, no other study other than that by Millington et al. (2015) considered visual acuity.

Gluten ataxia (GA) is worth mentioning again here. Two studies investigating GA were captured by the search criteria used in this review (7 & 8) they were included as they met the inclusion criteria, however, this does complicate the interpretation of the studies' findings as the neurological symptoms could be the result of GA rather than CD or NCGS, which is why

they have been discussed separately here. Hadjivassiliou et al. (2003) suggested that gluten sensitivity is the most common cause of idiopathic ataxia. GA occurs with and without CD and is a separate neuropathy that belongs under the umbrella of gluten sensitivities (Hadjivassiliou et al., 2003). Ihara et al. (2005) reported that individuals with ataxia (not defined in this study as GA) were more likely to be gluten sensitive than the general population. This study was carried out in Japan where CD is less than 1%, but suggested that gluten sensitivity is present in the population, just not in the form of CD. There are criticisms that can be levelled against these studies however, for example Ihara et al. (2005) did not test participants for CD or NCGS, which may act as confounding variables in the study. Similarly, Hadjivassiliou et al. (2003) did not consider the presence of NCGS in their participants. This lack of consideration of NCGS may be typical, but it still raises the question of whether the neurological symptoms reported in GA are related to NCGS rather than being a separate condition altogether. Currently the literature around the neurological and cognitive symptoms of CD and NCGS and the neurological symptoms of GA and possibly non-GA ataxia are not yet differentiated enough to confidently establish which symptoms are CD, NCGS, GA or something else.

Overall, the neurological symptoms most consistently reported include unsteady gait, slowed motor control and altered sensation in extremities such as numbness or pins and needles. These findings are reported across both higher and lower quality studies.

Cognitive

There were fewer studies looking at cognitive symptoms (n=11) of CD and NCGS than those looking at the neurological symptoms (n=16). However, the majority of these studies scored well against the quality assessment framework (2, 4, 5, 10, 12, 13 & 15). NCGS was represented more equally in the cognitive studies compared to the neurological research

where the focus appeared to be on CD. The cognitive symptoms in adults with CD and NCGS are shown below (Table 5).

There is disagreement between the highest scoring studies regarding the presence of cognitive symptoms. The highest scoring study (12) reported mild cognitive impairment in the areas of short term memory and word recall. While improvement of neurological symptoms was recorded following introduction of a GFD, the cognitive impairment was not reviewed. Thus, it was not possible to establish whether the identified mild cognitive impairment was responsive to a GFD, which may have suggested a link to NCGS. Pennisi et al. (2015) reported that participants with CD had normal cognitive function with no impairment and, although a less robust study, Hallert and Astrom (1983) also found no evidence of cognitive impairment in adults with CD. Participants did, however, report fatigue as a cognitive symptom (15), this was reflected by the poorest performing study against the quality framework (20) which presents a case study on a 47-year-old Croatian woman who experienced fatigue as a cognitive symptom of CD.

The results of Cervio et al.'s (2007) research found evidence of memory and attention deficits in adults with CD, however this information was taken from participants' self-reports rather than objective measurement. Despite this being a robust study, the focus was on the neurological symptoms and the investigation of cognitive symptoms was methodologically poor, which makes it difficult to rely on these findings.

Table 5: *Cognitive symptoms in adults with CD and NCGS*

Study	NCGS or CD	Symptoms
Reporting only Cognitive results:		- Mild cognitive impairment (short term memory and word recall) - Tiredness/Fatigue - Normal cognitive function - Poor memory - Poor attention - Malaise - "Foggy mind" - Slowed processing speed, executive function (attention, sequencing and flexibility) and visuospatial memory - Alexithymia - Progressive frontal cognitive deficit - Loss of language
Cervio et al (2007)	CD	
Lichtwark et al. (2014)	CD	
Collin et al. (2008)	CD	
Hallert & Alstrom (1983)	CD	
Reporting Cognitive and Neurological results:		
Ihara et al. (2005)	NCGS	
Pennisi et al. (2014)	CD	
Cervio et al. (2007)	CD	
Di Sabatino et al. (2015)	NCGS	
Poloni et al. (2009)	CD	
Stipic et al. (2002)	CD	

Note: Studies and symptoms ordered by quality; light grey indicates poorest studies

Fatigue, malaise and foggy mind were reported by Di Sabatino et al. (2015). In this study participants completed a questionnaire assessing the frequency of these and other symptoms. After completion of each arm of the study these symptoms were re-assessed and found to increase following the ingestion of gluten. This is the first study in which cognitive symptoms were investigated pre- and post-intervention, for this reason these results are more robust.

The complicated picture continues where the particular areas of cognitive impairment are reported. Ihara et al. (2005) identified verbal ability as an area of difficulty for participants with ataxia, whereas Lichtwark et al. (2013) found minimal (i.e. not significant) results in this area. Lichtwark et al. (2013) did find that removing gluten significantly improved performance on tests of processing speed, executive function and visuospatial memory, as measured by the subtle cognitive impairment test (Yelland et al., 2004), trail making tests A and B (Reitan & Wolfson, 1985) and the Rey-Osterrieth complex figure (Rey, 1941),

respectively. There is further disagreement as Ihara et al. (2005) report immediate and delayed recall (short term memory) is impaired and Lichtwark et al. (2013) found no evidence of a significant impact on memory. Poloni et al.'s (2009) case study reported "progressive…frontal cognitive deficit" (p. 2), but no further information was given as to how this diagnosis was made, however it can be understood as meaning impairment in executive functions (Otero & Barker, 2014), which supports the findings of high scoring studies (13).

Collin et al. (2008) investigated the idea of a cognitive "coeliac profile" (page 1331), which was first suggested by De Rosa et al. (2004). This coeliac profile included the presence of alexithymia, which is described as having a cognitive and affective dimension (Van Der Veld et al., 2015). The cognitive dimension involves the inability to identify, describe verbally and analyse one's own emotions. Collin et al. (2008) found the presence of alexithymia in only 10% of participants in their study, which is the same as the prevalence in the general population. There was no evidence for the coeliac profile of alexithymia in gluten sensitive individuals.

The variable methods used to examine cognitive ability, including: the Hasegawa dementia rating scale (Imai & Hasegawa, 1994; 12), the subtle cognitive impairment test (Yelland et al. 2004; 12), and participant self-report (15 and others) may be partly the reason why the picture is unclear. Sensitivity of tests is also important. Neurological symptoms would often not be picked up by standard neurological examination or participant self-report, but were identified only when very sensitive tests were used. This may also be the case for cognitive symptoms and tests to identify suspected dementia (11) are unlikely to be sensitive enough (De Jager et al., 2009).

Investigations of cognitive symptoms seem generally to be poorer than those of neurological symptoms. Even within high-scoring studies the results relating to cognitive symptoms can

be weak. There is no consistent set of tests used and no consistent agreement across the literature as to what areas of cognition, if any, may be affected in adults with CD or NCGS. However, from the results discussed above, short term memory, fatigue, executive function and processing speed were found in the most robust studies using objective measurements. In addition to this, these studies sought to explore the results of GFD on these symptoms and found that performance improved across these areas. This supports the notion that these symptoms are related to CD and NCGS as they reduce when these conditions are treated and well managed.

Mechanisms of Damage

The role of antibodies is well-established in CD and the presence of anti-gliadin antibodies (AGA) are an important indicator of diagnosis. Ihara et al. (2005) reported the presence of AGA is associated with more severe motor neuropathy in a group of non-CD participants when compared to non-CD patients without AGA. An area of particularly strong evidence is the involvement of anti-ganglioside or anti-neuronal antibodies (antibodies that react with cerebellar cells) in the sera of individuals exhibiting neurological signs of gluten sensitivity. Aleadini et al. (2002) reported that 20% of their participants were found to have these antibodies and all showed signs of neuropathy. As further support of the importance of these antibodies, Cervio et al. (2007) showed that sera taken from adults with CD and anti-neuronal antibodies caused apoptosis (cell death) in previously healthy human neurone cells. Tursi et al. (2006) found that 42% of their CD participants had anti-neuronal antibodies circulating in their blood, while Cervio et al. (2007) reported this figure to be closer to 50%. Taking even the higher figure into account, however, the presence of these antibodies alone is not a robust enough explanation for neurological damage.

The role of inflammation as a mechanism of damage was not reported in these studies, however the mechanisms of damage were not the focus of the articles reviewed here and so this is not unexpected.

Treatment Strategies

The removal of gluten remains the only treatment strategy available for individuals who have CD or NCGS. Souayah et al. (2008) reported on the progress of three participants with ataxia who all showed reduction of neurological symptoms when treated with intra-venous immunoglobulin (IVIG). However, this study performed poorly against the quality framework across all areas of internal validity and the results need to be treated with caution.

Neurological symptoms were found to vary in their response to a GFD. Alaedini et al. (2002) found there was no link between GFD and neurological symptoms, however did point out that a link cannot be ruled out just on the basis of their findings. Hadjivassiliou et al. (2006) found that only seral nerve conduction significantly improved following implementation of a GFD while no other measures of neuropathy did. Tursi et al. (2006) clearly demonstrated that there was no "remission" (page 1873) or change in the number or severity of neurological symptoms of participants with CD when following a strict, 12-month, GFD. The authors did state that there may be a negative correlation between the duration of gluten exposure before the onset of a GFD and symptom reduction, but this was not examined. Cicarelli et al. (2003) did find a significant correlation between duration of untreated CD and number of neurological symptoms. Hadjivassiliou et al. (2003) suggested that this relationship between untreated disease and number of symptoms demonstrates that neurological symptoms may initially be reversible, however extended exposure (not yet defined in the literature, but linked to symptom severity) leads to irreversible neurological symptoms.

Methodological Issues

The quality framework used gave equal weighting to all items, which meant the accuracy of a paper's title was as important as the data analysis used. Poor guidance was given as to how the more judgement-based criteria should be scored e.g. "Are the authors credible?", which resulted in these items being more subjective as the decision was made by the reviewer. As shown by inter-rater comparison some of the questions were more subjective and influenced by previous professional approach. More guidance would help to develop a more objective rating system.

Quality assessment frameworks can sometimes measure the quality of reporting rather than reflecting methodological bias, and the framework used here was written specifically for medical research. As the studies here were gathered from multiple-disciplines and countries reporting standards may have varied, and some may have scored lower due to these different standards rather than poorer designs or analyses.

As mentioned previously, case studies would have scored poorly on some of the questions of this quality assessment framework. Although it is necessary for robust studies to be used to influence practice, it could mean that new and emerging issues – initially covered by case studies – are missed. It would be inappropriate for case studies to inform a developing evidence base, but it would be restricting for the data contained within them to be treated as too poor to be considered.

There were a small number of papers that were unavailable to the author, usually due to there being no English translation. In two cases abstracts/outlines of the research had been published in journal supplements, but the full articles were not available. Whether they had yet to be accepted for full publication or were not yet complete is not known. This may have meant high quality studies were inadvertently excluded from this review.

The biggest complication with the evidence itself is the lack of recognition throughout of the impact of NCGS and refractory CD[5] on the response to gluten. Studies measured adherence to a GFD via self-reports, which are known to have poor accuracy (Vitolins et al., 2000) and testing for the presence of AGA. In the studies discussed above data from participants who continue to have circulating AGA despite adherence to a GFD remain in the analysis. If these individuals are suffering from refractory CD their results may confound the findings as for them, damage may still be occurring. Individuals with NCGS may also respond differently to the removal of gluten as the mechanisms of the disease are different from that of CD and inclusion of individuals without screening for this condition may again give skewed results.

There is likely to be an effect of the disciplines that have carried out the above research. This topic has very much straddled the medical and psychological literature and it may be more difficult than first thought to directly compare literature from the two schools. This may be why cognitive symptoms' studies did less well against the quality framework. This is illustrated by the case studies; the wealth of information in these studies is vast, however the focus of the data varied widely depending on the epistemological background of the discipline. Not only this, but the interpretation of symptoms was also complicated by discipline. Stipic et al. (2002), for example, reported the symptom of fatigue, depending on the approach – medical or psychological – the interpretation of this symptoms could be neurological or cognitive. Fatigue is a self-report symptom with no objective test of assessment.

The above point raises another issue, which is the sensitivity and specificity of the tests used to assess cognitive function. Of the studies that used and reported formal cognitive tests there

[5] Refractory CD is defined as "the recurrence or persistence of malabsorptive symptoms and signs with villous atrophy despite a strict gluten-free diet for >12 months" (Ludvigsson et al., 2013; page 7). In a North American study (Rashan et al., 2011) reported 1.5% of individuals initially diagnosed with CD developed refractory CD.

was no agreement as to the tests used. Formal tests were designed to test a certain aspect of cognitive function rather than a general concept such as speed of nerve function. The internal validity of cognitive tests used may have affected the effectiveness of their results e.g. a test that measures planning may not be specific or sensitive enough to measure cognitive dysfunction as a result of gluten ingestion in adults with CD or NCGS.

In summary, neurological symptoms of slowed nerve conduction, pain and altered perception in extremities can be accepted with confidence. They were found repeatedly across studies in both samples of patients with CD and NCGS. Neurological symptoms can be subtle and unnoticeable to the individual or severe; there does appear to be a dose effect based on duration of exposure to gluten and recovery on GFD depends on severity and duration of symptoms. The role of ataxia is not clear, although it is reported in the most robust studies, there are issues around whether NCGS was adequately ruled out in these samples. Fatigue and short-term memory can be most readily accepted as cognitive symptoms of CD and NCGS. There is agreement that cognitive symptoms reduce following a GFD. There does not appear to be any significant differences between CD and NCGS in terms of the types of symptoms experienced, which suggests the response to gluten molecules may be key rather than an autoimmune process. Unfortunately, this conclusion needs to be treated with caution and would require direct testing before it could be accepted with confidence. One of the reasons for this is the far larger number of studies that looked at CD than NCGS, which reflects the current state of the literature across these two conditions.

CLINICAL AND RESEARCH IMPLICATIONS

The clinical implications of the above review point to the importance of early diagnosis and treatment in both CD and NCGS to potentially prevent permanent neurological damage;

which initially at least, some individuals may not be aware of. The removal of gluten from the diet needs to be the priority, because, although findings are mixed as to the breadth of its effectiveness in terms of remission of symptoms or damage, a GFD is the only way to stop further damage occurring to the gut and neurology.

Neurological examination is unlikely to be helpful in a true diagnostic setting as neurological changes seem to be, at least initially, subtle. It would however be beneficial to track any changes in more advanced neurological conditions such as ataxia following the introduction of a GFD. From the evidence above the only reliable way of doing this appears to be TMS and nerve conduction studies. Unfortunately, cognitively there are no tests that stand out as being sensitive enough at this time and tests to detect dementia are likely to be insensitive to very subtle cognitive changes.

There is also a question as to whether ethically and/or clinically there is any reason to detect subtle changes to cognition and neurology. It is likely that subtle changes indicate shorter periods of gluten exposure, which will respond well to a GFD, but these are questions for further empirical study.

There needs to be more robust research conducted on the cognitive symptoms of CD and NCGS, which would better inform and improve clinical practice. There may be a CD or NCGS cognitive profile that would enable health professionals to recognise these conditions without gastrointestinal symptoms and speed up the diagnosis and removal of gluten from the diet.

There needs to be more investigation into the phenomena of NCGS and refractory CD as the literature is currently limited. There may be significant clinical implications for these groups of individuals that cannot be identified with the scarcity of information currently available.

The development of a NCGS ‘community’ with as much presence as the CD ‘community’ may help to further this agenda.

Consideration should also be given of the impact of gluten on older adults and children. Although not in the scope of the current literature review the findings regarding the cognitive symptoms of adults with CD and NCGS are very relevant for younger and older people, especially when we remember that symptoms may present cognitively as opposed to gastro-intestinally. Children struggling to do well at school, or older adults concerned about memory may in fact be experiencing issues related to CD and NCGS.

In summary, the literature gives a clearer picture of the neurological symptoms found in adults with CD and to a lesser extent NCGS, the studies are generally more robust and there is more agreement across studies as to what the symptoms are, peripheral and central nervous system involvement is identified. It appears clear that symptoms can start very subtly and can become extremely severe. There is some opportunity to reduce or remove these symptoms, but the factors that enable this are not fully understood; however, duration of exposure to gluten, duration of symptoms and duration of GFD are likely to play a role.

The picture of cognitive symptoms in adults with CD and NCGS is less clear. There is no overall agreement as to whether there are indeed any cognitive symptoms and certainly not which cognitive abilities are affected. The mechanisms of impairment are not discussed. There is a requirement for more research in this area and further attention and higher quality studies may start to clarify the picture. Anecdotally there is considerable agreement that there are significant cognitive effects for certain individuals, particularly within the CD community and this remains an interesting and exciting area for research.

GLOSSARY

Alexithymia – An inability to recognise and describe your own emotions. Can impede ability to relate to and attach to others. Considered to have a cognitive and affective dimension.

Antibodies – Cells (proteins) produced by white blood cells that are part of the immune response. Antibodies recognise and attack invading molecules within the body.

Anti-ganglioside antibodies – Specific antibodies that react with cells in the brain.

Anti-gliadin antibodies – Specific antibodies that react to gliadin, a protein found in wheat.

Autoimmune – When the body's immune response mistakenly targets the body's own healthy cells. Different autoimmune diseases attack different cells. Cause of autoimmune diseases generally unknown, although genetic factors play a role in many.

Cytokines – Are produced by cells involved in an immune response. They cause other cells to behave in certain ways e.g. to target an invading virus or bacteria.

Guillian Barre syndrome – A rare autoimmune condition where the body attacks its own nerves. Weakness, numbness and tingling are common symptoms and can lead to paralysis if untreated.

Immunoglobulin (IG) – A concentrated form of natural human antibodies, usually used to treat individuals with compromised immune systems.

Motor cortex – An area of the frontal lobe if the brain that is involved with the planning, control and carrying out of voluntary movement.

Motor neurone disease – Is a term used for a number of conditions that share the characteristics of affecting the parts of the nervous system (brain and spinal cord) that control the movement of muscles. It is progressive and symptoms get worse over time from weakness to a total inability to move.

Moyamoya disease – A rare and progressive disease that is characterised by multiple, small blockages of the arteries at the base of the brain. The name means “puff of smoke”, which describes the look of the multiple small blood vessels that stem from the blockage to provide blood to the area affected.

