UNDERSTANDING THE EXPERIENCE OF 'BRAIN FOG' IN COELIAC DISEASE: AN INTERPRETATIVE PHENOMENOLOGICAL ANALYSIS

by

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Thesis Overview

This thesis is submitted by Emily May Ahmed in partial fulfilment of the degree of Doctor of Clinical Psychology at the University of Birmingham. The thesis is comprised of three chapters. The first chapter is a meta-analysis which aims to provide a current prevalence estimate of depression in adults with coeliac disease, including evaluation of risk of bias factors. Additionally, it includes a brief secondary analysis, within the appendix, describing prevalence and relative risk estimates for other mental health disorders associated with coeliac disease. The second chapter is a qualitative empirical study which uses interpretative phenomenological analysis (IPA) methodology to explore the complex lived experiences of one of the lesser-known symptoms associated with coeliac disease – 'brain fog', in seven participants. Both the meta-analysis and empirical studies have clear clinical implications for the cognitive and psychological support that individuals with coeliac disease should be offered during and after diagnosis. Finally, the third chapter is comprised of two press release documents, which provides an accessible summary of the main findings of both the meta-analysis and the empirical research study.

Keywords: Coeliac disease, mental health, depression, brain fog, cognitive impairment

Dedications

The biggest thanks to my Mum and Dad for your unwavering love and support throughout not only this doctorate, but my entire journey. You have always encouraged me to go after what I want and supported me when this has taken me all across the country from Plymouth to Kent to Nottingham! Getting to this final point in my doctorate would not have been possible without all the opportunities that you have created for me, and I thank you for all your hard work and sacrifices along the way. I appreciate all your patience when times have been a little stressful and your continued interest in my work and all that I do. I am so lucky, you are the greatest - this for you.

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A. Chapter and Sections:

1. Meta-Analysis: The Prevalence of Depression in Adult Coeliac Disease

Abstract

Mental health disorders, such as depression, have previously been associated with coeliac disease (CD), although prevalence estimates are limited by restricted use of databases, inclusion criteria and number of studies as well as limited exploration of sources of heterogeneity. This meta-analysis aimed to use an inclusive approach to synthesise current prevalence estimates of depression in adults with CD, with a secondary aim of estimating the prevalence of other mental health disorders in individuals with CD. An online systematic search of the databases PsycINFO, Medline, Embase and Web of Science was conducted. Studies were screened against inclusion criteria and the final studies included 47 papers relevant to all mental health disorders in this review, and 36 relevant to the primary analysis of depression. All studies measuring depression were appraised for risk of bias and heterogeneity was evaluated between studies. Results revealed a prevalence estimate of 21% (CI 0.19 to 0.24) for depression in adults with CD. A significant increased relative risk of depression was observed in comparison to the general population (RR 3.34, 95% CI 2.34-4.77). Significant heterogeneity between studies was observed (tau^2 = 0.0334, Higgin's I^2 = 97%; $p < 0.01$), and further analyses determined the impact of these biases. Furthermore, results suggest that those with CD are more at risk than the general population of anxiety disorder, eating disorders and bipolar disorder, however less risk from obsessive compulsive disorder and psychotic disorders. The findings point towards the need for integrated psychological screening and support for those with CD.

Introduction

Coeliac disease (CD) is a systemic, autoimmune disease resulting from exposure to gluten (a protein found in wheat, barley and rye) in genetically predisposed individuals (Butterworth & Los, 2019). In CD, an individual's immune system attacks its own tissues when gluten is ingested, leading to small intestinal enteropathy and preventing nutrients from food from being absorbed (Walker et al., 2017). Many individuals are asymptomatic, however symptoms, when present, can be extremely varied; they include gastrointestinal related symptoms such as diarrhoea, bloating, stomach pain and unintentional weight loss as well as extra-intestinal symptoms such as fatigue, dermatological conditions, infertility, and neurological disorders (Campagna et al., 2017; Castaño et al., 2019; Leffler et al., 2015; Riznik et al., 2021). The prevalence of CD is estimated to be around 1.4% globally, and 0.8% in Europe (Singh et al., 2018). Currently, the sole recommended treatment for CD is a life-long gluten free diet (GFD).

Living with CD can result in several challenges for individuals, such as the burden of adhering to a strict gluten free diet, missing out on valued activities and the difficulties associated with managing a chronic condition, being just some of the factors leading to an often, reduced quality of life (e.g. Crocker et al., 2018; Möller et al., 2021; Violato & Gray, 2019). Hallert et al. (2002) found that it was the perception of restriction, particularly in a social context related to dietary restrictions, that was a significant factor in an individual's feeling of disease burden. Research has demonstrated an association between CD and mental health difficulties or disorders for a long time now (Fera et al., 2003; Hallert & Derefeldt, 1982; Smith & Gerdes, 2012). The disorders most often reported within the literature include depression, anxiety, bipolar disorder, schizophrenia, psychotic disorders, eating disorders and obsessive-compulsive disorder (OCD) (Campagna et al., 2017; Clappison et al., 2020; Jackson et al., 2012). Depression in particular is associated with CD (Carta et al., 2015), with initial prevalence investigations suggesting that depression is more common and/or more severe in adults with CD compared to a healthy population and is similar in prevalence to other physical health

patient populations (Garud et al., 2009; Smith & Gerdes, 2012; Zingone et al., 2015). Recent reviews of the literature have supported this association (Clappison et al., 2020).

Research has suggested that the GFD can be associated with depression; Canova et al. (2021) found that levels of depression improved following CD diagnosis, particularly for those adhering to the GFD. However, other research has contrasting findings, suggesting that the severity of depression remains stable or increases whilst on the GFD (Siniscalchi et al., 2005; Zingone et al., 2010). In studies of intestinal mucosal healing, depression was more common in those who had achieved mucosal healing than those with persistent villous atrophy (Ludvigsson et al., 2018). This may be attributed to the extreme hypervigilance required in maintaining a GFD, which is associated with reduced illness-related quality of life (Wolf et al., 2018). However, it must be highlighted that studies investigating the association between depression and the GFD have multiple differences in their aims, focus and measurement of depression, such as using different methods of measuring GFD adherence and whether they were measuring levels of depression or the presence of a clinical diagnosis. Therefore, findings need to be interpreted with caution. Despite this, understanding the association between depression and CD has important implications. There may be a bidirectional relationship between depression and the GFD. In a CD population, depression may reduce an individual's ability to adhere to their treatment, the GFD. Sainsbury & Marques (2018) found a higher level of self-reported depressive symptoms was moderately associated with poorer adherence to the GFD, so depression may act as a barrier in treatment adherence. One hypothesis for this is that individuals with depression or low mood may find it harder to be vigilant, plan and monitor, which are all skills essential in maintaining good adherence to the GFD (Kwasnicka et al., 2016). Untreated CD can have serious long term health consequences such as an increased risk of cardiovascular diseases and cancers and is also associated with increased morbidity (Kaukinen, 2021). Furthermore, depression, more generally, has debilitating individual and societal impacts, with some of the possible consequences being death through suicide, reduced educational and work functioning, societal

economic burdens as well as poorer outcomes for co-morbid medical conditions (Cassano & Fava, 2002; Herrman et al., 2022). Whilst this is the case, individuals with the correct treatment and support can often make good recoveries (Herrman et al., 2022). Therefore, any further understanding of how depression may be associated with CD is vital in bettering outcomes for individuals.