Neuropathy – Damage or dysfunction of any of the nerves that make up the peripheral nervous system.

Occipital lobe – The area of the brain that is responsible for vision.

Transcranial magnetic stimulation (TMS) – In this case is a method to detect and diagnose dysfunction in motor nerve conduction using magnetic pulses delivered painlessly to the head.

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VOLUME I: EMPIRICAL PAPER

Adult Coeliac Disease: Illness Perceptions, Psychological Wellbeing, Quality of Life and the Moderating and Mediating Roles of Coping and Self-Efficacy

by

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ABSTRACT

Aim

The aim of this research is to investigate the moderated mediation effects of self-efficacy and coping style on the indirect relationships between illness perceptions and psychological wellbeing and quality of life in a sample of UK adults diagnosed with the autoimmune condition coeliac disease.

Method

The study follows an online, cross-sectional, questionnaire-based design, which gathered information from the sample (n=1578) at one time point. Data were collected on illness perceptions (IPQR), wellbeing (DASS21), quality of life (CDQ), dietary adherence, coping (Brief COPE) and self-efficacy (ASES) alongside demographics and information specific to coeliac disease diagnosis and management.

Results

Psychological wellbeing is best moderated and mediated via emotion focussed and dysfunctional coping for all illness perception sub-scales, other than personal control. Quality of life is more complicated, but significant moderated mediation routes were found through dysfunctional coping for all CDQ subscales, through emotional focussed coping for CDQ emotion and through problem focused coping for CDQ social and CDQ diagnosis and treatment worries.

Conclusion

This study shows that higher self-efficacy for the dietary management of coeliac disease leads to the reduction of dysfunctional coping strategies; using adaptive strategies improves psychological wellbeing and quality of life. Assessing self-efficacy following a diagnosis of coeliac disease could be helpful in identifying individuals who may struggle to manage their condition and achieve good outcomes. Alongside this, supporting the development of more adaptive and less dysfunctional coping strategies will improve outcomes and further increase self-efficacy, psychological wellbeing and quality of life.

INTRODUCTION

Coeliac Disease

Coeliac disease (CD) is a chronic autoimmune condition triggered by the ingestion of gluten in genetically susceptible individuals (NICE, 2015). Gluten causes the villi, hair like structures in the intestines, to become flattened. This reduces the surface area of the gut and reduces its ability to absorb nutrients from food, which can cause further issues; anaemia (Freeman, 2015) and osteoporosis (Scott, 2000). There are a wide range of symptoms associated with CD. Gastrointestinal symptoms include bloating, diarrhoea, constipation and abdominal pain (Hadjivassiliou et al., 2016). Extra-intestinal effects include fatigue (sometimes referred to as "brain fog") (Yelland, 2017), nervous system abnormalities (Hadjivassiliou et al., 2006) and skin conditions (Coeliac UK). Individuals with the condition may suffer a variety of these symptoms or may not be aware of any (Iwańczak et al., 2013); receiving a diagnosis after investigations for other conditions such as anaemia or unexplained weight loss (Green et al., 2005).

CD is diagnosed via blood tests followed by confirmatory intestinal biopsy if CD-specific antibodies are present or if symptoms persist (NICE, 2015). A life-long gluten free diet (GFD) is the only treatment for CD. Ingesting even 100ppm (parts per million) of gluten will cause intestinal damage to continue (Collin et al., 2004). Foods must be < 20ppm to be sold as "gluten free" (Codex Standard 118-1979, 2015). A strict GFD allows the intestines to heal (Collin et al., 2004; Rubio-Tapia et al., 2010) and within 12 months most individuals with CD will be symptom free (Galli et al., 2014); absorption can return to normal and symptoms disappear (Corbett et al., 2012). Each individual reacts to gluten ingestion differently in terms of duration of and severity of symptoms (Coeliac UK).

CD is the most frequently diagnosed food-related disorder in Europe (Baiardini et al., 2012), effecting around 1% of adults (Woodward, 2015); even so it is thought to be significantly

underdiagnosed (NICE, 2015; Coeliac UK; Hopper et al., 2007). Rates vary throughout the remainder of the world in relation to the amount of gluten-containing food in the national diet. The UK, USA and Europe consume a lot of gluten rich foods as dietary staples, whereas in other countries rice is the staple carbohydrate; CD is found in fewer than 0.05% of Japanese adults (Mai et al., 2017).

There are a number of factors that affect adherence to a GFD. These include understanding the requirements and being a member of a supportive CD-specific network (Leffler et al., 2008). Not only do these factors influence the ease with which people can follow a GFD, they also influence quality of life. In a Canadian adult sample, Zarkadas et al. (2006) reported that the quality of life of individuals with CD was related to dietary support and availability of gluten free foods. They also reported that when participants experienced improvement in symptoms it encouraged them to follow the GFD. Depression and anxiety can frequently be experienced by people with CD (Addolorato et al., 2004). The reasons for this are complicated and Sverka et al. (2005) qualitatively investigated exactly what could cause psychological distress by interviewing 43 adults with CD. They found a number of complex factors across three categories; the emotions related directly to having CD, interpersonal difficulties around the requirements of the diet, and risk-taking. Additionally, gluten-free foods remain substantially more expensive than their gluten-containing counterparts placing a further burden on individuals with CD (Lee et al., 2007; Missbach et al., 2015).

Psychological and behavioural factors play an important role in the management of chronic conditions. An understanding of the illness, treatment and outcomes are key in understanding how choices are made and what outcomes may be achieved. They also help in pointing to the focus of interventions if there are difficulties in keeping to a health regimen.

Illness Perception

Leventhal et al.'s (1980; Meyer et al., 1985) Common Sense Model of self-regulation (CSM) was developed to explain why people make, or do not make, health-related decisions. Illness was understood as a threat that induced fear, however it was found that people needed several types of information for their beliefs and actions to be influenced, not just fear of illness. Other theories sought to do the same, however the CSM was the first to combine cognitive and emotional factors and to model these as parallel processes for the individual (Huston & Houk, 2011). The CSM states that when an individual becomes unwell, the way in which they understand and perceive their illness effects the way they cope with it (Huston & Houk, 2011) and this then influences the way they manage the illness and effects the outcomes they achieve (Brownlee et al., 2000). Hale et al. (2007) describe the 3-stage process of illness perception described by Leventhal et al. (1980); the initial understanding, or representation, of the illness and what this means, the planning and taking action phase of managing an illness and a final phase where the effectiveness of the strategies used so far is reviewed by the individual. Initially there were five components; *identity*, *consequences*, *timeline (acute/chronic), control/cure* and *cause* (Weinman et al., 1996); more recently these factors were analysed and revised to the eight now included in the Illness Perception Questionnaire – Revised (IPQR), *identity, timeline (acute/chronic), timeline (cyclical), consequences, personal* and *treatment control*, *illness coherence* and *emotional impact* (Moss-Morris et al., 2002). Individuals who reported more perceived control experienced less distress (Gonzalez et al., 2015) and were better at adhering to the requirements of managing their illness (Ford et al., 2012). Huston & Houk (2011) found that young adults with well controlled type 1 diabetes discussed the emotional impact of their condition, had greater acceptance and greater illness coherence than young adults with poorly controlled type 1 diabetes. Illness perceptions have been shown to be significant in many chronic conditions (Zelber-Sagi et al.,

2017; Langston et al., 2017) and meta-analyses have reflected similar findings (Broadbent et al., 2015, Hagger & Orbell 2003; Hagger et al., 2017).

Illness perceptions are important determinants of behaviour (Petrie et al., 2007) and have been found to predict certain outcomes such as depression and anxiety (Costa et al., 2015) and health related quality of life (Rochelle & Fidler, 2012) in chronic and autoimmune conditions respectively.

Psychological Wellbeing

One of the outcomes in this study is psychological wellbeing. Psychological wellbeing can be difficult to define (Dodge et al., 2012), however for this study it is understood to mean the absence of symptoms of psychological illness such as anxiety and depression. The interaction between psychological wellbeing and health has long been an area of research (Das, 2016; Pratt et al., 2015). Park et al. (2013) reported symptoms of depression to be linked to long-term outcomes, including mortality, in diabetes. Wellbeing, indicated by factors such as joy, happiness and contentment, can positively impact health and longevity (Chida & Steptoe, 2008). Ironson et al. (2017) looked at wellbeing, health behaviours and biomarkers of cardiac illness and found a relationship between reduced C-reactive proteins – biomarkers of inflammation - and positive wellbeing.

In terms of CD research, Barratt et al. (2011) found that depression and anxiety were correlated with poorer perceived adherence to a GFD. Brands et al. (2004) found the impact of the dietary restrictions required to remain healthy have a negative impact on psychological wellbeing. Adults with CD have poorer reported wellbeing and score worse on measures of anxiety, general health and vitality (all measured by the Psychological General Wellbeing Index) than the general population (Baiardini et al., 2012). Depression has a larger impact on

subjective wellness than the presence and severity of gastrointestinal symptoms (Sainsbury et al., 2013) and affects adherence to the GFD. However, Van Hees et al. (2013) found that longer term adherence to a GFD reduces depressive symptoms. This possibly points to a relationship between wellbeing and other factors such as self-efficacy, which will be discussed later.

Quality of Life

The second outcome in this study is health related quality of life. While quality of life and wellbeing are sometimes used to describe the same construct (Frisch et al., 1992), quality of life describes a wider set of factors that includes psychological, physical and social considerations (Cooke et al., 2016). Health related quality of life (HRQOL) is defined as the "way health is empirically estimated to affect quality of life" (Karimi & Brazier, 2016; pg 648). Assessing health related quality of life (HRQOL) is a key area for health research including oncology (Cella & Stone, 2015), paediatrics (Baumann et al., 2015) and weight management (Minet Kinge & Morris, 2010).

Katsanos et al., (2016) found that HRQOL (measured by the EQ-5D; Group E, 1990) varied depending on which technique was used to surgically treat cardiac disease. Wound healing was also more rapid for the higher HRQOL group; however, it was not possible to establish the direction of this relationship. Mishra et al., (2015) reported that adults who were undergoing cancer treatment experienced increased HRQOL if they engaged in a moderate, regular exercise program. Ayis et al., (2015) found that higher HRQOL predicted survival past one year in adults and older adults who had experienced stroke. HRQOL may improve clinical outcomes across a number of acute or chronic conditions.

Hauser et al., (2007a) found European studies generally reported that individuals with CD had lower HRQOL, while American and Canadian studies reported levels comparable with the general population. HRQOL is more important than disease severity in determining CD patients' level of distress (Dorn et al, 2010).

Considering the second phase of the CSM, illness perceptions are used to predict the coping strategies that are likely to be used by individuals. This is discussed in detail below.

Coping

Another area for consideration is that of coping and how different strategies may predict different outcomes in long-term conditions (Hagger & Orbell, 2003). In Drossman et al.'s (2000) study, higher scores on the catastrophising scale and lower scores on the ability to decrease symptoms scale (Coping Strategies Questionnaire) in women with gastrointestinal disorders predicted poorer health outcomes and higher neuroticism. Lawson et al., (2007) found that adults with diabetes who regularly attended health-management clinics used more adaptive coping strategies than those who did not attend.

German and Austrian adolescents rated their own adherence to a GFD; those who reported no gluten consumption each month were classed as "compliant", all others were "non-compliant". Wagner et al., (2016) found compliant adolescents were less likely to use emotional regulation and distraction strategies. Dowd and Jung (2017) examined self-compassion as a coping strategy in North American adults with CD and the impact this may have had on adherence to the GFD. The study reported that participants who were self-compassionate had better HRQOL and better dietary self-management. Self-compassion can be interpreted as being related to positive emotional coping, or opposite to dysfunctional coping, which includes self-blame (Carver, 1997).

Optimism is associated with positive coping strategies and better health outcomes in individuals with chronic conditions (Fournier et al., 2002; Fournier et al., 2003). Karademas et al. (2011) found that pre-CD diagnosis optimism mediated illness outcomes using the CSM; more optimistic participants used more adaptive coping styles. This study also highlighted the importance of an illness perception "feedback loop" (page 568) in which effective coping strategies feeds back and impacts illness perceptions causing them to become more positive and less negative. This demonstrates Hale et al.'s (2007) final stage of the CSM. In more self-efficacious individuals using adaptive coping strategies, may result in a similar feedback loop as they experience less symptoms of CD and more confidence in their own ability to manage the disease.

Self-Efficacy

Self-efficacy is the idea that a person needs to believe in their ability to take action to achieve a goal before they start to take action (Bandura, 1997). Bandura (1994) explained that self-efficacy increased as a result of previous effective behaviour. Self-efficacy has been shown to play an important role in the maintenance of healthy choices such as exercise (Higgins et al., 2014) and smoking abstinence (Hoeppner et al., 2014) and is important to consider in the context of CD given that ongoing commitment to a GFD is vital. Improving self-efficacy through targeted interventions (McCarroll et al., 2014) has been shown to improve health outcomes such as weight loss following cancer treatment.

Schwarzer & Renner (2000), however, found that high self-efficacy alone is not sufficient to explain positive health decisions in healthy adults. Individuals also need to hold outcome expectancies linked with the behavioural change being undertaken. This was reflected in the results of Nouwen et al., (2009) who reported that dietary self-efficacy combined with short-term treatment effectiveness was a significant predictor of dietary adherence in individuals

with diabetes. When individuals with CD choose to consume gluten containing foods, low self-efficacy has been found to be a reliable predictive factor (Hall et al., 2013).

While the evidence that self-efficacy is strongly related to health outcomes is robust, the direction of this relationship is not so clear (French, 2015). Many studies identify a link, but the methods and models used do not allow identification of whether high self-efficacy comes before or as a result of achieving a goal.

Moderated Mediation

In order to examine the complex relationships between the factors effecting health outcomes moderated mediation models are frequently used as they allow multiple variables to be considered within the same analysis. Hofer et al. (2017) investigated multiple moderators such as age, gender and self-efficacy on medication adherence in adults with diabetes and found that significance was not reached for any of the moderators used. The significant mediator was satisfaction with medication information, which improved medication adherence. Varni et al. (2017) found that perceived medication adherence barriers in patients with gastrointestinal symptoms moderated health related quality of life. This was further mediated by patient communication, meaning that when patients were able to effectively communicate with their healthcare providers the perceived barriers had less effect on quality of life.

This is a complex area and a number of relationships are possible between all the aspects discussed above, which need to be carefully considered and modelled. For the purpose of this study the CSM provided a model and basis of understanding for the outcomes of psychological wellbeing and HRQOL for adults with CD. The CSM states that illness perceptions predict coping and within this study coping is used as a mediator for the

outcomes. Level of self-efficacy is explored as a moderator, as different levels of self-efficacy may lead to a difference in individuals' ability to utilise coping strategies, which may in turn affect psychological wellbeing and HRQOL. Following existing precedent in health research a moderated mediation model was used to allow examination of these factors.

Aim

The aim of this study was to investigate whether there were relationships between illness perceptions, psychological wellbeing and quality of life and whether these relationships were mediated by coping and moderated by self-efficacy for the GFD in adults with CD.

Hypotheses

Hypothesis One:

There will be a relationship between illness perceptions and the outcomes (a & b) as illness perceptions become more negative (e.g. belief in long-term, serious consequences of CD) outcomes will reduce.

a) psychological wellbeing
b) quality of life

Hypothesis Two:

There will be a relationship between illness perceptions and coping strategies. As illness perceptions become more negative (e.g. belief in long-term, serious consequences of CD) more dysfunctional coping strategies will be used.

Hypothesis Three:

There will be a relationship between coping strategies and the outcomes (a & b). As more dysfunctional coping strategies are used outcomes will reduce.

Hypothesis Four:

The relationship between illness perceptions and the outcomes (a & b) will be mediated by coping strategies

Hypothesis Five:

Dietary self-efficacy will moderate the mediation of coping strategies on the relationship between illness perceptions and the outcomes (a & b)

METHOD

The data described below were collected for an exploratory study funded by Coeliac UK and carried out by researchers within the School of Psychology, University of Birmingham between 2009 and 2010. Preliminary, descriptive data analyses were included in an end of grant report but the data had not otherwise been analysed.

Participants

Participants were recruited via the Coeliac UK website and by advertising on a popular and well-established CD Facebook page. The study was further promoted through the Coeliac UK members' magazine. Data were gathered through an online questionnaire pack (Appendix A)

hosted by Survey Monkey. If preferred participants were able to request paper copies of the questionnaire pack. In this case, completed questionnaire packs were returned to the University of Birmingham in pre-paid envelopes.

The following inclusion criteria were a requirement of participation:

1. A self-reported diagnosis of CD (made by either blood test and biopsy or blood test alone)
2. Adults aged over 18 years
3. A UK resident at the time of the survey

In total 1672 participants logged in to start the survey with 1410 participants (84%) completing and submitting the online pack. In addition, 262 requests were made for paper copies and 218 (83%) of those were returned. Following data collection, participants with more than 25% missing data across all measures were excluded from analysis; this resulted in a final sample of 1578 participants. Participants with < 25% missing data were included and missing data values were dealt with as appropriate for each stage of analysis as described below.

The ages of participants ranged from 18 – 85 years with a mean of 47 years (SD 14.29); 1228 respondents were female (83%) and 259 were male (17%). Most of the participants were 'White British' (n=1383, 94%), 5% identified as 'White Other' and less than 1% (n=25) as other ethnicities ('Asian', 'Black', 'Mixed - White and Asian', 'Mixed - White and Black'). Additional participant demographics below (Figure 1).