The mechanisms by which mental health disorders and CD are associated are still not fully understood, however there are multiple mechanisms that have been proposed from both a biological (direct gut-brain relationship) and from a psychosocial perspective. One arm of research suggests that mental health difficulties are a result of nutritional deficiencies caused by sub-optimal adherence to the GFD, restricted diet whilst on the GFD or from hyperhomocysteinemia, with a lack of vitamins such as B6, B12 and Folic Acid being associated with the risk of depression (Campagna et al., 2017; Ferretti et al., 2013; Hallert et al., 2009; Thompson et al., 2005). Additional proposed mechanisms are that mental health disorders may be due to a serotonin imbalance or opioid neurotransmission caused by the effect of gluten upon the central nervous system (CNS) as well as cerebral hypoperfusion, which is increased blood flow in the brain (Addolorato et al., 2004; Cossu et al., 2017; Kukla et al., 2015). Moreover, it has also been suggested that mental health disorders, such as depression, may be a result of other co-morbid auto-immune conditions associated with CD, such as diabetes (Garud et al., 2009).

Furthermore, other research proposes that it may be the psychological burden that CD imposes that may then lead to mental health difficulties. Firstly, the culmination of the CD symptoms, particularly before diagnosis, may lead to a decreased quality of life and wellbeing, leading to mental health disorders (Kurppa et al., 2011; Möller et al., 2021). In addition, there are many lifestyle changes involved with a diagnosis of CD which may lead to higher psychological distress, from managing strict dietary restrictions and the impact of these upon social situations, to a change in relationships and daily worries that influence the development of mental health disorders in

individuals with CD (Lee et al., 2012; Möller et al., 2021; Zingone et al., 2021). It is outside the scope of this review to discuss further the complexities of the relationship between psychosocial factors and depression in CD, however research suggests the relationship is bidirectional in nature and may be the result of several different mechanisms (Möller et al., 2021).

Understanding the prevalence of depression and other mental health disorders in those with CD in relation to the normal population is important in being able to identify and plan the clinical and service needs of those with this disease. In their guidelines on the recognition, assessment and management of CD, the National Institute for Health and Care Excellence (NICE) highlight that individuals with CD may experience anxiety and depression (NICE, 2015), so health professionals should be aware of this. However, this is only mentioned very briefly within the guideline. Lebwohl et al. (2021) suggests that mental health care should be embedded within CD services alongside the monitoring of an individual's physical health. Carta et al. (2015) recommends implementation of screening for affective disorders in individuals with CD or with a family history of mental health conditions. This would not only have a positive impact at an individual level but have wider positive systemic implications, for example in potentially reducing involvement of secondary mental health services, if preventative and proactive measures are in place at a primary care level for individuals with CD and mental health disorders. Further understanding on this topic may also have benefit for those yet to be diagnosed with CD but may be struggling with their mental health; the better that healthcare professionals can understand the associations between CD and mental health disorders, the better equipped they may be in considering CD when presented with patients with mental health difficulties.

In summary, CD has been associated with multiple mental health disorders and understanding these associations has clear implications for the diagnosis and care of individuals with CD. Whilst there is a body of research exploring depression and other mental health disorders in CD,

due to differing review questions, recent prevalence estimate literature reviews are limited by the inclusion of only a small number of studies (Busby et al., 2018; Sainsbury & Marques, 2018; Sharma et al., 2021), and studies that do not evaluate the influence of person and study characteristics upon prevalence rates or search only one database (Clappison et al., 2020). Furthermore, some current prevalence estimates are based upon a formal diagnosis of the disorder only, which excludes those studies using other measures of depression, such as self-report measures with clinical cut off scores, and therefore may produce misleading conclusions of the prevalence of mental health disorders in those with CD; for example some of those experiencing depressive symptoms may not have formal diagnoses (Clappison et al., 2020). To expand upon this, the prevalence of mental health disorders defined by clinician assessment, standardised self-report measures with clinical cut-off scores and those recorded on patient case notes will be included in this meta-analysis. This meta-analysis will focus on exploring the prevalence of depression in those with CD.

Aims and Objectives

The present meta-analysis aims for a more inclusive approach to included studies, leading to a larger number of studies evaluated and consequently leading to a more robust prevalence estimate of depression. As described, the literature on the association between CD and depression is vast and has mixed conclusions therefore this review aims to synthesise this. Overall, this review aims to describe and evaluate the current literature estimating the prevalence of depression in adults with a diagnosis of CD by:

1. Synthesising prevalence rates of depression in adults with CD in order to generate a current, robust prevalence and relative risk estimates.
2. Evaluating how study and participant characteristics influence the prevalence rates of depression in adults with CD.

Further analyses will include comparing the prevalence rates of depression for individuals with optimal and suboptimal adherence to the GFD (where reported) as well as to examine whether the method used to identify depression (clinician assessment; usually using formal diagnostic tools, self-report measures or case note reviews) influences the prevalence rates reported.

Method

Identifying Primary Studies

Search of Electronic Databases

A systematic search of the literature was completed in October 2022 using PsycINFO, Medline, Embase and Web of Science combining all variations of CD and mental health search terms. The choice of databases was guided by Bramer et al. (2017) who suggested these as appropriate databases to be used in systematic reviews with a biomedical and psychological focus. The aim of the search was to obtain a comprehensive overview of the literature into the prevalence of depression and other mental health disorders in individuals with CD. To enable comparisons between the prevalence of depression and other mental health disorders, a search was undertaken encompassing all of the following disorders: depression, anxiety, eating disorders, psychotic disorders (including schizophrenia), bipolar disorder and OCD. The search terms that were used to identify these studies are outlined in Table 1. Search terms were informed by similar meta-analyses as well as the Diagnostic and Statistical Manual of Mental Health Disorders (5th ed.; DSM-5; American Psychiatric Association, 2013) and the International Statistical Classification of Diseases and Related Health Problems (11th ed.; ICD-11; World Health Organization, 2019).

Table 1

Systematic Search Terms and Criteria

Key Concepts	Keyword Search Terms	Subject Headings (Database) All terms exploded	Method of Search	Limits
Coeliac disease	"Celiac" "Coeliac" "Celiac disease*" "Coeliac disease*" "Gluten-related disease*"	Celiac Disease (PsycINFO, Medline, Embase)	For PsycINFO, Medline and Embase, keyword and subject heading searches were completed. For Web of Science, keyword searches were completed only. Keywords within each key concept were combined with "OR" and the key concepts combined with "AND"	Where possible, the limits of 'human', 'peer reviewed text' and 'English language' were applied to the searches. For Medline and Embase, the limit 'peer reviewed text' was not possible. For Web of Science, the limit 'human' was not possible. For Embase, the limit 'remove medline records' was applied, as this search was completed following the Medline search.
Depression and other mental health disorders (Anxiety, eating disorders, psychotic disorders, bipolar disorder and OCD)	"Depression" "Depressive" "Depressed" "Low mood" "Mood disorder*" "Psychiat* diagnos*" "Psychiat* disorder* "Psychiat* Illness*" "Psychiat* distress" "Mental health" "Mental health diagnos*" "Mental health disorder*" "Mental health illness*" "Mental illness*" "Mental disorder*" "Mental distress" "Psychological diagnos*" "Psychological illness*" "Psychological distress" "Psychological disorder*" "Psychosi*" "Schizophrenia" "Schizoaffective" "Anxiety" "Anxious" "Anorexi*" "Bulimi*" "Eating disorder*" "Binge" "Binge eating*" "Bipolar" "Manic" "Mania" "Hypomani*" "OCD" "Obsessive compulsive disorder*"	Depression (emotion) (PsycINFO) Depressive Disorder, major (Medline) Depressive Disorder (Medline) Affective Disorders (PsycINFO) Mood Disorders (Medline, Embase) Mental Disorders (PsycINFO, Medline) Psychological Distress (Medline) Psychiatric Diagnosis (Embase) Psychodiagnosis (PsycINFO) Mental Health (PsycINFO, Medline, Embase) Mental Disease (Embase) Mental Stress (Embase) Major Depression (PsycINFO, Medline, Embase) Psychiatric Symptoms (PsycINFO) Psychosis (PsycINFO, Embase) Psychotic Disorders (Medline) Schizophrenia (PsycINFO, Medline, Embase) Schizoaffective Disorder (PsycINFO) Anxiety (PsycINFO, Medline, Embase) Anxiety Disorders (PsycINFO, Medline, Embase) Eating Disorders (PsycINFO, Embase) Feeding and Eating Disorders (Medline) Anorexia Nervosa (PsycINFO, Medline, Embase) Anorexia (Medline, Embase) Bulimia (PsycINFO, Medline, Embase) Bulimia Nervosa (Medline) Binge Eating (PsycINFO) Binge Eating Disorder (PsycINFO, Medline, Embase) Bipolar Disorder (PsycINFO, Medline, Embase) Bipolar I Disorder (PsycINFO, Embase) Bipolar II Disorder (PsycINFO) Mania (PsycINFO, Medline, Embase) Hypomania (PsycINFO, Embase) Obsessive Compulsive Disorder (PsycINFO, Medline, Embase)		

Inclusion and Exclusion Criteria

Identification of the included papers was completed in the following steps:

- **Stage 1: Screening**
  - All articles returned from the database searches were screened by title and abstract to assess whether they met initial screening inclusion and exclusion criteria.
- **Stage 2: Eligibility Assessment**
  - Those papers that met the initial screening inclusion and exclusion criteria were then assessed for eligibility by reviewing the full text.

The inclusion and exclusion criteria for Stage 1: Screening are shown in Table 2. Criteria for the full text eligibility assessment are described in Table 3.

Table 2

Inclusion and Exclusion Criteria for Stage 1: Screening

Inclusion and Exclusion Criteria	Justification
Type of Article The article had to present original, peer reviewed empirical research. The following article types were excluded: literature reviews, dissertations, conference materials, letters, responses to authors and book chapters.	This is to ensure that no grey literature was included, and results are based on peer reviewed articles. Excluded articles do not present the data needed to calculate this meta-analysis.
Study Design The article should be of a quantitative nature. Articles using a design meaning prevalence rates could not be calculated, such as qualitative and case studies were excluded.	To obtain the required results to calculate this meta-analysis.
Participants Participants must be human and have a diagnosis of CD, which is explicitly stated in the article. They can be from any geographical location.	This was the focus of the article and ensured that prevalence estimates can be generalised to the CD population.
Outcomes The article must include data on the relationship between CD and the mental health disorders focused upon in this review. Articles must include the measurement or identification of the specific mental health disorders stated in this review in a CD population.	This is the focus of the meta-analysis. Measurement of CD in a population with mental health disorders does not give the correct data to show prevalence of mental health disorders in a CD population and were therefore excluded and deemed not relevant.

Table 3

Inclusion and Exclusion Criteria for Stage 2: Eligibility Assessment

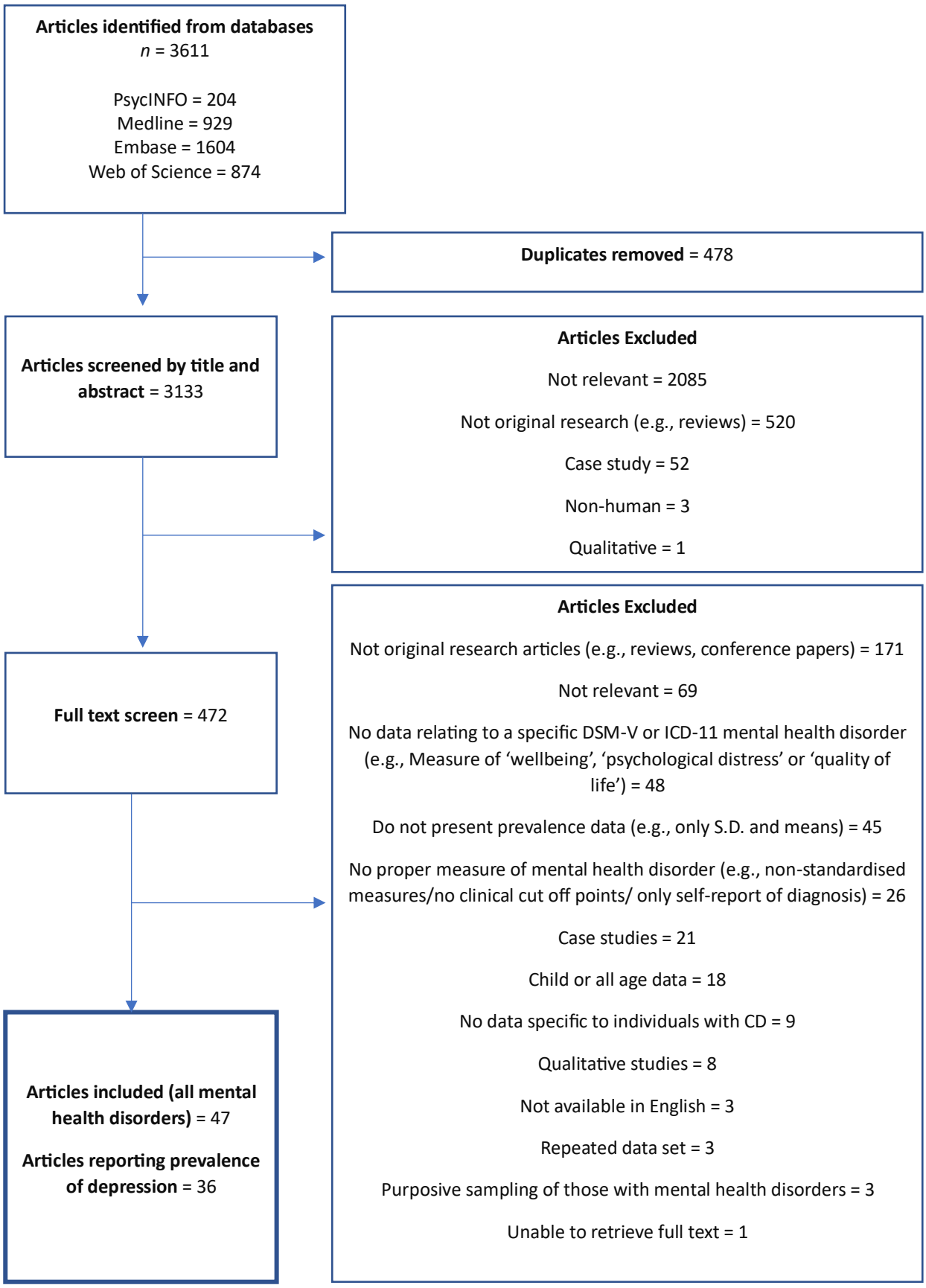
Inclusion and Exclusion Criteria	Justification
Participant Characteristics Studies must include data specific to an adult age group of 16 years and above. Studies which included data for below age 16 only or all age data without specific data for adults aged 16 and over were excluded.	The focus of this review is adults with CD. There is lots of heterogeneity in studies measuring mental health disorders in children and therefore these studies were excluded to reduce bias.
Sample The study must present data specific to a sample of individuals with CD only, and not any other conditions within the sample. Any studies that presented data only for 'gastrointestinal disorders', 'chronic conditions' or alike were excluded.	The focus of this meta-analysis is understanding the prevalence of mental health disorders specifically in individuals with CD. Studies reporting samples with different conditions as well as CD would give an inaccurate answer to the meta-analysis question.
Study Design Studies must include an assessment or identification of mental health disorders in a CD population, studies had to either: - report the number/percentage of subjects with one of the specific DSM-5 or ICD-11 mental health diagnoses in this review, based on a clinician assessment or a diagnosis was stated on their medical case notes. - and/or the number/percentage of subjects falling above a clinical cut-off score for a mental health disorder on a standardised self-report measure or questionnaire. Studies that presented only self-reported presence of a mental health disorder and did not measure the construct were excluded. Studies using measures that were not standardised or validated were excluded.	To enhance the validity of the prevalence rates estimates in this meta-analysis and to include a large number of studies. This meta-analysis aimed to provide prevalence estimates for mental health disorder, and not just the presence of any level of the mental health condition. Self-reported presence of a mental health disorder, i.e., a participant ticking 'yes' to "I have depression" was not included. This is because self-report in this way may lead to an increased bias in over or underreporting of the construct (Davis et al., 2012; Watts et al., 2016). This may be due to several factors such as social desirability bias and be influenced by insight into one's own mental state (Van de Mortel, 2008). Furthermore, this may be influenced by the way in which studies recruited to their research, such as the possible bias in a self-selecting sample to be more likely to have the characteristic that the study is measuring (Tripepi et al., 2010). Whilst self-report measures are included in the search and are recognised to also have limitations when measuring constructs, these were only included if they were standardised, validated and widely used measures to ensure a level of reliability. Therefore, whilst an aim of this meta-analysis is to be inclusive, rigour in the methodology was ensured by excluding these types of self-report in the reporting of mental health disorders.
Outcome Data Data must be presented in a way that prevalence levels could be calculated. Articles presenting only standard deviations and means for mental health disorders were excluded. Qualitative studies were excluded. Prevalence of mental health disorder could be presented with point, lifetime or incidence prevalence rates.	To ensure that outcomes can be calculated into a prevalence effect size. Event rates cannot be calculated from studies presenting only S.D and means, with no event rates.
Language The full text must be available in English.	To be able to understand and extract data effectively.