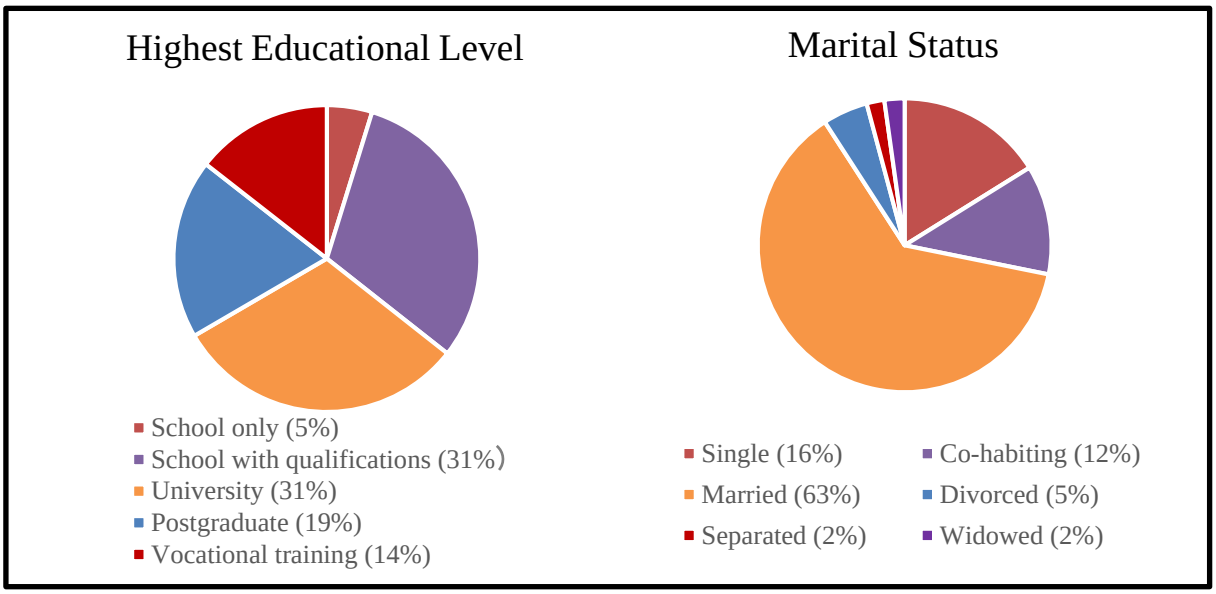

Figure 1: *Participants' highest educational level and marital status*

Design

The study follows a cross-sectional, questionnaire-based design. Data were collected on illness perceptions, wellbeing, quality of life, dietary adherence, coping and self-efficacy alongside demographic information and information specific to CD diagnosis and management.

For the purposes of the current analysis, the predictor variable is illness perceptions (x); dependent variables (y) are psychological wellbeing and quality of life, coping is a mediator (m) and self-efficacy acts as a moderator (w).

Ethical Approval

Ethical approval was received from the University of Birmingham Human Research Ethics committee in 2008 before data was collected (Appendix B).

Materials

Participants completed questionnaires to assess each area. A summary of these are presented below:

- **The Illness Perceptions Questionnaire Revised** (IPQR: Moss-Morris et al., 2002) is a 58-item scale that assesses individuals' beliefs about their illness across eight subscales of identity, timeline acute/chronic (α= .89) or cyclical (α= .79), consequences (α= .84), personal control (α= .81), treatment control (α= .80), illness coherence (α= .87) and emotional representations (α= .88). There is a further subscale that assesses participants' attributions of the cause of their illness. As is not uncommon in research regarding specific diseases (Baiardini et al., 2012; Karademas et al., 2011) this subscale was not included.
  - Higher scores indicate strong agreement with each subscale.
- **The Depression Anxiety Stress Scale 21** (DASS21: Lovibond & Lovibond, 1995) contains a total of 21 items (α= .88), seven each for depression (α= .72), anxiety (α= .77) and stress (α= .70). High scores on the depression measure map onto mood disorders, high scores on the anxiety measure correspond to panic disorder and high scores on the stress scale are associated with generalised anxiety (Brown et al., 1997).
  - Higher scores indicate poorer psychological wellbeing.
- **The Coeliac Disease Questionnaire-Health Related Quality of Life** (CDQ: Hauser et al., 2007b) is a 28-item scale developed to specifically examine health related quality of life in individuals with CD across four subscales; gastrointestinal symptoms (α= .80), emotional impact (α= .91), social impact (α= .81) and worries related to the disease (α= .81).
  - Higher scores indicate higher quality of life.
- **The Brief Coping Orientation to Problems Experienced** (Brief COPE: Carver, 1997) is a 28-item version of the full COPE inventory (Carver et al., 1989), which is divided into 14 sub-scales; self-distraction (α= .71), active (α= .68), denial (α= .54), substance use (α= .90), emotional support (α= .71), behavioural disengagement (α= .65), venting (α= .50), instrumental support (α= .64), positive reframing (α= .64), self-blame (α= .69), planning (α= .73), religion (α= .82), humour (α= .73) and acceptance (α= .57). These subscales are condensed into three; problem focussed coping, emotion focussed coping and dysfunctional coping (Cooper et al., 2008).

- Higher scores indicate more use of these coping strategies.

- **Adult Self-Efficacy (for the Gluten Free Diet) Scale** (ASES: Based on Senecal et al., 2000) is a 34-item scale that measures self-efficacy in maintaining a GFD when faced with a number of scenarios.
  - Higher scores indicate higher self-efficacy for the GFD.
- **Gluten Free Diet Questionnaire** is a 6-item measure written by the original research team. It asks participants to report how often in the last two weeks they have knowingly eaten gluten and how well they stick to their GFD both at home and away from home. Participants also report how concerned they are about gluten exposure and how harmful they think it is.
  - Responses were given on a 5-point Likert scale, higher scores indicate poorer adherence to the GFD and more concern about the danger of gluten.

Participants and Procedure

A licence was purchased from Survey Monkey to enable online data gathering. Prior to the public launch the online site was tested for ease of access, ease of use and technical issues by the research team.

Staff at Coeliac UK provided their advice and support regarding the design of the online materials and recruitment of participants both before and during data collection.

Informed consent was gathered for all participants at the first stage of the questionnaire. Participants read and agreed to consent to the study before they were given access to the questionnaire pack.

Confidentiality was explained and maintained by assigning participant numbers to each completed questionnaire. No personal data were included in the database.

When the project was launched in October 2009, potential participants were provided with online links to the survey pack. All the information regarding the research and consent were included in this link. After reading the project information sheet participants who were happy

to continue gave their consent online. They could then complete the online questionnaire pack or request a paper copy.

The online survey was closed on 30th September 2010; no further paper questionnaire packs were sent out after this date, although completed packs received afterwards were included. The initial response was huge, with over 800 online questionnaire packs being completed within the first five weeks.

For the purposes of the initial study an end of study report was produced in May 2011. This provided mainly descriptive information of the data gathered and the participants who took part.

Analysis

Data were initially coded and input into SPSS by the original research team. The author completed data "cleaning" or screening of data for errors and potential coding mistakes; unknown coding strategies were treated as missing data. Following this, detailed statistical analysis of the dataset was completed using SPSS (IBM SPSS Statistics version 23) as described below.

The demographic information was examined using frequencies and descriptive statistical techniques which provided information on age, gender, ethnicity, education level, history of CD diagnosis and management.

Data were examined for normality using Kolmogorov-Smirnov to indicate whether they violated the assumptions for parametric analysis.

Running analyses with missing data can bias results and reduce statistical power (Zhang & Wang, 2013). Missing items were analysed across scales to examine whether absent data

followed random or non-random patterns using SPSS's Missing Values Analysis. Non-random missing data patterns were excluded from further analysis.

Missing values were imputed for all items of missing data using 10 multiple imputations. Pooled multiple imputation data was used to describe means and standard errors for each subscale. Inter-correlations were completed where appropriate. The effects of gender and time since diagnosis were also considered through correlation and Mann-Whitney U tests.

Final hypothesis testing was carried out using the LAVAAN package of R Studio (R Studio Team, 2015) combined with a project-specific program written by Dr Chris Jones (University of Birmingham) to allow a full information maximum likelihood version of Hayes (2013) Model 7 to be analysed; the reason for this is discussed further below. No other program existed to enable this analysis to be completed.

RESULTS

Further Demographic Information

Sixty-five per cent (n=1029) of the sample reported they were diagnosed with CD following blood tests and biopsy with a further 20% (n=316) reporting they were diagnosed through biopsy alone. Duration of diagnosis ranged from < 6 months to 67 years with a mean of nine years three months (SD=10.47). Of the participants who answered the question relating to the results of their last blood test most had normal antibody results (n=592, 46%), some could not remember (n=365, 28%) and the rest were abnormal (n=287, 22%); 38 participants had not had a blood test.

Five hundred and ninety-six respondents (38%) reported other health conditions, of these 216 (57%) had thyroid disease, 187 (31%) had asthma, 58 (10%) had heart disease and 25 (4%) type 1 diabetes. Other food intolerances were also present in 23% of respondents. The most common of these were intolerance to dairy (n=140, 39%), caffeine (n=47, 13%), alcohol (n=37, 10%), yeast (n=19, 5%) and fructose (n=11, 3%) respectively. Other food intolerances were reported by 107 participants. Participants were asked to rate how well they followed their GFD at home and away from home (GFD Questionnaire). In this sample participants reported being extremely good at following their GFD with 95% (n=1438) reporting they had been exposed to gluten fewer than twice in the last two weeks while at home and 93% (n=1413) reporting the same while away from home. There was a small, but not significant difference between ability to stick to a GFD when at home or away from home with participants reporting 97% (n=1472) and 92% (1392) respectively. Most participants were ‘extremely’ concerned by the prospect of accidental gluten ingestion (n=465, 31%), however, most frequently reported accidental ingestion of gluten was ‘quite’ (n=772, 51%) or ‘a little’ (n=715, 47%) harmful.

Missing Data

If statistical analyses were performed only on datasets without missing data then this would result in a significant reduction in sample size (i.e., to approximately 60% of the original sample for some variables). This loss of data would, in itself, constitute a significant bias to further statistical analysis. Therefore, treatment of missing data needs to be considered prior to statistical analysis in all research (Zhang & Wang, 2013), not dealing appropriately with missing data can ultimately result in weak or incorrect conclusions (Little & Rubin, 2002) and will produce bias.

Missing data were analysed to identify whether there were any patterns in the missing data that suggested that certain questions were systematically not answered i.e. not missed at random. These patterns of missing data (Little & Rubin, 2002) may bias results if it is assumed all missed data points occurred at random when they in fact did not. The table below (Table 1) shows the results of this analysis.

***Table 1**: Missing data patterns by variable*

Measure (Variable)	Summary of missing data	Pattern Analysis	Action
IPQR	Across 36 (98%) items in the variable 124 (< 1%) values were missing from 66 (4%) cases	**Random** missing data patterns identified	Replace missing data using multiple imputation
ASES	Across 100% of items in the variable 2061 (4%) values were missing from 698 (44%) cases	**Non-random** missing data pattern identified – Question 5 was systematically not answered	Remove ASES question 5 from further analysis
CDQ	Across 100% of items in the variable 1526 (3%) values were missing from 393 (25%) cases	**Random** missing data patterns identified	Replace missing data using multiple imputation
Brief COPE	Across 100% of items in the variable 1946 (4%) values were missing from 243 (15%) cases	**Random** missing data patterns identified	Replace missing data using multiple imputation
DASS21	Across 100% of items in the variable 1658 (5%) values were missing from 199 (13%) cases	**Random** missing data patterns identified	Replace missing data using multiple imputation

Note: **IPQR** Illness Perception Questionnaire – Revised, **ASES** Adult Self-Efficacy Scale, **CDQ** Coeliac Disease Questionnaire – Health Related Quality of Life, **Brief COPE** Brief Coping Orientation to Problems Experienced, **DASS21** Depression Anxiety and Stress Scale 21

A number of methods to deal with missing data were considered such as list-wise (LW) and pair-wise (PW) deletion, however, although these remain common methods (Chen et al., 2005) Zhang & Wang (2013) point out that they have not been specifically examined in terms of their performance in moderated mediation models. There are other issues with using these methods such as assumptions about the data (LW) and that analysis might be based on different samples (PW). Mean substitution (MS) was rejected as there is a risk that bias would be produced (Malhotra, 1987) as a result of the means replacing the missing data not being random.

Multiple imputation (MI) is not affected by the issues raised above. According to the literature MI is superior to PW, LW and MS (Kang, 2013; Zhang & Wang, 2013; Baldwin et

al., 2016) particularly with large samples. MI does not distort the original data (Mercer et al., 2011), whether it was skewed or normally distributed. For these reasons, it was chosen here and used in all analysis below unless stated otherwise.

Multiple Imputation

An important consideration therefore is how many imputations to use. Initially guidance based on Rubin's (1987) formula suggested that five to 10 imputations were enough, however, this focussed on efficiency, but not, as highlighted by Allison (2012), standard error estimates, confidence intervals, and p-values. Graham et al. (2007) recommends a higher number of imputations dependent on how much missing data are present. Using this guidance, 10 imputations were used (Graham et al., 2007; Bodner, 2008). Many statistical packages use 100 imputations as standard, however the use of such a considerable number adds nothing to the strength of the outcome and is not necessary (Allison, 2012). All further analyses present the results of pooled multiple imputation unless otherwise stated.

Normality of distribution

The Kolmogorov-Smirnov test indicated results across all measures were skewed from normal. This is not unusual in health research (Pallant, 2007; Baldwin et al., 2016) and in this case, is particularly likely as the inclusion criteria required participants to have a diagnosis of CD which increases the likelihood that responses to CD-related questions would be skewed.

Internal Consistency

Overall, across all subscales, all alpha levels were acceptable or better and only three were questionable or poor (Table 2). Removal of items within these lower scoring subscales would

not significantly increase the alpha level and no items were removed. Subscales with reliability below 0.6 (grey in table) were excluded from further analysis as they held too much risk of biasing the results and causing errors.

***Table 2**: Internal consistency values by subscale*

Measure	Internal Validity (Cronbach's Alpha)		Measure	Internal Validity (Cronbach's Alpha)
Illness Perceptions Questionnaire Revised			**Celiac Disease Questionnaire-Health Related Quality of Life**	
Identity	.84			
Timeline	.56			.85
Acute/Chronic			Gastrointestinal	.90
Consequences	.79		Emotional	.84
Personal control	.78		Social	
Treatment Control	.51		Diagnosis and Treatment	.86
Illness Coherence	.87		Worries	
Timeline Cyclical	.90			
Emotional Responses	.91			
Depression Anxiety Stress Scale			**Brief COPE**	
			Problem focussed	.81
Depression	.93		Emotion focussed	.68
Anxiety	.86		Dysfunctional	.73
Stress	.91			

Illness Perceptions – IPQ-R

Table 3 shows the means and standard errors for illness perception subscales. Most participants reported that 4 of the 20 symptoms listed in the Identity subscale were related to their CD. There was a belief that the consequences of CD were moderately severe. A strong sense of personal control was reported by this sample; with participants agreeing that their actions affected the outcome of their CD. A good understanding of the condition (illness coherence) is also evident. This sample disagreed that the symptoms of their CD were cyclical, or changeable and unpredictable from day to day, and equally disagreed that having CD caused negative emotional responses.

***Table 3**: Means and standard errors for illness perception subscales*

	Identity	Consequences	Personal Control	Illness Coherence	Cyclical	Emotional
N	1578	1578	1578	1578	1578	1578
Mean	4.51	3.48	4.31	4.21	2.26	2.55
Std. Error	.10	.02	.02	.02	.03	.03

Note: Scores for **Identity** range from 0-20, all other scores range from 1-5

Overall, this sample reported they understood their CD and believed they could influence it through their actions. They felt their CD was generally predictable and they knew what to expect day to day. They had few negative emotional reactions to the condition, possibly because of the confidence they had in their own ability to manage it.

To further explore these results bivariate correlations (Spearman's Rho for non-parametric data) were completed for the IPQ-R subscales (Table 4). All results were significant at $p < .01$ apart from personal control and consequences ($r_s = -0.03$, $p < .19$), there is no significant link between believing your own actions influence the outcome of your CD and belief in the severity of the consequences of the condition. Although not significant, the direction of the correlation suggests that as personal control increased belief in the negative consequences of CD decreased.

The strongest correlation ($r_s = -.78$, $p < .01$) was between personal control and identity and reflected the confidence this sample had in their ability to manage their CD through their own actions; the more people felt they themselves could affect their CD the fewer symptoms they reported as being related to the condition.

There was a strong link between emotion and consequences ($r_s = .62$, $p < .01$), which means the more participants reported negative emotional reactions to their condition, the more they believed the consequences of having CD were serious.

***Table 4**: Spearman's Rho correlations for IPQ-R subscales*

	Identity	Consequences	Personal Control	Illness Coherence	Cyclical
Consequences	.28**				
Personal Control	-.78**	-.03			
Illness Coherence	-.16**	-.23**	.40**		
Cyclical	.39**	.27**	-.27**	-.45**	
Emotional	.30**	.62**	-.23**	-.43**	.44**

** Correlation is significant at p< .01

Wellbeing – DASS21

Following recent precedent (Eisendrath, 2016; Henning et al., 2014) DASS21 total scores were used as a robust indication of general psychological wellbeing in this sample, lower scores indicated better outcomes. Mean score was M=9.24 (SE=0.123, possible range 0 to 21), which indicated scores in the normal range 0-14.

The results were also examined to identify if there were changes to psychological wellbeing in relation to gender and duration of diagnosis (Table 5; from original dataset). There was no significant correlation between duration of CD diagnosis and DASS21 total score for male participants (rs=-.011, p>.05), but female participants showed a small, but significant (rs=-.157, p< .01) negative correlation. This meant that over time DASS21 total scores were likely to fall, indicating that psychological wellbeing increases with time following CD diagnosis.

***Table 5**: Spearman's Rho correlation for DASS21 total and years since diagnosis by gender*

Male			Female	
	Years Since Diagnosis			**Years Since Diagnosis**
DASS 21 Total	-.011		**DASS 21 Total**	-.157**

** Correlation is significant at p< .01

Quality of Life – CDQ

Lower mean scores indicate lower quality of life (Table 6). This sample was least concerned with the social implications of CD (M=5.72, SE= .03) and reported that they only altered or cancelled social plans ‘a little of the time’ as a result of CD. The sample also reported struggling with the gastrointestinal symptoms of the disease ‘a little of the time’ (M=5.34, SE= .03). This reflected previous findings that this is a sample who had well-managed CD and experienced few gastrointestinal symptoms.

There was more concern regarding the diagnosis and treatment of CD (M=5.02, SE= .04) however, the emotional consequences of the condition had the greatest negative effect on quality of life (M=4.64, SE= .03).