The results of the systematic search are presented in Figure 1. The search yielded 3611 articles, resulting in 3113 once duplicates were removed. These articles were then screened by title and abstract using the inclusion and exclusion criteria stated in Table 2. The most common reasons for exclusion were: not being relevant to the meta-analysis topic and question *(n* = 2086), not containing original research (e.g. literature reviews) (*n* = 520) and being of case study design (*n* = 52). There were multiple reasons that an article was deemed 'not relevant', such as the focus of the article not concerning the relationship between the concepts of CD and mental health disorders and that the article involved measurement of CD in those with mental health disorders, rather than vice versa.

The full text of the remaining 472 articles were then reviewed against the inclusion and exclusion criteria (Table 3). Forty-seven articles met full inclusion criteria. In addition to the literature search, the reference lists of the final 47 included articles were reviewed to identify any relevant additional articles; however, none meeting inclusion criteria were identified. Thus, 47 articles satisfied the criteria for inclusion within this meta-analysis (across all specified mental health disorders), with 36 of these reporting data on the prevalence of depression in a CD population. Many studies reported prevalence outcomes for multiple mental health disorders, for more than one type of prevalence (point, incidence and lifetime), and for multiple groups of individuals with CD (i.e., on the GFD and not on the GFD), therefore there were more effects than studies. Point prevalence reports the presence of the disorder at a specific point in time (such as when a self-report measure was completed), incidence prevalence reports the number of those with a disorder over a specific period of time (such as the number of new diagnoses of depression within a one year period) and lifetime prevalence reports the number of individuals who have experienced the disorder at some point over the course of their lifetime. The main meta-analysis will be conducted on the studies reporting point and incidence prevalence combined (hereafter referred to as 'point prevalence'; this included 32 studies (covering 36 effects) and will be referred to as the primary studies.

Figure 1

Application of the Inclusion and Exclusion Criteria and Results of the Systematic Search



As previously stated, as part of the systematic search and data extraction for this meta-analysis, in addition to depression, data was collected across the mental health disorders most associated with CD, which are anxiety, eating disorders, bipolar disorder, psychotic disorders and OCD. The aim of this was to compare these to the prevalence of depression. Following the search, it was decided that to ensure a thorough meta-analysis within the limits of the doctoral thesis, depression will be the focus of the review only. Therefore, data containing information solely on depression is analysed and presented in this thesis. However, Appendix A contains a list of all the studies that data was extracted from following the initial search, by mental health disorder. A brief summary of the prevalence and relative risk rates for all of the above mental health disorders is contained within Appendix B.

Data Extraction

All data were extracted by the author. It is assumed that event rates are reported as the number of participants with and without the condition of interest. If relative risk or risk difference estimate are to be calculated, then event rates should be reported as the number of participants with and without the condition of interest in both a control and exposure/risk groups. Multiple reporting of outcomes can result from primary studies reporting multiple measures of the same outcome or reporting the same outcome measure in multiple subgroups. Where possible, multiple outcomes were combined in a single quantitative outcome using the procedures described by Borenstein et al. (2021). When it was not possible to combine the multiple effects into a single quantitative effect, then the multiple effects will be directly included into the meta-analysis. The inclusion of multiple

reporting of outcomes from the same primary study may result in a slight reduction in confidence intervals for the random effects model as the sample size of that primary study will be included twice.

Defining Problematic Variance

A study level effect is considered heterogeneous if it presents with variation from the meta-analysis synthesis that cannot be attributed to true variation in the distribution of effect in the population. Heterogeneity can result from methodological variation in the studies, measurement error or uncontrolled individual difference factors within the body of literature. Higgins I^2 is a commonly used measure of heterogeneity, with greater values of I^2 indicating variation in effect that cannot be attributed to true variation in the distribution of effect in the population. As there is considerable variation in methodologies of the primary studies that was used to calculate the meta-analytic synthesis, problematic heterogeneity was defined as a Higgins I^2 value greater than 75%. Where unacceptable or problematic heterogeneity is observed then the focus of the subsequent analyses will be upon the identification of the sources of heterogeneity between the estimates of prevalence in the primary studies.

Risk of Bias Assessment

A set of quality criteria were developed to assess risk of bias within each of the final articles included. The quality criteria were adapted from existing risk of bias frameworks, including The Cochrane Collaboration Risk of Bias Tool (Higgins et al., 2011) and the Risk of Bias Assessment Tool for Nonrandomised Studies (Kim et al., 2013). The framework used in this meta-analysis assesses risk of bias in six domains: selection bias, performance bias, detection bias, statistical bias, reporting bias, and generalisability. The risk of bias in the six domains and the criteria for Low, Unclear or High risk is described in Table 4.

Table 4

Domains of Risk of Bias and the Criteria for Ratings of Low, Unclear or High Risk

Domain	Details	Risk of Bias
Selection Bias	Does the study design yield a sample of respondent's representative of the target population? Is the target population defined clearly? Was some form of random sampling used to select potential respondents?	**High Risk –** Target sampling was used. Includes an unacceptable (reporting less than 30% of the data) level of non-response rate. The characteristics of the study population are not reported at all. The characteristics of the study group are not representative of the target population. The thoroughness of the selection method (i.e. outcome) is secondary to the main outcome of the study (e.g. study's main focus is not on MH disorders). Other exclusion/inclusion criteria may contaminate estimate of events. **Unclear Risk –** Convenience/ non-random/opportunistic sampling was used or sampling method is unclear. Non-response rate is not reported or unclear. Minimal characteristics of the study population are reported. For example, the country, setting, location, population demographics were not adequately reported. Sampling is adequate but is selected from a pre-existing (clinical) sample. Not clear whether the selection of participants would contaminate estimate of event. **Low Risk –** Sampling method used is unbiased (i.e. some form of random sampling taken from representative population). The recruitment method is clearly reported and well defined. Non-response rate is reported and of an acceptable level (set at 50%). The characteristics of the study population are clearly described and without evidence of bias. The source population is well described, and the study reports the characteristics of the sample e.g. the study details subgroups. The article provides some reassurance that there is no selection bias
Performance Bias	Performance bias may occur through participants underreporting or over reporting symptoms due to social desirability, as well as other factors such as shame. Were these adequately controlled for? Differences in the levels/type of motivation between the groups.	**High Risk -** Responses are not confidential or anonymous. Participants were rewarded for their participation in the study. Participants were told which condition/ what questionnaires they were completing and why and any proposed hypotheses. Failure to report symptoms or inability to report symptoms (e.g. due to shame, social desirability). Under-reporting symptoms (e.g. not available to introspective awareness). Over reporting. **Unclear Risk -** The study does not report levels of confidentiality and anonymity. It is not clear if participants were rewarded for their participation (e.g. motivation to respond in a certain way). It is unclear how much information was provided to the participant prior to taking part in the study. High risk of social desirability and inadequate or unclear attempts to adjust for this. Data is self-report, although attempts are made to blind personnel to outcome assessments and check for inter-rater reliability, or anonymisation has taken place. **Low Risk -**

Domain	Details	Risk of Bias
		Study reports level of confidentiality and anonymity, and it is adequate. Participants were not rewarded for their participation in the study. Information and procedures are provided in a way that does not differentially motivate participants. Low risk of social desirability or high risk of social desirability but attempts made to control for this (e.g. introduction of validity scales or triangulation of information).
Detection Bias	Was the study instrument that measured the parameter of interest shown to have reliability and validity?	**High Risk -** The outcome measures were implemented differently across participants. The outcome measures used had poor reliability and validity reported e.g Crobach's Alpha < 0.6. and/or test/retest reliability < 0.6. Outcome measures used are non-standardised and do not report psychometric properties. Measure not fit for purpose. **Unclear Risk -** Information regarding the outcome measures are either not reported or not clearly reported e.g. definition, validity, reliability. Cronbach's Alpha for outcome measures is between 0.6 and 0.7. Test-retest reliability for outcome measures is between .6 and .7 It is not clear if the measure was implemented consistently across all participants. Assessment measure is not widely recognised, or peer reviewed and/or the psychometric properties are reported but poor. Unclear whether diagnosis (if on case notes) is made by ICD-11/DSM-5 diagnostic criteria. **Low Risk -** The outcome measures are clearly defined, valid and reliable, and are implemented consistently across all participants. Standardised and well-known measures with good psychometric properties are used to assess the presence of MH disorder and/or validated diagnostic interview used by clinician. If a case review, there is evidence of diagnoses made by DSM-5 or ICD-11 diagnostic criteria.
Statistical Bias	Bias resulting from the statistical treatment of the data. Were prevalence rates appropriately reported (e.g. including descriptive statistics such as gender)? Was there missing or incomplete data (e.g. the *n* in one section is different to the *n* in another section of the report) Does the study provide reasons for attrition or exclusions where reported, and any re-inclusions in analyses for the review?	**High Risk -** Statistics were not reported. Wrong statistical test was used and/or not appropriate for the study design. Attrition rate – data loss is reported at analysis at an unacceptable level (30%) or is clear and reasons not reported. Event rate is unclear, inadequately reported, not provided or calculated based on additional statistical analyses e.g. logistical regression. Event rates are adjusted for methodological confounds**.** **Unclear Risk -** Unclear what statistical test was used. Attrition rate – data loss is not reported at analysis and is therefore unclear. Raw event rate or percentage is provided, however descriptive statistics are not clearly provided (e.g. no breakdown by gender for prevalence rates). **Low Risk -** Appropriate statistical testing was used. Attrition rate – data loss is reported at analysis at an acceptable level (50%). Reasons for attrition and exclusions reported. Adequate descriptive statistics are provided including raw event rate or percentage.

Domain	Details	Risk of Bias
Reporting Bias	Reporting bias due to selective outcome reporting. Does the study describe the completeness of outcome data for each main outcome (including attrition and exclusions from the analysis)?	**High Risk -** Not reported full outcome measures that are stated in the method section/ reported only a subsample of results/only significant results/ not reported the measure as it should be (e.g. HADS should report separate subscale for anxiety and depression and not total them). Data does not appear to be accurately reported (e.g. final values are suspect or data is reported in a manner requiring reconstruction from description). **Unclear Risk -** Not all descriptive and/or summary statistics are presented. There is a description (narrative) in the results but do not record statistics. Unclear or vague whether the results of all measures used to assess MH disorders is reported. **Low Risk -** Reported all results of measures as outlined in the method. Full sample size reported. Reported results of all measures used within the study.
Generalisability	Are there sufficient numbers of participants for the study to be statistically meaningful? Does the study describe any differences between the study participants and those persons to whom the review is applicable?	**High Risk -** Small sample with or without idiosyncratic feature. High percentage (over 80%) of sample is represented by one professional and cannot be generalised to a variety of healthcare professionals. The sample size is not adequate to detect an effect (n<20) **Unclear Risk -** Sufficient sample for generalisation but with some idiosyncratic features. A sample size justification, estimate and power analysis were not provided Sample size has not been optimised to detect the prevalence of mental health (n between 20 and 40 participants) **Low Risk -** Sufficient sample for generalisation and representative of target population. A sample size justification, estimate and power analysis was provided. Based on the World Health Organisation estimate of one in eight people living with a mental health disorder in the general population, an adequate sample size would be greater than 40 persons. The sample size is adequate to detect an effect

Each article's study design was also assessed, which in conjunction with the risk of bias assessment, formed the overall quality index for each study. Description of each study design and its corresponding quality score are shown in Table 5. Study designs were placed in a quality hierarchy from lowest to highest as follows: cross sectional (*n* = 15 studies), case-control (*n* = 13), retrospective case cohort (*n* = 2) and prospective case cohort (*n* = 2). There were no before and after/ case series studies. A score was awarded to each study which reflected its position in the study design hierarchy.

Table 5

Study Design Hierarchy

Study Design	Quality Score	Description
Prospective case cohort study	40	Cohort Study (prospective) is a study of a group of individuals, some of whom are exposed to a variable of interest (e.g., drug or environmental exposure), in which participants are followed up over time to determine who develops the outcome of interest and whether the outcome is associated with the exposure.
Retrospective case cohort study	30	Cohort Study (retrospective) is when data is gathered for a cohort that was formed sometime in the past. Exposures and outcomes have already occurred at the start of the study. You are studying the risk factor and see if you can associate a disease to it. Individuals split by exposure.
Case control study	20	Case Control Study is a study in which patients who already have a specific condition or outcome are compared with people who do not. Researchers look back in time (retrospective) to identify possible exposures. They often rely on medical records and patient recall for data collection.
Cross-sectional studies	10	Cross-Sectional Study is the observation of a defined population at a single point in time or during a specific time interval to examine associations between the outcomes and exposure to interventions. Exposure and outcome are determined simultaneously. Often rely on data originally collected for other purposes.
Before and after study/ Case Series	0	Before and After Study is a study in which within-subject observations are made before (pre) and after (post) the implementation of an intervention/exposure.

Table 6 displays the application of the risk of bias evaluation and overall quality index for each of the 32 primary studies (reporting 36 effects), reporting depression in individuals with CD. The final quality index is the sum of the risk of bias score and the study design score expressed as a percentage of the maximum possible score. Overall, higher quality index scores represents higher quality and reduced risk of bias.