***Table 6**: Means and standard errors for the CDQ subscales*

	Gastrointestinal	**Emotional**	**Social**	**Diagnosis and Treatment Worries**
N	1578	1578	1578	1578
Mean	5.34	4.64	5.72	5.02
Std. Error	0.03	0.03	0.03	0.04

Note: Scores range from 1-7

Bivariate correlations (Spearman’s Rho) were completed for the subscales of the CDQ (Table 7). All were significantly, positively correlated ($p < .01$) showing that as quality of life in one area was affected, all other areas were also affected. The strongest correlation was between treatment and diagnosis worries and social effects ($r_s=0.70$, $p < .01$). The more individuals worried about the diagnosis and treatment of CD, and the burdens that this involved, the more they reported changed and cancelled social plans or felt unsupported by their social network.

***Table 7**: Spearman's Rho correlations for CDQ subscales*

	Gastrointestinal	Emotional	Social
Emotional	0.60**		
Social	0.56**	0.62**	
Diagnosis and Treatment Worries	0.53**	0.55**	0.70**

** Correlation is significant at p< .01

The CDQ asked participants to give their answers based on the past two weeks of their experience, rather than over a longer or undefined period of time such as the IPQ-R. To investigate the effect of duration of diagnosis on quality of life, CDQ subscales were compared to years since diagnosis (from original dataset) the results are shown in Table 8 below.

***Table 8**: Spearman's Rho correlations for CDQ and years since diagnosis of CD*

	Years Since Diagnosis
Gastrointestinal	.026
Social	.024
Emotional	.059*
Diagnosis and Treatment Worries	.062*

* Correlation is significant at p< .05

As years since diagnosis increased, emotional and diagnosis and treatment worries around CD increased (rs= .059, p< .05 and rs= .062, p< .05 respectively), which had a positive impact on quality of life. These relationships were small, but significant at p< .05 in this sample. The reason for this may be that this sample was confident in their own ability to manage their CD well, however, when they were in social situations this was initially more difficult, but became easier as their experience and confidence increased with years since diagnosis. As years since diagnosis increase, individuals may experience less accidental exposure to gluten than they expected when not at home and could initially be more inclined

to cancel social plans to avoid accidental exposure until they realise this fear is unfounded. Worries about diagnosis and treatment may be time sensitive as participants have fewer worries about these issues as years since they were diagnosed increases.

Coping – Brief COPE

The Brief COPE measures coping styles across 14 subscales, which are frequently combined to the three used here. Higher scores indicated more coping strategies from this subscale were used (Table 9).

Table 9*: Means and standard errors for the Brief COPE subscales*

	Problem Focussed	**Emotion Focussed**	**Dysfunctional**
N	1578	1578	1578
Mean	1.930	1.949	1.381
Std. Error	.021	.016	.011

Note: Scores range from 1-4

This sample most commonly used emotion focussed coping strategies of *positive re-framing*, *using emotional support*, *humour*, *acceptance* and *religion* to enable them to cope with their CD (M=1.949, SE=.016). They also used problem focussed coping strategies of *using instrumental support*, being *active* in the way they deal with issues and *planning* for problems before they occur (M=1.930, SE=.021). The final coping style is dysfunctional, this is the least used type of strategy and is made up of *self-distraction*, *denial*, *substance use*, *behavioural disengagement*, *venting* and *self-blame* (M=1.381, SE= .011).

Inter-correlations between subscales were examined using Spearman's Rho as the data violated the assumptions for parametric analysis (Table 10).

***Table 10**: Spearman's Rho correlations for the Brief COPE subscales*

	Problem Focussed	Emotion Focussed
Emotion focussed	.736**	
Dysfunctional	.571**	.478**

** Correlation is significant at p< .01

All subscales were positively correlated at p< .01. It might have been assumed that adaptive (problem focussed or emotion focussed) copers would not use dysfunctional coping strategies, however this result suggested that people who used a lot of strategies used adaptive and dysfunctional techniques rather than using strategies from one subscale only.

There was some indication that adaptive copers used more adaptive strategies; the strongest correlation was between emotion and problem focussed strategies (rs= .736, p< .01) and the weakest correlation is between dysfunctional and emotion focussed coping (rs= .478, p< .01).

Self-Efficacy – ASES

Higher self-efficacy for the GFD was indicated by higher scores; range 0 to 10. The sample in this study were highly self-efficacious (M=8.398, SE= .039). There was no significant correlation between ASES total score and duration of diagnosis (rs= .022, p= .535). A Mann-Whitney U test (non-parametric data) revealed there was no significant difference between males' and females' scores on the ASES.

ASES correlated with all mediating and outcome variable subscales at significance p< .01 and with the Brief COPE subscales (Table 11).

***Table 11:** Spearman's Rho correlations for ASES, DASS, CDQ and Brief COPE subscales*

	DASS	**CDQ**				**Brief COPE**		
	Total	Gastro.	Emo.	Social	D and T Worries	Emotion	Problem	Dysfunc.
ASES	-.270**	.259**	.301**	.317**	.305**	-.095**	-.169**	-.297**

** Correlation is significant at p< .01

As self-efficacy increased, quality of life also increased across all subscales, the largest effect was for social impact. Conversely as self-efficacy increased DASS21 total reduced meaning psychological wellbeing improved. Interestingly self-efficacy was negatively correlated with the Brief COPE, which indicated that as self-efficacy increased the number of coping strategies reduced. This effect was largest for dysfunctional coping strategies and although very small, was also the case for problem and emotion focussed coping as well.

Hypothesis Testing

Hypothesis One:

"There will be a relationship between illness perception and the outcomes (a & b) as illness perceptions become more negative outcomes will reduce

a) **psychological wellbeing**
b) **quality of life"**

To test this hypothesis bivariate correlations were completed to identify the presence and direction of relationships between variables, correlation coefficients are shown in Table 12 below. All correlations were significant at p= .01 and the direction of the relationships were as expected so the null hypothesis can be rejected; there is a relationship between illness perception, psychological wellbeing and quality of life.

***Table 12**: Spearman's Rho correlations for illness perception, psychological wellbeing and quality of life subscales*

	Psychological Wellbeing	Quality of Life			
	DASS Total	CDQ			
		Gastrointestinal	Emotional	Social	D and T Worries
Identity	.176**	-.407**	-.313**	-.340**	-.310**
Consequences	.226**	-.342**	-.422**	-.544**	-.511
Personal Control	-.132**	.212**	.210**	.186**	.162**
Illness Coherence	-.212**	.299**	.317**	.314**	.327**
Cyclical	.264**	-.533**	-.428**	-.417**	-.374**
Emotional	.410**	-.419**	-.583**	-.587**	-.564**

** Correlation is significant at p< .01

Hypothesis Two:

"There will be a relationship between illness perception and coping strategies. As illness perceptions become more negative more dysfunctional coping strategies will be used."

To test this hypothesis bivariate correlations were completed to identify the presence and direction of relationships between variables, correlation coefficients are shown in Table 13 below. All correlations were significant at p< .001 apart from personal control and problem focussed coping (rs= .039, p= .25). An explanation for this may be that participants who have high personal control use a lot of problem focussed coping strategies, such as advanced planning. Alternatively, people with a strong sense of personal control may feel that they do not have to use many problem focussed strategies because they have confidence in their ability to deal with any issues at the time, should they arise. Individuals with lower personal control may not be able to plan for problems before they occur and so would use fewer

problem focussed coping strategies or they may unsuccessfully or unnecessarily use a lot of problem focussed coping strategies because they feel their ability to personally control the outcome of their CD is poorer.

Excluding personal control and problem focused coping, the null hypothesis can be rejected; there is a relationship between illness perceptions and coping strategies. However, the direction of these relationships does not match those made in the hypothesis.

***Table 13**: Spearman's Rho correlations for illness perception and coping subscales*

	Coping Strategies		
	Problem Focussed	**Emotion Focussed**	**Dysfunctional**
Identity	.184**	.159**	.231**
Consequences	.300**	.233**	.387**
Personal Control	.039	.089**	-.162**
Illness Coherence	-.159**	-.082**	-.284**
Cyclical	.228**	.159**	.340**
Emotional	.309**	.234**	.547**

** Correlation is significant at p< .01

Hypothesis Three:

"There will be a relationship between coping strategies and the outcomes (a & b). As more dysfunctional coping strategies are used outcomes will reduce"

To test this hypothesis Spearman's Rho correlations were completed to identify the presence and direction of relationships between variables (Table 14). All correlations were significant at p< .01, and the direction of the relationships were identified by the hypothesis so the null hypothesis can be rejected; there is a relationship between coping strategies, psychological wellbeing and quality of life and as more dysfunctional coping strategies are used outcomes will reduce.

Table 14*: Spearman's Rho correlations for coping, psychological wellbeing and quality of life subscales*

	Psychological Wellbeing	**Quality of Life (CDQ)**			
	DASS Total	**Gastro.**	**Emotional**	**Social**	**D + T Worries**
Problem Focussed	.292**	-.257**	-.308**	-.337*	-.363**
Emotion Focussed	.239**	-.185**	-.198**	-.238**	-.250**
Dysfunctional	.507**	-.407**	-.603**	-.523**	-.483**

** Correlation is significant at p< .01

The PROCESS algorithm by Hayes (2013) has become a popular resource for the analysis of moderation and mediation models. Unfortunately, the PROCESS algorithm is not appropriate for use with multiple imputation (MI) data as it requires bootstrap estimates of standard error of the indirect effects within the model and there is currently no consensus on how to apply the bootstrap across MI data. As an alternative, the LAVAAN (Rosseel, 2012) package in R Studio calculates structural equation models (SEM) with missing data accommodated using full information maximum likelihood (FIML) estimators. FIML is found to be at least as robust as MI (Peyre et al., 2010) and produces comparable results (Collins et al., 2001) in fact FIML produces slightly smaller standard errors than MI (Dong & Peng, 2013).

To test the final two hypotheses, therefore, a project-specific program was written by Dr Christopher Jones (University of Birmingham) to allow a FIML version of Hayes (2013) moderated mediation model (Hayes, 2013) model 7 to be analysed using the LAVAAN package within R Studio.

Hypothesis Four:

"The relationship between illness perceptions and the outcomes (a & b) will be mediated by coping strategies"

Conceptual and statistical illustrations shown below (Figure 2.1 & 2.2). Mediated pathways were shown by significant route estimates for both routes x~m and m~y for each variable. In this model, there were multiple variables in x, m and y; with the exception of the mediator variables each variable was analysed separately. The direction of the relationship was indicated by positive or negative route estimates.

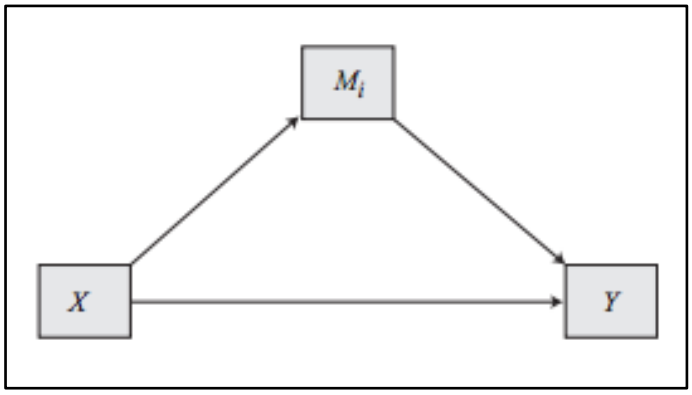

***Figure 2.1**: Conceptual illustration of a mediated model with multiple mediators (taken from Hayes, 2013)*

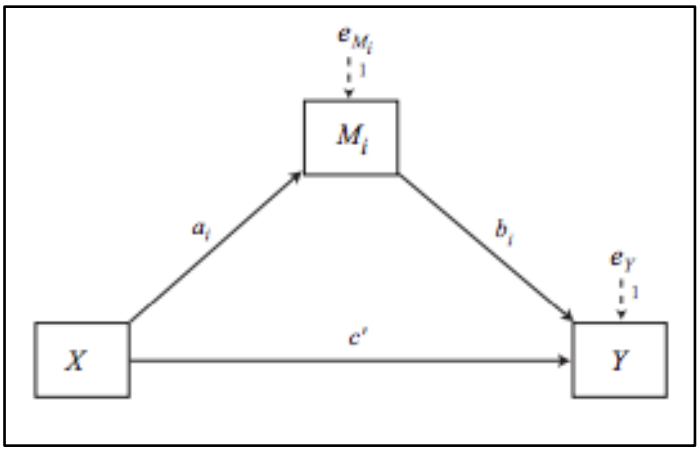

***Figure 2.2**: Statistical illustration of a mediated model with multiple mediators (taken from Hayes, 2013)*

Tables 15 to 18 show significant route estimates, standard error and alpha levels from illness perceptions to psychological wellbeing and quality of life mediated by coping strategy. For illustrations of significant pathways see Appendix C.

***Table 15**: Significant routes from x~m for DASS*

Route x~m (outcome DASS)		**m=Brief COPE**					
		Emotion Focussed (**m1**)			Dysfunctional (**m3**)		
		Est.	**SE**	**p**	**Est.**	**SE**	**p**
x=IPQR	Emotion	0.192	.025	< .001	0.378	.018	< .001
	Coherence	-0.090	.042	< .001	-.0283	.033	< .001
	Consequences	0.255	.033	< .001	0.303	.025	< .001
	Personal Control	-	-	-	-0.138	.030	< .001
	Cyclical	0.194	.040	< .001	0.350	.031	< .001

Mediation occurred across all included variables in the IPQR apart from personal control and emotion focussed coping. There were no mediated pathways between the IPQR and problem focussed coping. The null hypothesis can be partially rejected as the majority of the relationships between illness perceptions and psychological wellbeing were mediated by coping.

***Table 16**: Significant routes from m~y for DASS*

Route m~y			**y=DASS** Total		
			Est.	**SE**	**P**
m=Brief COPE	m1	Emotion	-.055	.022	.011
		Coherence	-.047	.022	.035
		Consequences	-.058	.022	.008
		Personal Control	-	-	-
		Cyclical	-.049	.022	.026
	m3	Emotion	.483	.024	< .001
		Coherence	.567	.023	< .001
		Consequences	.550	.023	< .001
		Personal Control	.569	.022	< .001
		Cyclical	.553	.023	< .001

***Table 17**: Significant routes from x~m for CDQ*

Route x~m		**m=Brief COPE**								
		Emotion Focussed (**m1**)			Problem Focussed (**m2**)			Dysfunctional (**m3**)		
Outcome CDQ Gastro		**Est.**	**SE**	**p**	**Est.**	**SE**	**P**	**Est.**	**SE**	**p**
x=IPQR	Emotion	-	-	-	-	-	-	.378	.018	< .001
	Coherence	-	-	-	-	-	-	-.282	.033	< .001
	Consequences	-	-	-	-	-	-	.303	.025	< .001
	Personal Control	-	-	-	.088	.030	.003	-.135	.030	< .001
	Cyclical	-	-	-	-	-	-	.356	.031	< .001
Outcome CDQ Emotion										
x=IPQR	Emotion	.191	.025	< .001	-	-	-	.375	.018	< .001
	Coherence	-.088	.042	.035	-	-	-	-.276	.033	< .001
	Consequences	.255	.033	< .001	-	-	-	.303	.025	< .001
	Personal Control	.169	.038	< .001	.089	.030	.003	-.130	.029	< .001
	Cyclical	.192	.040	< .001	-	-	-	.353	.031	< .001
Outcome CDQ Social										
x=IPQR	Emotion	.192	.025	< .001	.172	.020	< .001	.378	.018	< .001
	Coherence	-	-	-	-.140	.033	< .001	-.287	.033	< .001
	Consequences	.256	.033	< .001	-	-	-	.302	.025	< .001
	Personal Control	-	-	-	.088	.030	.003	-.141	.002	< .001
	Cyclical	-	-	-	.203	.031	< .001	.353	.031	< .001
Outcome CDQ Diagnosis and Treatment										
x=IPQR	Emotion	-	-	-	.174	.020	< .001	.377	.018	< .001
	Coherence	-	-	-	-.141	.033	< .001	-.286	.033	< .001
	Consequences	.259	.033	< .001	.224	.025	< .001	.298	.025	< .001
	Personal Control	-	-	-	.086	.029	.003	-.142	.030	< .001
	Cyclical	-	-	-	.203	.031	< .001	.349	.031	< .001

" – " No significant route

***Table 18**: Significant routes from m~y for CDQ*

Route m~y			**y=CDQ**											
			Gastrointestinal			Emotional			Social			Diagnosis + Treatment		
			Est.	**SE**	**p**	**Est.**	**SE**	**p**	**Est.**	**SE**	**p**	**Est.**	**SE**	**p**
m=Brief COPE	m1	Emotion	-	-	-	.129	.040	.001	.107	.041	.009	-	-	-
		Coherence	-	-	-	.086	.042	.041	-	-	-	-	-	-
		Consequences	-	-	-	.136	.041	.001	.131	.042	.002	.126	.052	.015
		Personal Control	-	-	-	.094	.043	.029	-	-	-	-	-	-
		Cyclical	-	-	-	.105	.041	.011	-	-	-	-	-	-
	m2	Emotion	-	-	-	-	-	-	-.155	.055	.005	-.355	.066	< .001
		Coherence	-	-	-	-	-	-	-.121	.060	.042	-.342	.072	< .001
		Consequences	-	-	-	-	-	-	-	-	-	-.311	.068	< .001
		Personal Control	-.123	.057	.031	-.113	.057	.046	-.181	.060	.003	-.406	.073	< .001
		Cyclical	-	-	-	-	-	-	-.122	.058	.036	-.340	.071	< .001
	m3	Emotion	-.369	.047	< .001	-.699	.043	< .001	-.418	.045	< .001	-.364	.055	< .001
		Coherence	-.503	.043	< .001	-.942	.042	< .001	-.696	.045	< .001	-.669	.054	< .001
		Consequences	-.491	.043	< .001	-.909	.041	< .001	-.612	.042	< .001	-.589	.052	< .001
		Personal Control	-.528	.043	< .001	-.979	.042	< .001	-.739	.045	< .001	-.719	.055	< .001
		Cyclical	-.381	.039	< .001	-.899	.041	< .001	-.665	.044	< .001	-.649	.054	< .001

" - " No significant route

Mediation occurred via dysfunctional coping across all predictor variables at $p < .001$. Personal control was also mediated by problem focussed coping across all outcomes of the CDQ. Emotion focussed coping mediated the CDQ emotion pathway across all subscales of the IPQR. Problem focussed coping mediated all routes from the IPQR variables for CDQ social and CDQ diagnosis and treatment (apart from the IPQR consequences subscale, which had no significant mediation from problem focussed coping). The final significant mediation effects were from the IPQR consequences subscale via emotion focussed coping for CDQ social and CDQ diagnosis and treatment where both x~m and m~y $p \leq .01$ and IPQR emotion subscale to CDQ social via emotion focussed coping (x~m $p < .001$, m~y $p = .009$). Again, the null hypothesis can be partially rejected as the majority of the relationships between illness perceptions and quality of life were mediated by coping.