Table 6

Ratings of Risk of Bias

Study Name	Selection Bias	Performance Bias	Detection Bias	Statistical Bias	Reporting Bias	Generalisability	Quality Index
Addolorato et al. (1996)	Unclear risk	Unclear risk	Low risk	Unclear risk	Low risk	High risk	52%
Addolorato et al. (2001)	High risk	Unclear risk	Low risk	Low risk	Low risk	Unclear risk	54%
Addolorato et al. (2004)	High risk	Unclear risk	Low risk	Low risk	Low risk	High risk	52%
Addolorato et al. (2008a)	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	58%
Addolorato et al. (2008b)	High risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	56%
Alharbi et al. (2017)	High risk	Unclear risk	Low risk	High risk	Low risk	Low risk	33%
Arigo et al. (2011)	Unclear risk	Unclear risk	Low risk	Unclear risk	High risk	Low risk	33%
Barratt et al. (2013)	Unclear risk	Unclear risk	Low risk	Unclear risk	Low risk	Low risk	37%
Briani et al. (2008)	Unclear risk	Unclear risk	High risk	High risk	Unclear risk	Low risk	29%
Carta et al. (2002)	Unclear risk	Unclear risk	High risk	Low risk	High risk	Unclear risk	48%
Ciacci et al. (1998)	Unclear risk	Unclear risk	Low risk	Low risk	High risk	Low risk	54%
Dana et al. (2020)	Unclear risk	Unclear risk	Low risk	Low risk	High risk	Low risk	35%
Dorn et al. (2010)	Unclear risk	Unclear risk	Low risk	Unclear risk	Low risk	Low risk	37%
Fera et al. (2003)	Unclear risk	Unclear risk	Low risk	Unclear risk	High risk	Low risk	52%
Guedes et al. (2020)	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	38%
Hallert & Derefeldt (1982)	Unclear risk	Unclear risk	Unclear risk	High risk	Unclear risk	Low risk	69%
Hauser et al. (2006)	Low risk	Unclear risk	Low risk	High risk	Low risk	Low risk	37%
Longarini et al. (2018)	High risk	Unclear risk	Low risk	Low risk	High risk	Unclear risk	88%
Ludvigsson et al. (2007a)	High risk	Unclear risk	Low risk	Low risk	High risk	Low risk	71%
Morris et al. (1970)	High risk	Unclear risk	High risk	High risk	Low risk	Unclear risk	27%
Nachman et al. (2010)	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	96%
O'Shaughnessy et al. (2022)	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	High risk	54%
Parker et al. (2022)	Low risk	Unclear risk	Low risk	Low risk	Unclear risk	Low risk	38%
Passananti et al. (2013)	High risk	Unclear risk	Low risk	Low risk	High risk	Low risk	52%
Ramirez-Cervantes et al. (2015)	Unclear risk	Unclear risk	High risk	Low risk	Low risk	Low risk	35%
Siniscalchi et al. (2005)	High risk	Unclear risk	Low risk	High risk	High risk	Low risk	48%
Stone et al. (2012)	Unclear risk	High risk	Low risk	Low risk	Unclear risk	Low risk	35%
van Hees et al. (2012)	Unclear risk	Unclear risk	Low risk	Unclear risk	High risk	Low risk	33%
van Hees et al. (2014)	High risk	Unclear risk	Low risk	Unclear risk	Low risk	Low risk	35%
Zingone et al. (2010)	High risk	Unclear risk	Low risk	Low risk	High risk	Unclear risk	50%
Zingone et al. (2021)	Unclear risk	Unclear risk	Low risk	Low risk	High risk	Low risk	35%
Zylberberg et al. (2017)	Unclear risk	Unclear risk	Low risk	High risk	High risk	Low risk	50%

Note. Red indicates high risk of bias, amber marks an unclear risk of bias and green is a low risk of bias.

Selection Bias

Overall, from the total of 32 studies included, selection bias was varied across the studies. Nineteen studies were rated as unclear risk of bias, with 11 rated as high risk of bias and two rated as low risk of bias. The unclear risk studies often used non-random sampling such as convenience and opportunistic sampling, vague inclusion/exclusion criteria and little description of the characteristics of the study population (Addolorato et al., 1996; Addolorato et al., 2008a; Arigo et al., 2011; Barratt

et al.,2013; Briani et al., 2008; Carta et al., 2002; Ciacci et al., 1998; Dana et al., 2020; Dorn et al., 2010; Fera et al., 2003; Guedes et al., 2020; Hallert & Derefeldt., 1982; Nachman et al., 2010; O'Shaughnessy et al., 2022; Ramirez-Cervantes et al., 2015; Stone et al., 2012; van Hees et al., 2012; Zingone et al., 2021; Zylberberg et al., 2017). Most of the high-risk studies excluded those with a previous psychiatric diagnosis from their study, which would therefore give invalid prevalence rates of depression. Other reasons for studies being rated as high risk include unclear sample selection methods, oversampling of those with depressive symptoms and the use of friends and family as a control group which could be therefore biased (Addolorato et al., 2001; Addolorato et al., 2004; Addolorato et al., 2008b; Alharbi et al., 2017; Longarini et al., 2018; Ludvigsson et al., 2007a; Morris et al., 1970; Passananti et al., 2013; Siniscalchi et al., 2005; van Hees et al., 2014; Zingone et al., 2010). The low-risk studies used a random sampling technique and reported levels of non-response (Hauser et al., 2006; Parker et al., 2022).

Performance Bias

Performance bias was mostly rated as unclear across the studies. Thirty-one studies were rated as unclear risk of bias and 1 was rated as high. Most unclear risk studies used self-report measures without accounting for social desirability and did not report on levels of confidentiality, anonymity and reward (Addolorato et al., 1996; Addolorato et al., 2001; Addolorato et al., 2004; Addolorato et al., 2008a; Addolorato et al., 2008b; Alharbi et al., 2017; Arigo et al., 2011; Barratt et al.,2013; Briani et al., 2008; Carta et al., 2002; Ciacci et al., 1998; Dana et al., 2020; Dorn et al., 2010; Fera et al., 2003; Guedes et al., 2020; Hallert & Derefeldt., 1982; Hauser et al., 2006; Longarini et al., 2018; Ludvigsson et al., 2007a; Morris et al., 1970; Nachman et al., 2010; O'Shaughnessy et al., 2022; Parker et al., 2022; Passananti et al., 2013; Ramirez-Cervantes et al., 2015; Siniscalchi et al., 2005; van Hees et al., 2012; van Hees et al., 2014; Zingone et al., 2010; Zingone et al., 2021; Zylberberg et al., 2017). Given the topic of this meta-analysis and the selection techniques used, it may be those reporting higher levels of mental health disorders may have been more inclined to participate in the

studies and therefore it is unclear how this may have influenced true prevalence rates of depression. The high-risk study rewarded participants for their participation, with the chance to win a prize (Stone et al., 2012).

Detection Bias

The majority of studies were rated as low risk for detection bias (*n*=27), with four rated as high risk and one as unclear risk. The low-risk studies often used well known, validated measures of depression (Addolorato et al., 1996; Addolorato et al., 2001; Addolorato et al., 2004; Addolorato et al., 2008a; Addolorato et al., 2008b; Alharbi et al., 2017; Arigo et al., 2011; Barratt et al.,2013; Ciacci et al., 1998; Dana et al., 2020; Dorn et al., 2010; Fera et al., 2003; Guedes et al., 2020; Hauser et al., 2006; ; Longarini et al., 2018; Ludvigsson et al., 2007a; Nachman et al., 2010; O'Shaughnessy et al., 2022; Parker et al., 2022; Passananti et al., 2013; ; Siniscalchi et al., 2005; Stone et al., 2012; van Hees et al., 2012; van Hees et al., 2014; Zingone et al., 2010; Zingone et al., 2021; Zylberberg et al., 2017). The high-risk studies used inconsistent measurement methods across groups in the study (Carta et al., 2002), did not give specific information on how depression was identified, just that it was a clinician assessment based upon a 'neurological examination' (Briani et al., 2008; Morris et al., 1970) and used a self-report measure differently to what it was intended for (Ramirez-Cervantes et al., 2015). The unclear risk study gave vague information on how depression was identified or measured and did not give reference to any DSM-5 or ICD-11 criteria (Hallert & Derefeldt, 1982).