Hypothesis Five:

"Dietary self-efficacy will moderate the mediation of coping strategies on the relationships between illness perceptions and the outcomes (a & b)"

A conceptual illustration of this model is shown in Figure 3.1 and 3.2 below. For illustrations of significant routes and amount of variance explained by the model see Appendix D.

This model examined whether different levels of the moderator acted on the mediator to change the indirect relationship between the predictor (x) and dependant (y) variables. In this model, the moderator (ASES) was centred and three levels; 1 standard deviation (SD) above, at and below the mean were used to identify the direction of any moderated mediation effects (Tables 19 and 20).

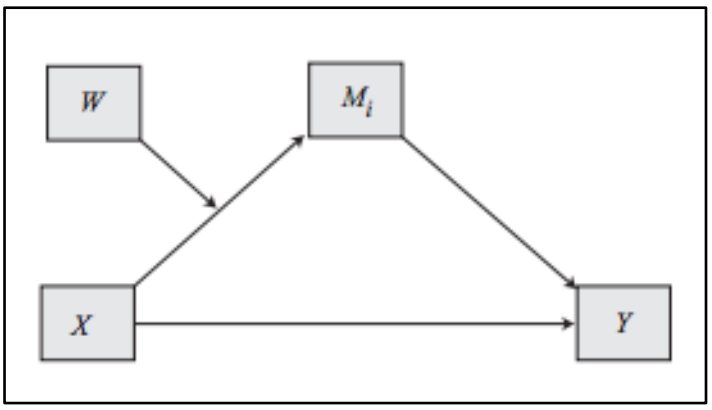

***Figure 3.1**: Conceptual illustration of a moderated mediated model with multiple mediators (taken from Hayes, 2013)*

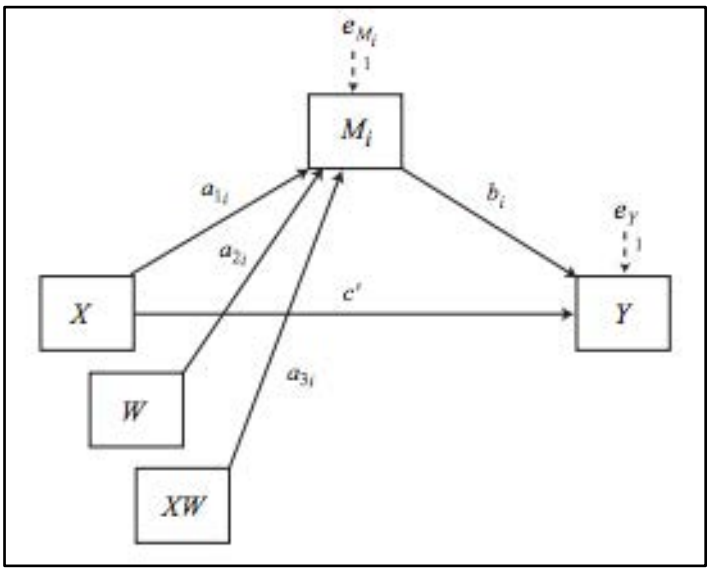

***Figure 3.2**: Statistical illustration of a moderated mediated model with multiple mediators (taken from Hayes, 2013)*

Moderated mediation further explained all the significant routes found using the mediation model for the outcome of DASS total, apart from IPQR emotion and Brief COPE dysfunctional coping and IPQR personal control and Brief COPE dysfunctional coping. In these cases, mediated routes were found, but they were not moderated by self-efficacy. All other routes were moderated by self-efficacy and 71% (n=5) of these showed that as self-

efficacy went up the model became more significant. For the other 2 routes p< .001 and a direction could not be identified as a result of the sensitivity of the test being reached.

Tables 19 and 20 showed that there were a number of wx~m routes that were mediated by coping, but were not moderated by self-efficacy (highlighted). All of these fell into the dysfunctional coping subscale and are IPQR emotion or IPQR personal control routes.

All other mediated routes previously identified were further explained by including the moderating effects of self-efficacy; 52% (n=17) of the significant routes showed moderation was more significant as self-efficacy scores increased, a further 9 (27%) were significant at p< .001 at all levels of the moderator, 15% (n=5) increased in significance as self-efficacy reduced and 2 (6%) do not reach significance (p< .05) at any level.

For all outcomes, the null hypothesis can be partially rejected as the majority of the mediated relationships between illness perceptions, psychological wellbeing and quality of life were moderated by self-efficacy.

***Table 19**: Significant routes from wx~m for DASS*

Route wx~m (outcome DASS)		**m=Brief COPE**							
		Emotion Focussed (**m1**)		**w**		Dysfunctional (**m3**)		**W**	
		Est.	**SE**	**p**	**ASES**	**Est.**	**SE**	**p**	**ASES**
x=IPQR	Emotion	.005	.001	< .001	↑	-	-	-	-
	Coherence	-.005	.001	< .001	↑	-.003	.001	< .001	↑
	Consequences	.005	.001	< .001	↑	.002	.001	.014	All
	Personal Control	-	-	-	-	-	-	-	-
	Cyclical	.004	.001	.001	↑	.002	.001	.001	All

Note: Arrows indicate significance at 1 SD above (↑), at (--) or below (↓) M, "All" indicates significance of p< .001 at all levels of moderator 0 indicates no level achieves significance at p< .05

Table 20: Significant routes from wx~m for CDQ

Route wx~m		**m=Brief COPE**											
		Emotion Focussed (**m1**)			**w**	Problem Focussed (**m2**)			**w**	Dysfunctional (**m3**)			**w**
CDQ Gastro		**Est.**	**SE**	**p**	**ASES**	**Est.**	**SE**	**P**	**ASES**	**Est.**	**SE**	**p**	**ASES**
x=IPQR	Emotion	-	-	-	-	-	-	-	-	.001	.000	.04	All
	Coherence	-	-	-	-	-	-	-	-	-.003	.001	< .001	↑
	Consequences	-	-	-	-	-	-	-	-	.002	.001	.005	All
	Personal Control	-	-	-	-	-.002	.001	< .001	↑	-	-	-	-
	Cyclical	-	-	-	-	-	-	-	-	.002	.001	< .001	All
CDQ Emotion													
x=IPQR	Emotional	.005	.001	< .001	0	-	-	-	-	-	-	-	-
	Coherence	-.005	.001	< .001	↓	-	-	-	-	-.003	.001	< .001	↑
	Consequences	.005	.001	< .001	↑	-	-	-	-	.002	.001	.007	All
	Personal Control	-.003	.001	< .001	↓	-.002	.001	< .001	0	-	-	-	-
	Cyclical	.004	.001	< .001	↑	-	-	-	-	.002	.001	< .001	All
CDQ Social													
x=IPQR	Emotional	.005	.001	< .001	↓	.003	.000	< .001	↑	-	-	-	-
	Coherence	-	-	-	-	-.004	.001	< .001	↑	-.003	.001	< .001	↑
	Consequences	.005	.001	< .001	↑	-	-	-	-	.002	.001	.010	All
	Personal Control	-	-	-	-	-.002	.001	< .001	↓	-.001	.001	.049	↑
	Cyclical	-	-	-	-	.003	.001	< .001	↑	.002	.001	< .001	All
CDQ Diagnosis and Treatment													
x=IPQR	Emotion	-	-	-	-	.003	.000	< .001	↑	-	-	-	-
	Coherence	-	-	-	-	-.004	.001	< .001	↑	-.003	.001	< .001	↑
	Consequences	.005	.001	< .001	↑	.004	.001	< .001	↑	.002	.001	.007	All
	Personal Control	-	-	-	-	-.002	.001	< .001	↓	-	-	-	-
	Cyclical	-	-	-	-	.003	.001	< .001	↑	.002	.001	< .001	All

‘‘ – ‘‘ No significant route

DISCUSSION

To the author's knowledge this is the first study that has examined moderated mediation effects of dietary self-efficacy and coping style on illness perceptions and the outcomes of psychological wellbeing and quality of life. It is certainly the first study to use the LAVAAN package and FIML missing data handling to analyse Hayes (2013) model 7 with multiple mediators.

The results of this study concur with those of Gonzalez et al. (2015); participants with more perceived control report better psychological wellbeing and better quality of life. Personal control is negatively correlated with dysfunctional coping. Individuals who feel more in control manage their illness better and use fewer dysfunctional coping strategies (Ford et al., 2012).

This study challenges the findings of others who have reported reduced psychological wellbeing over time (Brands et al., 2004) and that adults with CD experience anxiety (Baiardini et al., 2012), but supports those who have found depression reduces as time post-diagnosis increases (Van Hees et al., 2013). This sample experienced levels of psychological distress similar to that of the general population. No significant impact of duration of diagnosis was found for male participants and female participants showed an increase in wellbeing with years since diagnosis. Bearing in mind that this is a highly self-efficacious sample, this increase in wellbeing may be evidence of the feedback loop Karademas et al. (2011) described.

As has been suggested previously (Barratt et al., 2011) poorer psychological wellbeing was correlated with dysfunctional coping as well as less perceived personal control and a more negative emotional impact of CD.

The results were more congruous with American and Canadian studies identified by Hauser et al. (2007) as quality of life was high. This may be due to the sampling method used: People who are involved with Coeliac UK and who have the time and inclination to take part in a survey such as this may be less likely to be those who feel overwhelmed by their condition.

Previous studies have reported individuals with well-managed CD are less likely to use emotional regulation or distraction as coping strategies (Wagner et al., 2016) and those who are self-compassionate have better quality of life (Dowd & Jung, 2017). These finding are suggested here; self-compassion most closely resembles the activities identified in the emotional coping subscale of the Brief COPE (Neff, 2003 & 2009) and this subscale has the smallest correlation with dysfunctional coping suggesting that to a small degree people who use dysfunctional coping strategies are less likely to use emotion focussed ones.

There are negative correlations between all coping strategies and all quality of life subscales. The same is true for self-efficacy and coping strategies. For both quality of life and self-efficacy this effect is largest for dysfunctional coping strategies. An explanation for this may be that as self-efficacy and quality of life increase coping strategies are no longer seen as 'strategies' and so are not reported in the same way.

High self-efficacy alone is not enough to account for positive health outcomes (Schwarzer & Renner, 2000); the complex results of the moderated mediation of self-efficacy found in this study would certainly support this. McDonald (2002) warns against assigning causality to the results of SEM. This study, however, formulates the effects of self-efficacy prior to coping strategies and the number of significant routes identified shows that, for these variables at least, the direction is correct.

For psychological wellbeing, the indirect relationship between all illness perceptions and psychological wellbeing is moderated by level of self-efficacy via emotion focussed coping

and dysfunctional coping, but not problem focussed coping. This may appear surprising as Jex et al. (2001) found that active coping (contained within the problem focussed subscale) and self-efficacy mediated stressor-strain relations. However, Knowles et al. (2014) report comparable results; emotion and dysfunctional coping mediated anxiety and depression in adults with stoma. They also found self-efficacy reduces depression, but not anxiety. The cause of difficulty may also be relevant here. Byrd O'Brien & De Longis (1996) looked at interpersonal and agentic stressors on a small sample of adolescents with anxiety and found that different types of coping were used depending on where the stressor originated; for agentic (situational) stressors, problem-focussed strategies were more likely to be used. If participants did not consider their CD or the management of it to be situational, but rather felt that the issues were interpersonal – which is suggested by the higher mean score on the social impact on quality of life – it follows that problem focussed coping would not be mediated or moderated in this study.

There is no moderated mediation effect of personal control and psychological wellbeing through any coping style and emotion and psychological wellbeing is only moderated via emotion focussed coping. Perceived personal control and emotional impact were not originally included in the IPQR and were added to the measure later (Moss-Morris et al., 2002); if the theory behind the constructs differs slightly from the original scale, this may be why they produce different results.

For quality of life, moderated mediation occurs via dysfunctional coping across all IPQR variables at $p < .001$ other than personal control x dysfunctional coping for any CDQ outcome or for IPQR emotion x dysfunctional coping for CDQ emotion or diagnosis and treatment outcomes. Level of self-efficacy appears to have a particular role within dysfunctional coping. Thomasson & Psouni (2010) report that low self-efficacy is linked with the use of dysfunctional coping strategies and in turn this type of coping leads to increased negative

emotional responses and reduced quality of life. Norcini Pala & Steca (2015) also found dysfunctional coping played a significant role in the relationship between illness perception and disease outcomes in HIV positive adults.

Personal control is mediated by problem focussed coping and moderated by self-efficacy across all outcomes of the CDQ. This relationship generally increases in significance as self-efficacy reduces, which means the lower an individual's self-efficacy is, the more likely they are to use problem-focussed coping strategies to help manage their CD and improve their quality of life. Diehl & Hay (2010) demonstrate that levels of perceived personal control fluctuate depending on daily stresses. In the current study stresses may relate directly to CD and its management as this was the focus of measures and questioning. This corresponds with Bandura (1994) and Karademis et al's (2001) idea that examples of positive coping lead to higher confidence and higher self-efficacy to continue to deal with the problem in the future.

Emotion focussed coping moderates all subscales of the IPQR via the CDQ emotion pathway. For the illness perceptions of coherence and personal control the relationship gets more significant as self-efficacy decreases. For consequences and cyclical subscales, the opposite is true. In this sample, believing there are serious negative consequences of CD and that CD is cyclical and unpredictable in nature leads to use of more emotion focussed coping strategies the more self-efficacious participants are.

Similarly, problem focussed coping mediates all routes from the IPQR variables for CDQ social (apart from the IPQR consequences subscale) and CDQ diagnosis and treatment. The indirect relationship from personal control becomes more significant as self-efficacy decreases for all other significant variables the opposite is true and routes increase in significance as self-efficacy improves.

The final significant moderated mediation effects are from the IPQR consequences subscale via emotion focussed coping for CDQ social and CDQ diagnosis and treatment. Both increase in significance as self-efficacy increases. This suggests that having higher self-efficacy for a GFD will make it more likely an individual will use emotional coping strategies if they feel their quality of life is affected by the social and diagnosis and treatment process of CD.

Limitations, Strengths and Future Research

There were a number of limitations to this study. The time frame for the different measures used varies from the last 2 weeks to no end date. This makes it difficult to directly compare the results across variables. This was handled during the analysis by looking at correlations between duration of diagnosis and various variables, but this is perhaps not the most reliable method. Future research may be able to more fully address this issue.

Although widely used in research, Moss-Morris et al. (2002) do not recommend condensing the 14 subscales of the Brief COPE, in doing so the nuances of relationships between the different aspects of the problem focused coping subscale may be lost. Unfortunately, to do this would have been beyond the capabilities of this study.

McDonald (2002) warns about the issues of establishing causality from the results of SEMs and with the design of this study being new in its field such warnings should be given greater consideration to avoid accepting spurious results. However, at each stage of the design and analysis of this study, up to date literature as to the most robust and reliable methods were consulted and considered to avoid error as far as possible.

As a sample, participants were highly self-efficacious when it came to their GFD. It might have been useful to include a more general measure of self-efficacy alongside the ASES used. However, as this study was looking directly as CD-related self-efficacy, illness

perceptions and outcomes, this measure was appropriate. Another test of dietary self-management such as that developed by Leffler et al. (2009) could have been useful to provide a less subjective measure. Although the 6-item questionnaire used here had excellent internal validity (.96) it was not able to assess detail.

Recruitment of the sample through the Coeliac UK website may have caused some sampling bias. The individuals that use the website may be more self-efficacious and motivated than the general CD population as they are actively seeking help and support for their condition. The breakdown of educational level also suggests this sample may not be typical of the general population it represents as 50% of participants were educated to at least university level.

The data used in this research was gathered in 2009-2010; therefore, it is possible that the increased recognition of CD by the public and catering establishments (Aziz et al., 2014), and greater availability of gluten-free foods in supermarkets may influence findings if this study were to be repeated today. However, despite the increased availability of gluten free foods for consumption at home and when out (Burden et al., 2015), these options remain expensive. The participants in this sample were already very good at following a GFD and were highly self-efficacious, so this change may have had less of an impact on this sample than others who were finding dietary management more difficult or who were from lower socio-economic backgrounds.

As a comment on the process of producing this research, using data collected and coded by a previous research team made initial data cleaning difficult and time consuming. It was necessary to deal with possible coding mistakes or unknown coding strategies as missing data, which increased the importance of strong and reliable methods to deal with missing data throughout analysis.

The study here included a large number of variables and as a result the results are complex. In future particular aspects of the findings could be explored in more detail to add further detail to the field of psychological and quality of life outcomes for adults with CD. Of particular interest may be the lack of any indirect effect of problem-focussed coping for any illness perception for the outcome of psychological wellbeing. This is an interesting result as it might have been expected that coping strategies such as being active and planning played a large part in effectively managing a chronic condition such as CD. Further investigation would show whether this finding is specific to this sample or more general.

Research using a longitudinal design would be informative as changes over time could be examined directly. The participants included here were asked to consent to future research as part of the survey and repeating this study design with current data would be a fascinating project.

Model Testing

The final limitation is also a strength; this was a model-driven study including a new procedure for handling missing data using FIML analysis with multiple mediators in a moderated mediation model based on Hayes (2013) model 7. This makes it harder to compare to the existing literature, but outlines an exciting new possibility for researchers wishing to look at more complex moderated mediation effects with a robust treatment of missing data. In addition to the hypotheses outlined above this study was also testing the model. The presence of multiple, significant, moderated mediation pathways suggests that this was a valid model to apply to this type of investigation, as does the amount of variance explained by the model for each moderated mediation.