Statistical Bias

Statistical bias was varied across the primary studies; 18 studies were rated as low risk, seven as unclear and seven as high risk. Low risk studies used appropriate descriptive and inferential statistics along with demographic data reported and acceptable attrition rates (Addolorato et al., 2001; Addolorato et al., 2004; Addolorato et al., 2008a; Addolorato et al., 2008b; Carta et al., 2002; Ciacci et al., 1998; Dana et al., 2020; Guedes et al., 2020; Longarini et al., 2018; Ludvigsson et al.,

2007a; Nachman et al., 2010; O'Shaughnessy et al., 2022; Parker et al., 2022; Passananti et al., 2013; Ramirez-Cervantes et al., 2015; Stone et al., 2012; Zingone et al., 2010; Zingone et al., 2021). Meanwhile, the unclear risk studies often used appropriate statistics however they were used inconsistently across measures and groups (Addolorato et al., 1996; Arigo et al., 2011; Barratt et al., 2013; Dorn et al., 2010; Fera et al., 2003; van Hees et al., 2012; van Hees et al., 2014). The reasons for studies being rated as high risk included only descriptive statistics being reported, missing data being adjusted with median values and inconsistent n sizes across analyses without a rationale (Alharbi et al., 2017; Briani et al., 2008; Hallert & Derefeldt, 1982; Hauser et al., 2006; Morris et al., 1970; Siniscalchi et al., 2005; Zylberberg et al., 2017).

Reporting Bias

Overall, the full reporting of the outcomes within the studies was varied, with 15 studies rated as low risk, 13 as high risk and four as unclear risk. Studies found to be low risk presented all outcomes for the entire sample in a consistent way (Addolorato et al., 1996; Addolorato et al., 2001; Addolorato et al., 2004; Addolorato et al., 2008a; Addolorato et al., 2008b; Alharbi et al., 2017; Barratt et al., 2013; Dorn et al., 2010; Guedes et al., 2020; Hauser et al., 2006; Morris et al., 1970; Nachman et al., 2010; O'Shaughnessy et al., 2022; Ramirez-Cervantes et al., 2015; van Hees et al., 2014s). The papers rated as high risk selectively and inconsistently reported event rates across outcomes and groups and/or there appeared to be errors in the results (Arigo et al., 2011; Carta et al., 2002; Ciacci et al., 1998; Dana et al., 2020; Fera et al., 2003; Longarini et al., 2018; Ludvigsson et al., 2007a; Passananti et al., 2013; Siniscalchi et al., 2005; van Hees et al., 2012; Zingone et al., 2010; Zingone et al., 2021; Zylberberg et al., 2017). The studies deemed unclear risk reported data in a way that was difficult to decipher with no identified rationale as to why some results were presented in differing formats, only provided a narrative of the results rather than the statistical analysis completed and/or reported an 'approximate' sample size (Briani et al., 2008; Hallert & Derefeldt, 1982; Parker et al., 2022; Stone et al., 2012).

Generalisability

Overall, sample sizes were adequate, with 24 studies deemed as low risk. Sample size adequacy was calculated as 40, based on the World Health Organisation estimate of one in eight people living with a mental illness in the world (Institute of Health Metrics and Evaluation (IHME), 2019). The studies rated as low risk had sample sizes greater than 40 participants with a justification of the chosen sample size (Addolorato et al., 2008a; Addolorato et al., 2008b; Alharbi et al., 2017; Arigo et al., 2011; Barratt et al.,2013; Briani et al., 2008; Ciacci et al., 1998; Dana et al., 2020; Dorn et al., 2010; Fera et al., 2003; Guedes et al., 2020; Hallert & Derefeldt., 1982; Hauser et al., 2006; Ludvigsson et al., 2007a; Nachman et al., 2010; Parker et al., 2022; Passananti et al., 2013; Ramirez-Cervantes et al., 2015; Siniscalchi et al., 2005; Stone et al., 2012; van Hees et al., 2012; van Hees et al., 2014; Zingone et al., 2021; Zylberberg et al., 2017) . Five studies were unclear risk (between 20 to 40 participants) (Addolorato et al., 2001; Carta et al., 2002; Longarini et al., 2018; Morris et al., 1970; Zingone et al., 2010) and three studies were high risk (under 20 participants) (Addolorato et al., 1996; Addolorato et al., 2004; O'Shaughnessy et al., 2022. Therefore, for the majority of studies, the results can be applied to the wider CD population.

Summary

Overall, there was a mixed level of bias across the primary studies included in the meta-analysis. Only six studies did not have any high risk of bias ratings across any of the quality criteria (Addolorato et al., 2008a; Barratt et al., 2013; Dorn et al., 2010; Guedes et al., 2020; Nachman et al., 2010; Parker et al., 2022). There was a notable high risk of bias across studies for selection and reporting bias. Due to the relatively low number of studies in this field, studies with medium to high risk of bias were included and consequently, the results of this meta-analysis should be interpreted with some caution. However, the effect of risk of bias, the impact of influential studies, as well as the impact of publication and small study bias, was analysed within the meta-analysis.