More use of this FIML moderated mediation model with multiple mediators will provide further information as to the strengths and weaknesses of this approach and allow development of statistical requirements such as minimum sample size to be established. The model elegantly negates the confusion associated with bootstrapping multiple imputation data.

Clinical Implications

Clinical Services

The findings of this study suggest that improving self-efficacy for the GFD rather than focussing on nutritional or medical outcomes for self-management could be beneficial. The way this is done is also important; Gist et al. (2001) found that modelling new skills improved self-efficacy in participants who rated themselves as low in self-efficacy for a task. Modelling GFD choices may be more effective than giving people lists of gluten free food (Barlow et al., 2002).

Assessing for and, where necessary, teaching more adaptive coping strategies is likely to improve outcomes in adults with CD in the same way as Wager et al. (2016) suggested it would be beneficial for adolescents with CD. Elfstrom et al. (2005) similarly concluded that rehabilitation needed to include teaching acceptance and facilitative coping strategies as well as the usual physical and practical dimensions.

Developing treatment/support pathways across the lifespan would ensure individuals have access to the right support when it is needed. One in four adults with CD reported being dissatisfied with the information given to them by their consultant regarding a GFD (Ukkola et al., 2012) despite it being shown that understanding CD and a GFD improves adherence (Ludvigsson et al., 2015). The clinical pathway could include initial assessment of all newly

diagnosed patients with CD and provide access to additional interventions as and when needed.

Making use of the feedback loop of self-efficacy; support for newly diagnosed individuals could include identifying when they have exhibited good dietary self-efficacy. However, as self-efficacy reduces the use of dysfunctional coping strategies most, support in developing adaptive opposed to dysfunctional coping strategies also needs to occur.

Psychological practitioners would ideally be involved in the care of individuals diagnosed with CD, particularly if assessment concluded that they have poor self-efficacy for the GFD, or are likely to use dysfunctional coping strategies. Policy makers would need to be aware of this in the design of new CD services.

Service Users

Unfortunately, these provisions do not currently exist for service users to make use of. Individuals with CD would have to seek out this support. Support groups may be the most realistic way to access modelling of a GFD, an opportunity to learn adaptive coping strategies and to build self-efficacy.

While social support is certainly important for people with CD (Olsson et al., 2008), more structured groups may be more helpful for service users who need support with the GFD, developing coping strategies and improving self-efficacy.

Policy makers

Helping adults with CD develop skills around adaptive coping strategies and self-efficacy for a GFD may improve outcomes and may reduce the financial and time burdens on health

services. Better adherence to a GFD can reduce the need to treat conditions related to malabsorption. Other conditions such as low mood and anxiety may also reduce as people feel more confident in their ability to manage their condition, leading to less anxiety about accidental gluten ingestion and lower rates of depression as individuals will be more confident in their own self-efficacy, which as a result will improve further. Anxiety may further reduce if individuals know additional support is available should they need it. Conditions related to dysfunctional coping such as problematic alcohol use or substance misuse may also reduce as a result of modelling more adaptive coping strategies to individuals who are at risk of using dysfunctional ones.

Although CD is primarily thought of as a medical condition, a more holistic approach is likely to have medical benefits as well as others such as improved quality of life and psychological wellbeing. An approach similar to the DESMOND (Diabetes Education and Self-Management for Ongoing and Newly Diagnosed) program for type 2 diabetes, would be a structured program that included educational and self-management aspects delivered by trained professionals and more flexible support and education groups (Skinner et al., 2006). Individuals that go through the program can also become trainers for newly diagnosed individuals and ‘experts by experience’. This holistic approach will enable more people to live happy, healthy and well with CD.

CONCLUSION

A number of complex indirect moderated mediated relationships were identified in relation to illness perceptions, the outcomes of psychological wellbeing and quality of life and the roles of self-efficacy and coping style. Higher self-efficacy for the GFD leads to a reduction in the use of coping strategies, with the largest effect on dysfunctional coping strategies.

Assessing self-efficacy following diagnosis of coeliac disease could be helpful in identifying individuals who may struggle to manage their condition and who therefore might not achieve good outcomes. The use of targeted support to follow a GFD with an emphasis on encouraging a sense of personal control is most likely to improve self-efficacy.

Alongside this, supporting development of more adaptive coping strategies will further improve outcomes. The nature of this support is important, with modelling being the most effective way to enable individuals to learn and make use of new skills.

Psychological wellbeing and quality of life have been consistently found to be more influential on individuals' levels of disease-related distress than the number or severity of symptoms experienced. For the best outcomes, these factors need to be considered and treated as part of diagnosis and/or aftercare.

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Additional information taken from:

Coeliac UK (2017) https://www.coeliac.org.uk/home/

PUBLIC DISSEMINATION DOCUMENT

This document summarises the systematic review and empirical study included in the thesis submitted by Josephine Talbot to the University of Birmingham for the degree of Doctorate of Clinical Psychology.

Systematic review:

What is the Evidence for Neurological and Cognitive Symptoms Associated with Coeliac Disease and Non-Coeliac Gluten Sensitivity in Adults?

Introduction

Coeliac disease (CD) is an autoimmune condition that effects around 1% of the UK population. It is triggered when gluten (which is a protein found in wheat) is eaten by someone who is genetically vulnerable to the condition. In the past it was thought to include only gastro-intestinal symptoms such as stomach pain, bloating and diarrhoea. More recently however, other symptoms have been linked with CD that do not involve gastro-intestinal symptoms at all. People with CD have reported fatigue, forgetfulness and feeling confused. So far there has been little research done to identify exactly what these symptoms are and how common they might be.

Non-coeliac gluten sensitivity (NCGS) is a condition that has very similar symptoms to CD, however, whereas in CD there will be damage to the intestines that can be seen by biopsy, with NCGS the intestines remain healthy. The only treatment for both conditions is a life-long gluten free diet (GFD). NCGS has suffered from being under-investigated and very little is known about the non-gastro-intestinal symptoms of this condition.

The aim of this review was to gather information from multiple sources to identify what is known about the non-gastro-intestinal symptoms of CD and NCGS. Within this the review separated symptoms into those that involved the nervous system (or neurological) and those that involved different type of thinking (or cognitive).

Method

Six online databases were searched and 114 articles were found, a set of inclusion criteria were applied to each of these articles, and those that met the criteria were included in the review. The final number was 21. Each article was then assessed to make a judgement on its quality. It is important to identify any issues with the quality of a study because poorly designed research may lead to incorrect results.

Results

More was written about the symptoms of CD than NCGS, however there was little difference between the 2 conditions in terms of the symptoms reported. There was also a difference between the amount and the quality of research done on the neurological symptoms and the amount and quality of research done on the cognitive symptoms. The neurological symptoms of slowed nerve conduction, pain and unusual sensations in hands and feet (e.g. pins and needles) were reported in a lot of studies and the studies were of high quality. For the cognitive symptoms there was far less agreement, with some studies even disagreeing about whether there are any cognitive symptoms at all. The review did find evidence for short-term memory problems and fatigue, but these conclusions cannot be made with much confidence as a result of the disagreement between studies.

Discussion

Further research is needed to really clarify what, if any, cognitive symptoms are found in adults with CD and NCGS. There was agreement that both types of symptom improve or stop entirely when an individual follows a GFD. There was evidence that, for neurological symptoms, the level of improvement is linked to the severity of symptoms and the most unwell individuals are less likely to make a full recovery even on a GFD. This shows the importance of early diagnosis and treatment.

EMPIRICAL PAPER:

Adult Coeliac Disease (CD): Illness Perceptions, Psychological Wellbeing, Quality of Life and the Moderating and Mediating Roles of Coping and Self-Efficacy

Introduction

There are lots of factors that affect how well someone manages a long-term illness such as CD. Previous research has shown that one of the most important is the way an individual understands their condition, for example whether they feel they have any control over the outcome, whether they think the treatment will work and whether they feel it is a serious long-term condition. One way to measure how well someone is coping is to look at the medical progress they are making, however in psychological research it is more useful to look at how well people are doing in terms of their mental health or psychological wellbeing. Another area of interest is quality of life, this looks at different areas and assesses overall how well someone is living, there are specific measures that look at quality of life in relation to an illness, so any negative impact of this can be measured.

The way people cope with CD can have a significant impact on their psychological wellbeing and quality of life. An example might be that someone who denies there is a problem with their health or who uses alcohol so that they don't have to think about their illness is less likely to follow the proper diet, they are more likely to experience symptoms that affect their quality of life and this can also have a negative effect on their psychological wellbeing.

The final factor this research looked at was self-efficacy, this is the belief that you have the ability to achieve a goal that you set yourself. In this research self-efficacy for a GFD was measured. People who have high self-efficacy are confident that they can reach a particular goal. People with low self-efficacy are less likely to try and reach their goal.

All these factors are linked in the management of long-term conditions and the aim of this research was to take all of these factors into account and to explore whether level of self-efficacy and coping style could predict the psychological wellbeing and quality of life in adults with CD.

Method

Information was gathered through an online questionnaire that was advertised on the Coeliac UK website (the leading charity for people with CD in the UK). This information was then analysed using a program written specifically for this study. It was able to take all the above factors into account in order to show whether the predicted relationships did in fact exist.

Results

The results of examining these relationships were complex, however, the research identified a number of important relationships. Overall, a person with higher self-efficacy is more likely to use fewer negative coping strategies, such as using alcohol or denying they have CD.

However, they will also reduce the number of positive coping strategies they use, like planning for problems and getting emotional support from other people when needed, but don't reduce the use of these strategies as much as the negative ones. The results showed that using positive or negative coping strategies predicts someone's psychological wellbeing, whereas only the use of negative coping strategies was able to predict quality of life.

Discussion

There is much that can be done to help adults with CD improve their wellbeing and quality of life, and this does not need to focus solely on better knowledge of the GFD. Teaching positive coping strategies is important so that people have lots of positive coping options to use even if they start to use fewer of them as their self-efficacy increases. Finally, supporting someone to build on their sense of self-efficacy is likely to be helpful because their confidence in following the diet should grow, their ability to follow the diet should grow and their symptoms should reduce improving their psychological wellbeing and quality of life.

VOLUME I: APPENDICES

APPENDICES FOR SYSTEMATIC REVIEW

Appendix A - Reason articles rejected

Participants are children = 57

Mental health outcomes not neurological or cognitive = 20

Participants are older adults = 8

Participants do not have CD or NCGS = 1

Not reporting original data = 2

Appendix B - Full text articles not available

- Tirotta, Eusebi & Durante (2012) Celiac disease with epilepsy and minor neurological disorders. *Recenti progressi in medicina, 103* (5), 198-204

Requested via interlibrary loans: English translation not available

- Peters, Yelland, Moore, Ward, Majumdar, Muir & Gibson (2016) No effect of gluten on anxiety or depression in patients with NCGS, but could it be brain fog? *Journal of Gastroenterology and Hepatology, 150* (4)

Requested via interlibrary loans: Abstract only available – full article not published

- Longarini, Richly, De la Paz Temprano, Costa, Vazquez, Moreno, Niveloni, Lopez, Jer, Smecuol, Sugai, Mazure, Gonzelez, Maurino & Bai (2016) Cognitive performance in patients with celiac disease prevalence of cognitive impairment at diagnosis and effect of treatment assessed in a prospective controlled study. *Gastroenterology, 150* (4)

Requested via interlibrary loans: Summary only available

- Duggan (1997) Recent developments in our understanding of adult coeliac disease.

  The Medical Journal of Australia, 166 (6), 312-315

Author contacted via email – no response

- Iani, Giorgetti, Loberti, Palmieri, Caramia, Scalise, Ferrante, Giovannini & Bernardi (1998) Subacute combined degeneration in a patient with partial epilepsy symptomatic of coeliac disease: Neurophysiologic evaluation. *Bollettino - Lega Italiana contro l'Epilessia, 102* (103), 219-221

Requested via interlibrary loans: English translation not available

APPENDICES FOR EMPIRICAL PAPER

Appendix A – Questionnaire Pack

Psycho-Social Factors in Coeliac Disease

Adults with Coeliac Disease Questionnaire Pack

Research Team:

- Dr Ruth Howard - Clinical Psychologist
- Dr Gary Law - Clinical Psychologist
- Dr Jan Oyebode - Clinical Psychologist
- Dr Jane Petty - Research Fellow

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The Illness Perception Questionnaire (IPQR)

Your views about your Coeliac Disease (CD)

Listed below are a number of symptoms that you may or may not have experienced since being diagnosed with CD. Please indicate by circling *Yes* or *No,* whether you have experienced any of these symptoms and if you have, whether you believe that these symptoms are related to your CD.

	I have experienced this symptom since my CD			This symptom is caused by my CD	
Abdominal pain	Yes	No		Yes	No
Sore throat	Yes	No		Yes	No
Nausea	Yes	No		Yes	No
Weight loss	Yes	No		Yes	No
Fatigue	Yes	No		Yes	No
Stiff joints	Yes	No		Yes	No
Sore eyes	Yes	No		Yes	No
Headaches	Yes	No		Yes	No
Upset stomach/ diarrhoea	Yes	No		Yes	No
Sleep difficulties	Yes	No		Yes	No
Dizziness	Yes	No		Yes	No
Loss of strength	Yes	No		Yes	No
Bloating	Yes	No		Yes	No
Excessive wind	Yes	No		Yes	No
Breathlessness	Yes	No		Yes	No
Constipation	Yes	No		Yes	No
Heartburn/ indigestion	Yes	No		Yes	No
Mouth ulcers	Yes	No		Yes	No
Wheeziness	Yes	No		Yes	No
Hair loss	Yes	No		Yes	No

We are interested in your own personal views of how you now see your Coeliac Disease (CD). Please indicate how much you agree or disagree with the following statements about your CD by ticking the correct box.

(Disagree a lot: Disagree: Neither agree nor disagree: Agree: Agree a lot)

My CD will last a short time.

My CD is likely to be permanent rather than temporary.

My CD will last for a long time.

My CD will pass quickly.

I expect to have CD for the rest of my life.

My CD is a serious condition.

My CD has major consequences on my life.

My CD does not have much effect on my life.

My CD strongly affects the way others see me.

My CD has serious financial consequences.

My CD causes difficulties for those who are close to me.

There is a lot which I can do to control my symptoms.

What I do can determine whether my CD gets better or worse.

The course of my CD depends on me.

Nothing I do will affect my CD.

I have the power to influence my CD.

My actions will have no effect on the outcome of my CD.

My CD will improve in time.

There is very little that can be done to improve my CD.

My gluten-free diet will be effective in curing my CD.

The negative effects of my CD can be prevented (avoided) by my diet.

My gluten-free diet can control my CD.

There is nothing that can help my CD.

The symptoms of CD are puzzling to me.

My CD is a mystery to me.

I don’t understand my CD.

My CD doesn’t make any sense to me.

I have a clear picture or understanding of my CD.

The symptoms of my CD change a great deal from day to day.

My symptoms come and go in cycles.

My CD is very unpredictable.

I go through cycles in which my CD gets better and worse.

I get depressed when I think about my CD.

When I think about my CD I get upset.

My CD makes me feel angry.

My CD does not worry me.

Having CD makes me feel anxious.

My CD makes me feel afraid.

Following your Gluten Free Diet for Coeliac Disease

Sometimes it's hard to follow a gluten-free diet in certain situations. Some of these situations are listed in this questionnaire. We would like to know how confident you are that you would be able to regularly follow your gluten-free diet in these situations.

Using the scale below, please indicate how confident you are in your ability to follow your gluten-free diet on a regular basis by writing a number between 0 and 10 next to each situation. If the statement does not apply to you please write 'N/A'.

For example: 'Going to the cinema with friends'

When I go to the cinema with my friends they buy lots of foods that are not gluten free, like hotdogs and pick 'n' mix sweets. I feel like buying the same foods.

In that situation I am not very confident that I would resist buying those foods so my confidence score = 2.

If I always stick to my gluten-free diet when I go to the cinema with my friends, my confidence score = 10.

Confidence Scale

0	1	2	3	4	5	6	7	8	9	10
Not at all confident										Totally confident

Choose a number between 0 and 10 to show how confident you are that you could stick to your gluten-free diet...

When I'm watching television at home

When I'm feeling tired or bored

When I'm alone at home

When I'm feeling anxious, stressed or worried

When I see friends eating non- gluten-free foods

When I am upset

When eating out at my favourite restaurant

When I'm on holiday and staying in a hotel

When I'm feeling annoyed or angry

When it is difficult to get hold of the foods I should eat for my gluten-free diet because the chemist cannot fill my prescription

When I'm out and about and get very hungry

When I'm feeling sad

When I'm celebrating with others (e.g. at a birthday party)

When I'm preparing non- gluten-free food for other people

When eating out at a friend's house

When I'm offered non- gluten-free foods

When non- gluten-free foods are available at home

When it is difficult to get hold of the foods I should eat for my gluten-free diet because the supermarket does not have my usual items

When I'm eating out at an unknown restaurant

When I am ill

When I'm on holiday and catering for myself (e.g. self-catering)

At parties when non- gluten-free food is offered to me

When I am in a hurry

When I'm preparing my own meal

When I'm faced with appealing foods that are not gluten-free in a supermarket, vending machine, or café

When my life doesn't go to plan

When I'm feeling well (i.e. healthy, no symptoms)

When I'm on holiday and eating in restaurants

When I want more variety in my diet

When I'm craving foods containing gluten

When I'm on the way to or from work

When I'm staying in hospital

When I'm travelling (e.g. by aeroplane, train etc)

When I'm not sure if something is gluten-free or not

The Coeliac Disease Questionnaire (CDQ)

This questionnaire has been developed to find out how you have been feeling during the last two weeks. You will be asked about symptoms related to your Coeliac Disease, your general well-being and your mood. The questionnaire contains 28 questions. Each question offers seven possible answers ranked (1) to (7). Please read each question carefully and circle the answer that best describes how you felt during the past two weeks.

(Very much so: Quite a bit: Sometimes: A little: Not at all)

During the last two weeks...

How many times was your life affected by a sudden urge to visit a bathroom for a bowel movement?

How often did you feel physically exhausted or fatigued?

How often have you felt frustrated, impatient or restless?

How many times did you refuse or avoid an invitation for dinner with friends or relatives due to your Coeliac Disease?

How often have your bowel movements been loose?

How often were you concerned that your children could inherit or may have inherited your Coeliac Disease?

How often have you been troubled by cramps in your abdomen?

How much intellectual energy did you have?

Did you encounter any difficulties with recreational activities or sports due to your CD?

How often did you feel depressed or discouraged?

How often did you suffer from bloating or flatulence?

People with CD often have worries and fears related to their disease. How often did you worry about or were afraid of getting cancer as a result of your CD?

How often were you affected by a feeling of incomplete bowel evacuation?

How often have you felt relaxed and free of tension?

How often did you feel isolated of excluded by others due to your CD?

How often have you felt tearful or upset?

How often did you suffer from repeated belching?

To what extent did your CD restrict your sexual activity?

How satisfied, happy or pleased have you been with your personal life?

How often did you suffer from nausea or retching?

How often did you feel that important people such as members of your family or friends showed a lack of understanding for your CD?

How often did you feel that colleagues or superiors showed a lack of understanding for your CD?

How often did you feel limited in your professional training or career by your CD?

How often did you feel burdened by the expenses and time required obtaining gluten-free food?

How often did you feel burdened by problems with meeting the costs of gluten-free food or other coeliac therapies?

How often did you experience lack of expertise regarding CD from your doctors?

How often did you worry that your CD was diagnosed too late?

How often did you suffer from fear of medical examinations in relation to your CD, e.g. blood test or endoscopy?

The Brief COPE

These questions deal with ways you've been coping with your Coeliac Disease and gluten-free diet in the last month. There are many ways to try to deal with stressful situations. Obviously, different people deal with things in different ways, but I'm interested in how you've tried to deal with it. Each item says something about a particular way of coping. I want to know to what extent you've been doing what the item says. How much or how frequently. Don't answer on the basis of whether it seems to be working or not—just whether or not you've been doing it.

(I haven't done this at all: I've done this a little bit: I've done this a medium amount: I've done this a lot)

I've been turning to work or other activities to take my mind off things.

I've been concentrating my efforts on doing something about the situation I'm in.

I've been saying to myself "this isn't real.".

I've been using alcohol or other drugs to make myself feel better.

I've been getting emotional support from others.

I've been giving up trying to deal with it.

I've been taking action to try to make the situation better.

I've been refusing to believe that it has happened.

I've been saying things to let my unpleasant feelings escape.

I've been getting help and advice from other people.

I've been using alcohol or other drugs to help me get through it.

I've been trying to see it in a different light, to make it seem more positive.

I've been criticizing myself.

I've been trying to come up with a strategy about what to do.

I've been getting comfort and understanding from someone.

I've been giving up the attempt to cope.

I've been looking for something good in what is happening.

I've been making jokes about it.

I've been doing something to think about it less, such as going to movies, watching TV, reading, daydreaming, sleeping, or shopping.

I've been accepting the reality of the fact that it has happened.

I've been expressing my negative feelings.

I've been trying to find comfort in my religion or spiritual beliefs.

I've been trying to get advice or help from other people about what to do.

I've been learning to live with it.

I've been thinking hard about what steps to take.

I've been blaming myself for things that happened.

I've been trying to see it in a different light, to make it seem more positive.

I've been praying or meditating.

I've been making fun of the situation.

DASS 21

Please read each statement and circle a number 0, 1, 2 or 3 which indicates how much the statement applied to you over the past week. There are no right or wrong answers. Do not spend too much time on any statement.

The rating scale is as follows:

0 Did not apply to me at all

1 Applied to me to some degree, or some of the time

2 Applied to me to a considerable degree, or a good part of the time

3 Applied to me very much, or most of the time

I found it hard to wind down

I was aware of dryness in my mouth

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

I experienced breathing difficulty (eg, excessively rapid breathing, breathlessness in the absence of physical exertion)

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

I tended to over-react to situations

I experienced trembling (eg, in the hands)

I felt that I was using a lot of nervous energy

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

I felt that I had nothing to look forward to

I found myself getting agitated

I found it difficult to relax

I felt down-hearted and blue

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

I felt I was close to panic

I was unable to become enthusiastic about anything

I felt I wasn't worth much as a person

I felt that I was rather touchy

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

I felt scared without any good reason

I felt that life was meaningless

Diagnosis of Coeliac Disease

How were you diagnosed with Coeliac Disease?

Through an intestinal biopsy and blood test

Through an intestinal biopsy alone

Through a blood test alone

I diagnosed myself based on my symptoms and/or my reaction to dietary changes

Other (please specify)

Do you have any other long-term health conditions?

Do you have any other food intolerances? (please select all that apply)

Dairy (lactose)

Fructose

Alcohol

Yeast

Caffeine

No other intolerance

Other (please specify)

About Your Gluten-Free Diet

In the last two weeks...

How often have you knowingly eaten foods containing gluten while at home?

How often have you knowingly eaten foods containing gluten when away from home? (Never: Once or twice: A few times: Daily: All the time)

In general...

How well do you stick to your gluten-free diet when you are at home?

How well do you stick to your gluten-free diet when you are away from home? (Extremely well: Well: Quite well: Not very well: Not at all)

How concerned are you about accidental gluten-ingestion? (Extremely concerned: Very concerned: Quite concerned: A little concerned: Not concerned at all)

How harmful do you feel accidental gluten-exposure is to your health? (Extremely harmful: Very harmful: Quite harmful: A little harmful: Not at all harmful)

How often do you see a dietician about your Coeliac Disease?

Every 3 months or more frequently

Every 6 months

Every 12 months

Every 2 years

Every 3 years or less frequently

I've never seen a dietician about my Coeliac Disease

When did you last see a dietician about your Coeliac Disease?

When was your last antibody blood test?

What was the result of the test? (Normal: Can't remember: Abnormal: Haven't had a blood test)

Where you given a score (number) for the test? If so, can you remember what it was?

Food Quiz!

We'd like to know a little bit about your knowledge of gluten-free foods. Please read the items below and choose 'Yes' if you think the item is gluten-free and 'No' if you think it is not. If you're not sure, or you feel there is insufficient information to be sure, please score the item as 'Not sure'.

Modified starch
Potato starch
Monosodium glutamate
Seasoning
Flavouring
Xanthum gum
Modified wheat starch
Edible starch
Malt extract
Colouring
Hydrolysed vegetable protein (HVP)
Cereal binder
Textured Vegetable protein (TVP)
Added fibre
Gluten free wheat starch
Yeast extract
Powdered egg
Vanilla essence
Reduced gluten
Rusk

About You

You’re nearly there! The last few questions are about you.

Are you male or female?

What is your date of birth?

When were you diagnosed with Coeliac Disease?

Are you a member of Coeliac UK?

Yes No

If yes, how long have you been a member?

What is your marital status?
Single
Cohabiting
Married
Separated
Widowed
Divorced

What is your highest level of education?
School, no qualifications
School with qualifications
University qualifications
Postgraduate qualifications
Vocational training/qualifications

What is or was your highest level of occupation?
Professional
Managerial or technical
Non-manual skilled
Manual skilled

Partly skilled

Unskilled

Home maker

Which ethnic group do you belong to?

White British

White other

Asian

Black

Other (please specify)

Chinese

Mixed – White and Asian

Mixed – White and Black

Other mixed background

And Finally...

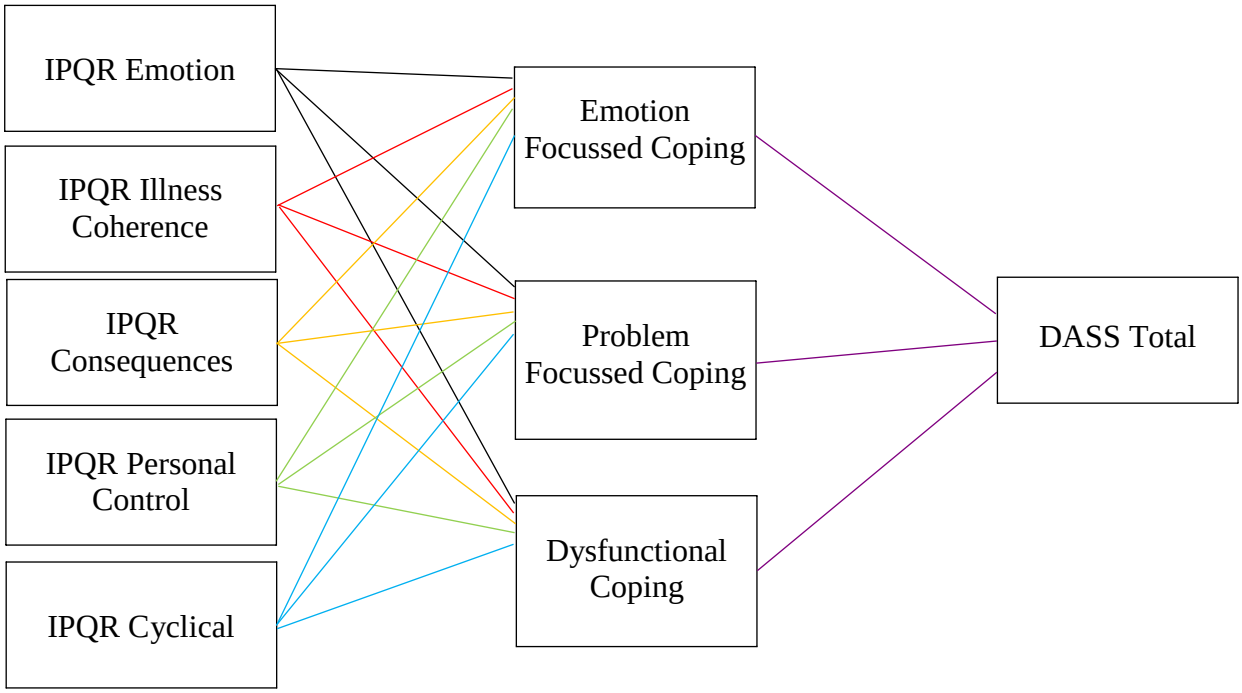
I give my permission for the research team to contact me about this and future research projects. I understand that this does not obligate me to take part in any further research.

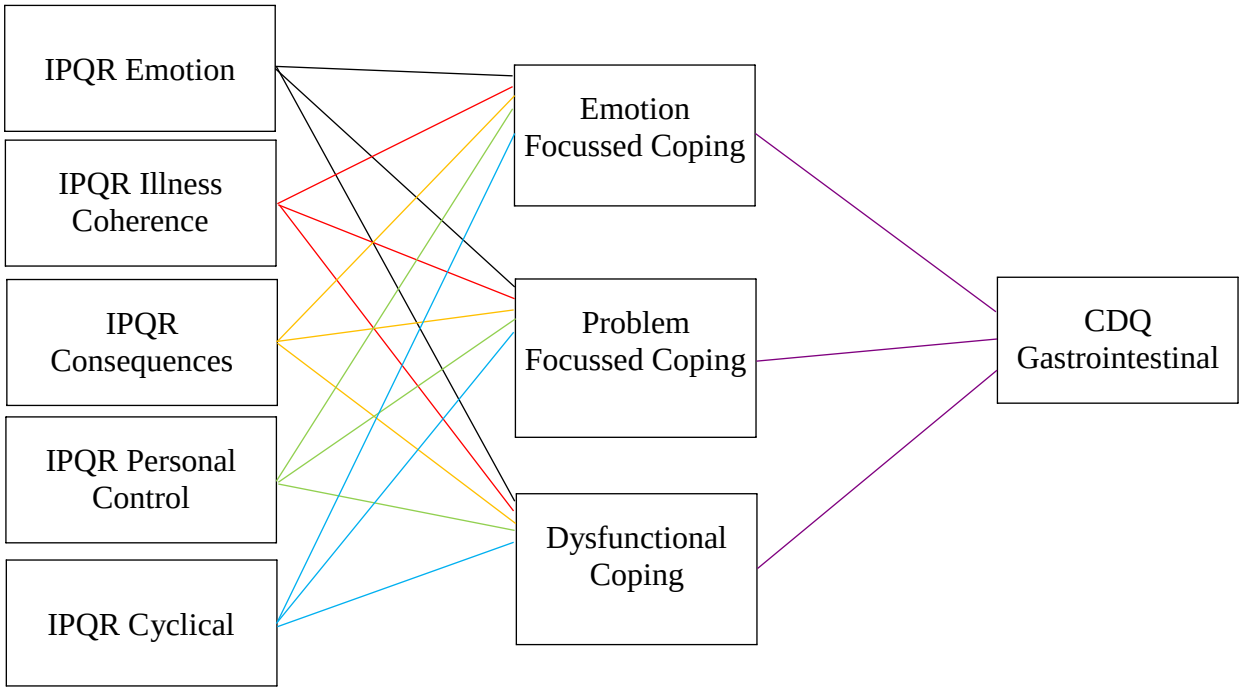
Yes No

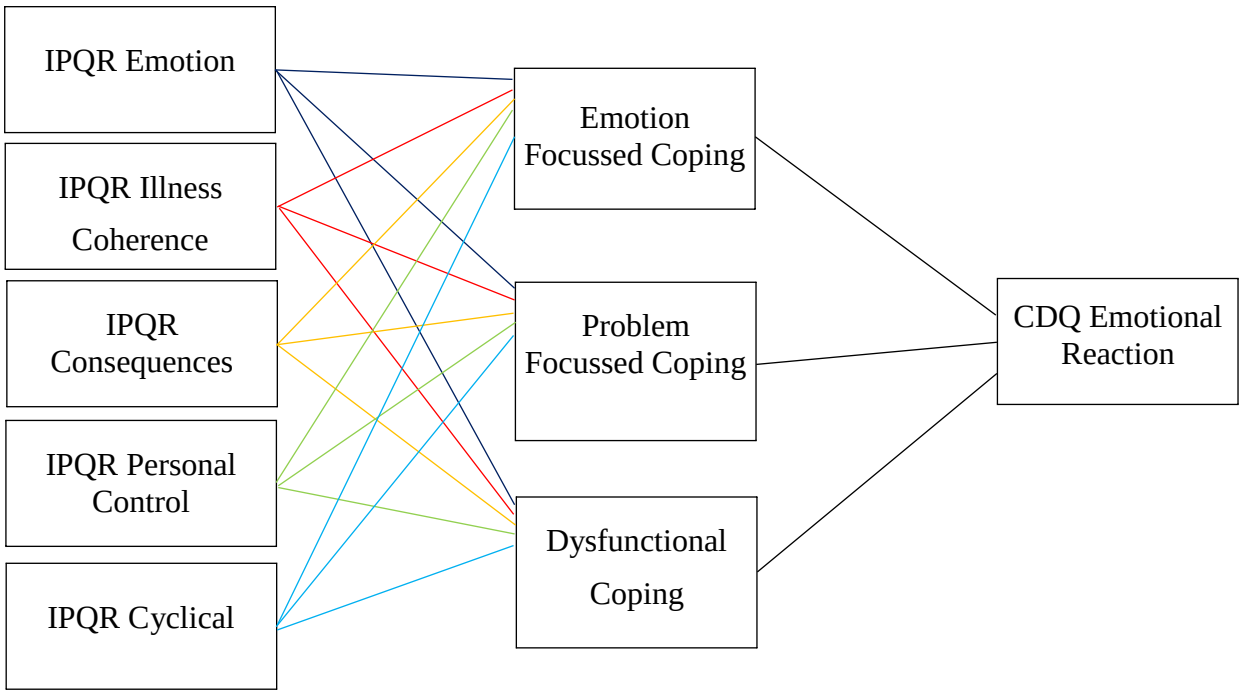
Thank You!

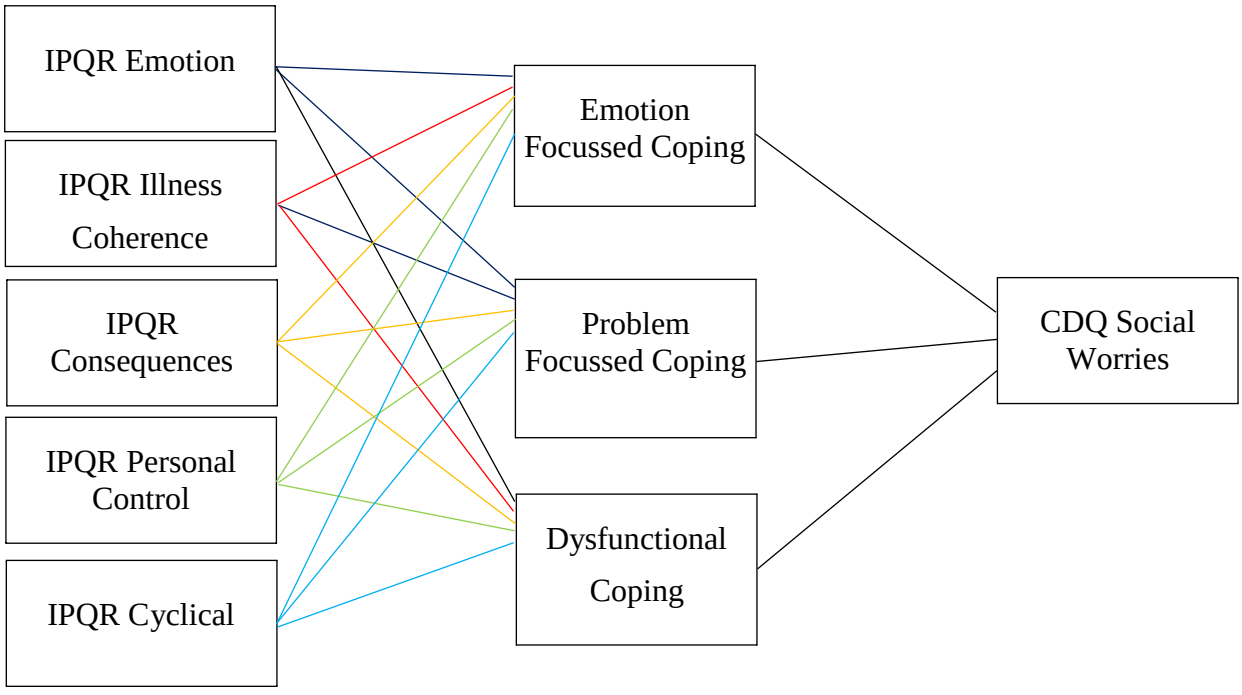
Appendix B – Ethics approval letter

Appendix C - Illustrations of significant x~m pathways for DASS and CDQ respectively






IPQR Emotion
IPQR Illness Coherence
IPQR Consequences
IPQR Personal Control
IPQR Cyclical
Emotion Focussed Coping
Problem Focussed Coping
Dysfunctional Coping
CDQ Emotional Reaction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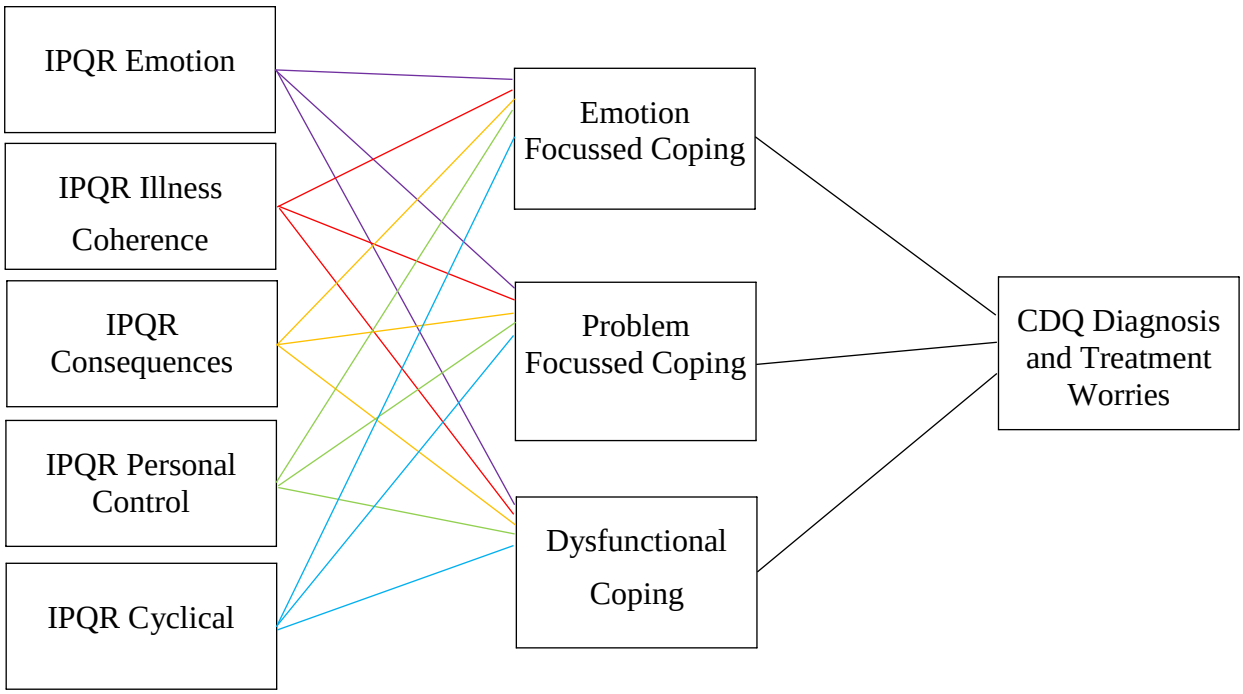
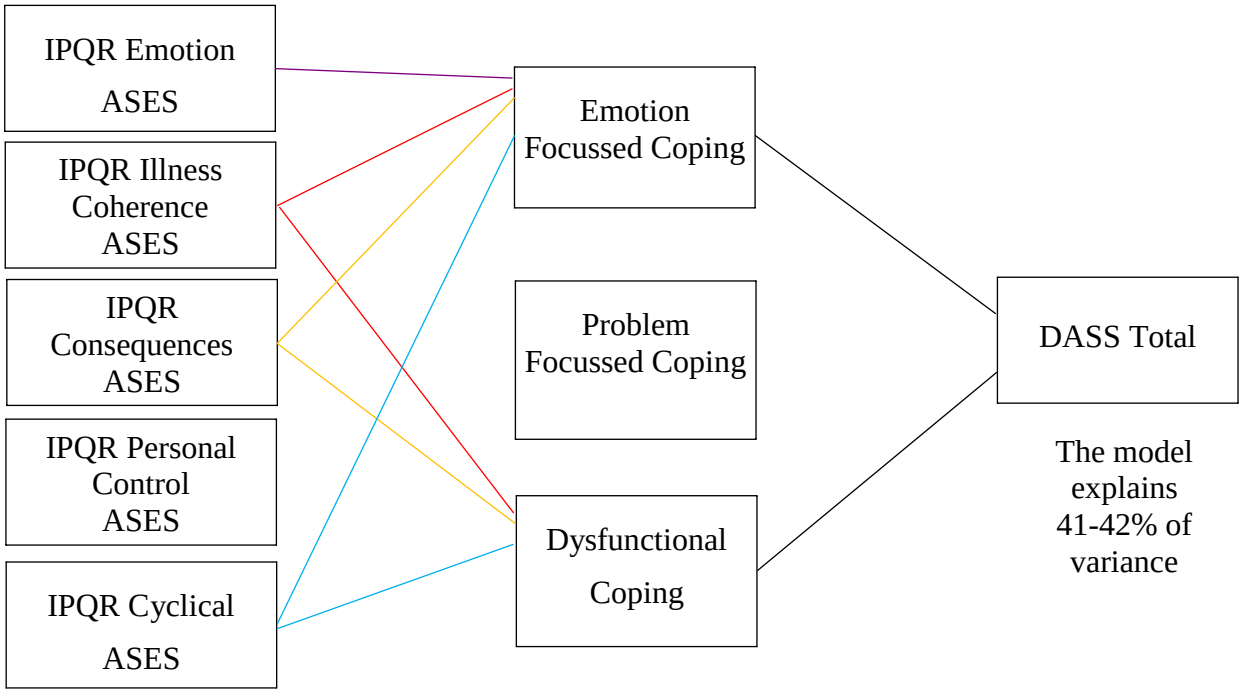
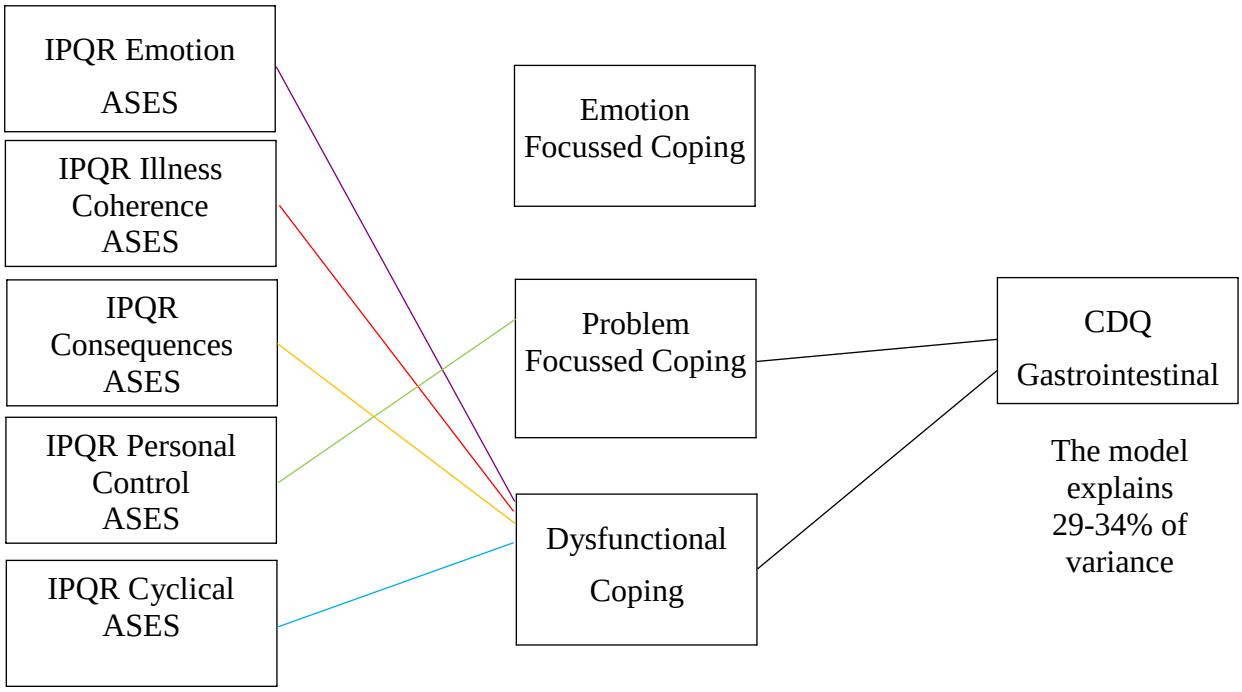
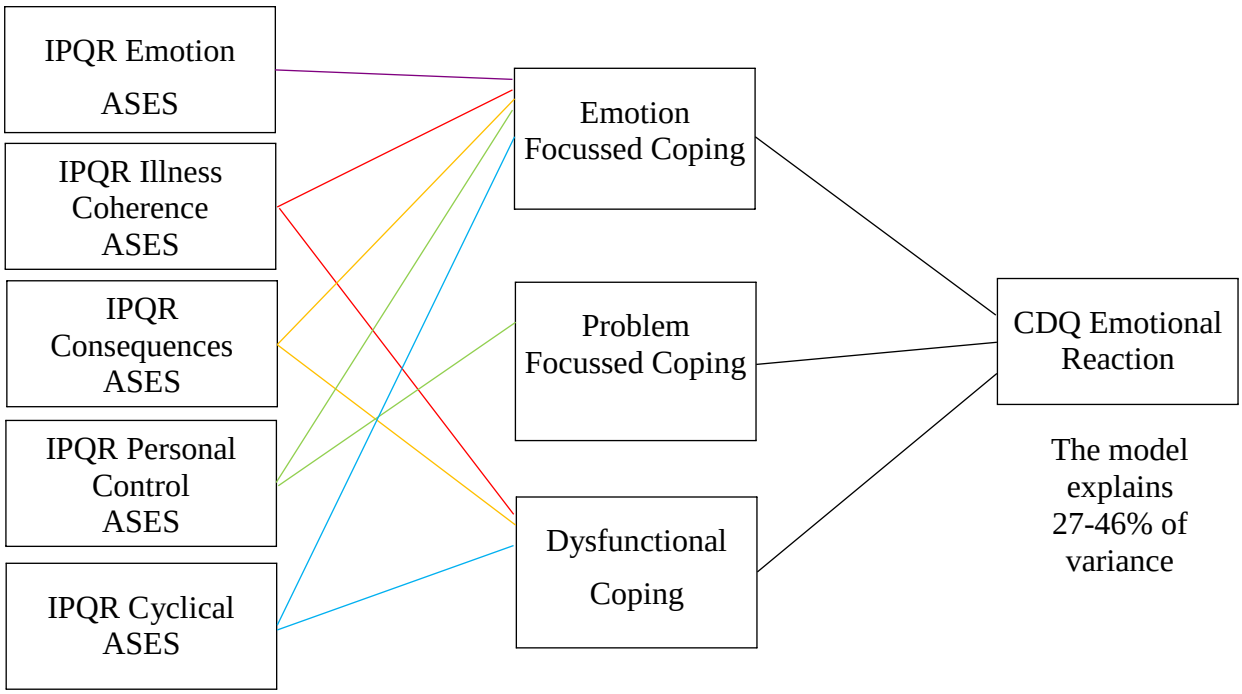
IPQR Illness Coherence
IPQR Consequences
IPQR Personal Control
IPQR Cyclical
Emotion Focussed Coping
Problem Focussed Coping
Dysfunctional Coping
CDQ Social Worries

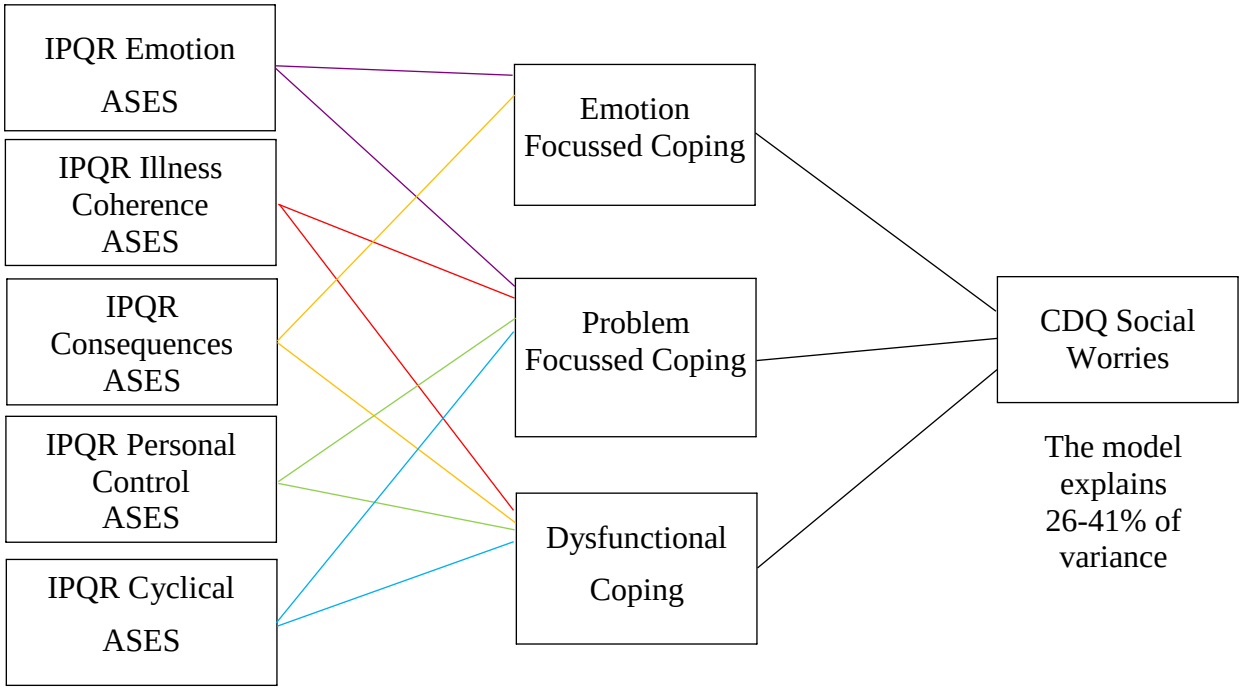

IPQR Emotion
IPQR Illness Coherence
IPQR Consequences
IPQR Personal Control
IPQR Cyclical
Emotion Focussed Coping
Problem Focussed Coping
Dysfunctional Coping
CDQ Diagnosis and Treatment Worries

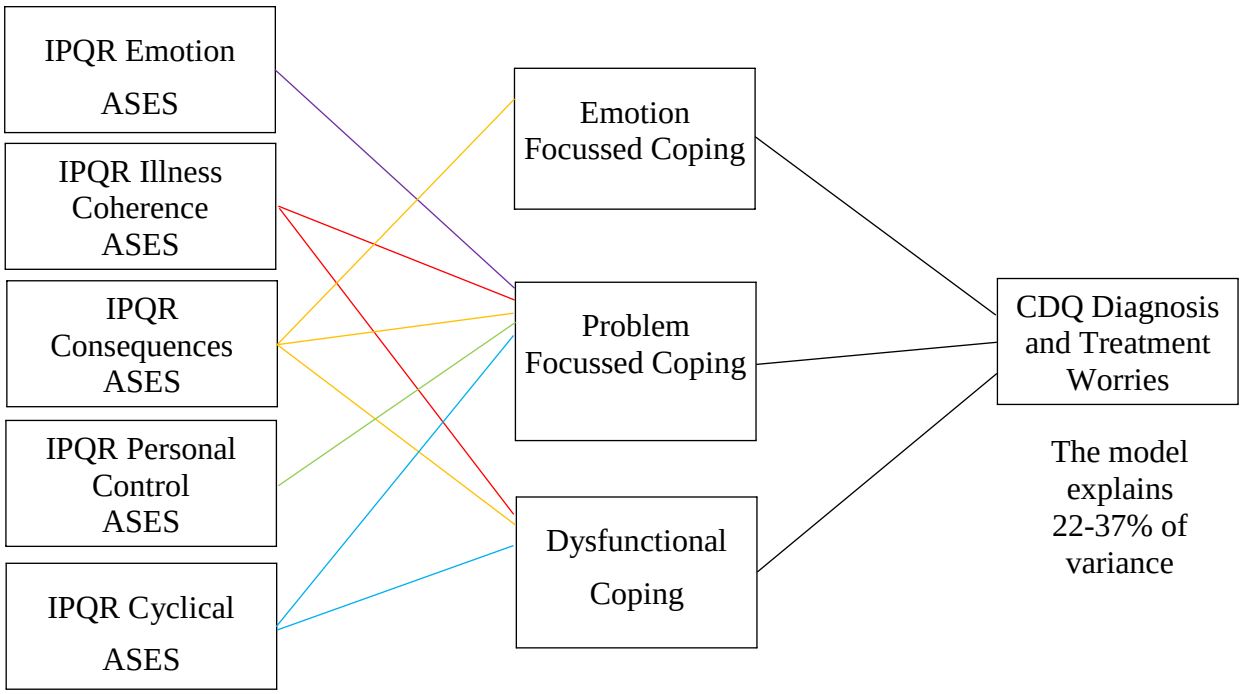
Appendix D - Illustrations of significant xw~m pathways for DASS and CDQ respectively including amount of variance explained by each model






IPQR Emotion ASES
IPQR Illness Coherence ASES
IPQR Consequences ASES
IPQR Personal Control ASES
IPQR Cyclical ASES
Emotion Focussed Coping
Problem Focussed Coping
Dysfunctional Coping
CDQ Emotional Reaction
The model explains 27-46% of variance


IPQR Emotion ASES
IPQR Illness Coherence ASES
IPQR Consequences ASES
IPQR Personal Control ASES
IPQR Cyclical ASES
Emotion Focussed Coping
Problem Focussed Coping
Dysfunctional Coping
CDQ Social Worries
The model explains 26-41% of variance


IPQR Emotion ASES
IPQR Illness Coherence ASES
IPQR Consequences ASES
IPQR Personal Control ASES
IPQR Cyclical ASES
Emotion Focussed Coping
Problem Focussed Coping
Dysfunctional Coping
CDQ Diagnosis and Treatment Worries
The model explains 22-37% of variance