Results

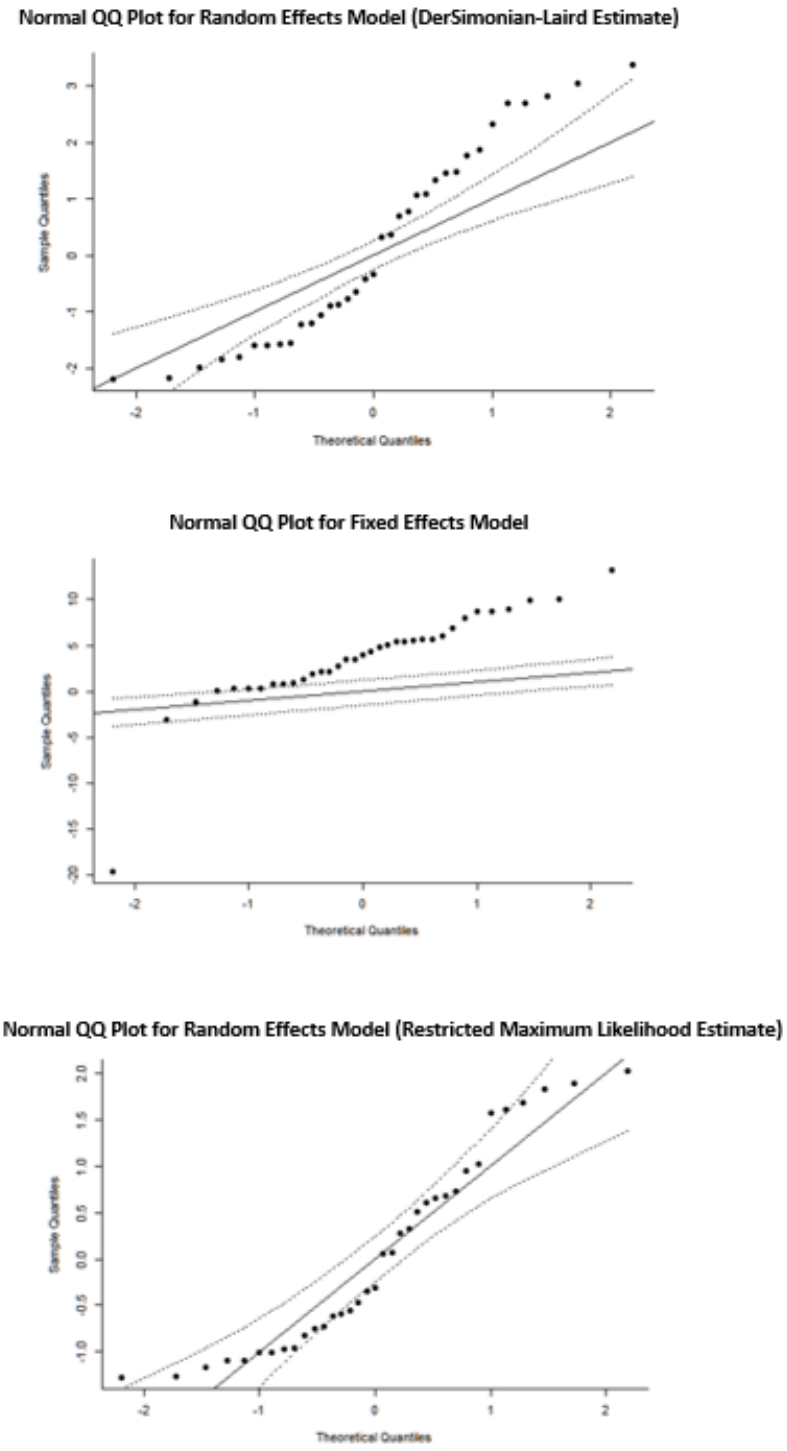
Depression

Selection of the Meta-Analytic Model

As previously stated, studies reporting point prevalence of depression are the main focus of this review, termed the 'primary studies'. There are 32 studies reporting point prevalence of depression out of the total 36 studies reporting prevalence of depression, with the remaining studies reporting lifetime prevalence. To enable further analysis, all effects have been labelled with the GFD status of the sample within each study i.e. if the sample includes participants that are all on the GFD (labelled: On GFD), the sample includes participants on the GFD and participants who are not on the GFD, but no distinction is made between them (Mixed GFD) or the sample is not on the GFD, for example because they are newly diagnosed (Not on GFD). In addition, studies were labelled with the depression measurement method which included self-report measures, clinician assessment or case note review. The distribution of primary study effects is shown in Figure 2.

Figure 2

QQ Plots of the Distribution of Prevalence Within the Primary Studies for the Random Effects Model (DerSimonian-Laird Estimate), Fixed Effects Model and Random Effects Model (Restricted Maximum Likelihood Estimate)



As can be seen from Figure 2, there is clear evidence of non-normality in the distribution of prevalence when the synthesis is calculated using the fixed effects model and the random effects model using the DerSimonian-Laird estimate of between studies variation. However, this non-normality is markedly reduced when using the random effects model calculated using the restricted maximum likelihood estimate of between studies variation. Therefore, this indicates the use of the restricted maximum likelihood estimator as the appropriate method for the calculation of the variation of the true effect, as this estimator has been shown to be more robust to deviations from normality (Banks et al., 1985).

The Omnibus Test

The prevalence rates (PR) described in the primary studies are reported in Table 7. There were 32 studies reporting a total of 11,209 participants with CD and 15,870 control group participants, for those studies with control groups. CD sample sizes ranged from 11 (O'Shaughnessy et al., 2022) to 4548 (Ludvigsson et al., 2007a). For this calculation, studies were categorised based on the reported outcome within the study– some studies explicitly stated the outcome was 'major depressive disorder' and therefore they were allocated to this grouping for analysis. For the rest, a type of depression was not explicitly reported therefore they were deemed to be reporting 'overall depression' symptomatology and diagnoses, thus allocated to this group for analysis.

Table 7

Study Level Effects of Depression in CD

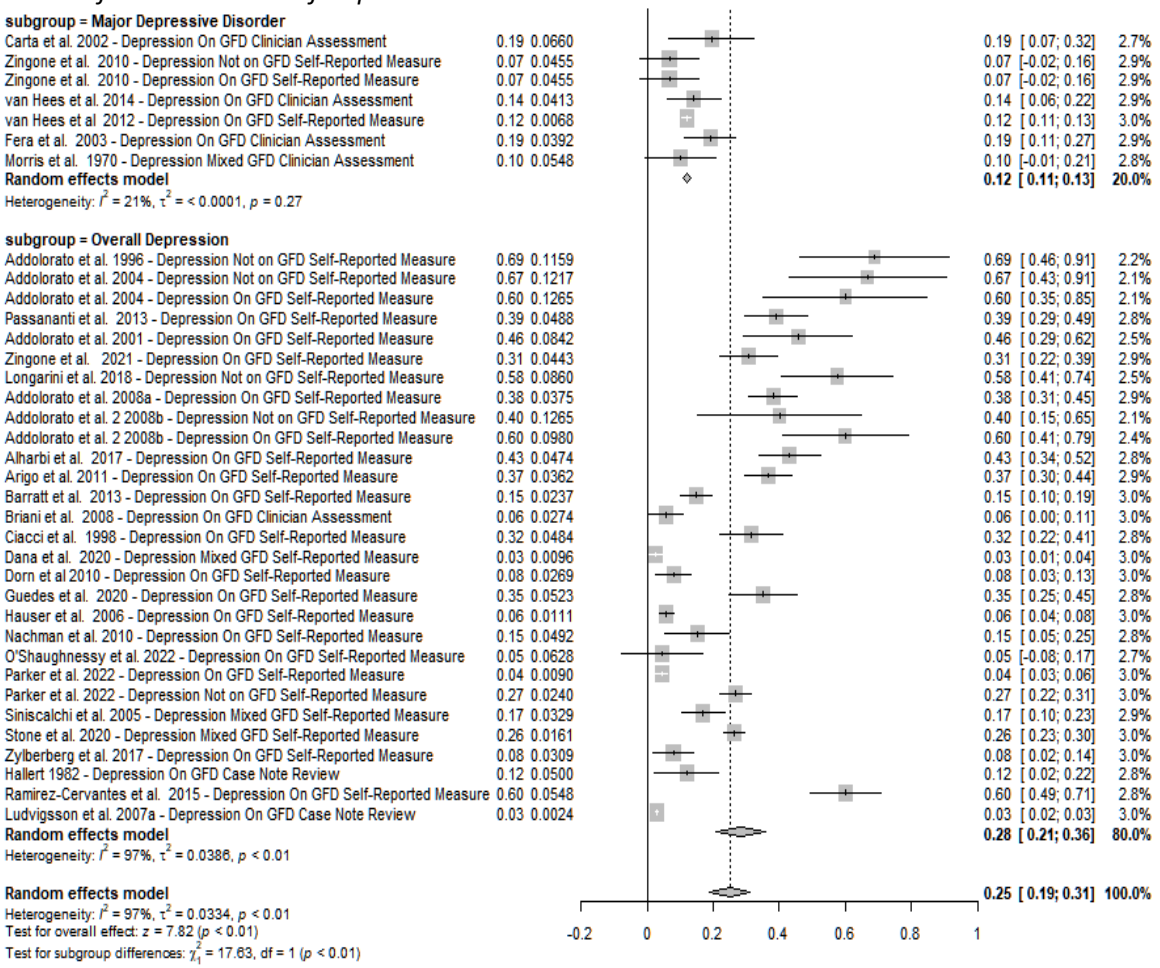
Study	GFD Status	Method of Depression Measurement/Identification	Prevalence Rate	Lower 95%-CI	Upper 95%-CI	% Weight
Major Depressive Disorder						
Morris et al. 1970	Mixed GFD	Clinician Assessment	0.10	-0.007	0.21	2.8
Zingone et al. 2010	Not on GFD	Self-report measure	0.07	-0.02	0.16	2.9
Carta et al. 2002	On GFD	Clinician Assessment	0.19	0.07	0.32	2.7
van Hees et al. 2014	On GFD	Clinician Assessment	0.14	0.06	0.22	2.9
Fera et al. 2003	On GFD	Clinician Assessment	0.19	0.11	0.27	2.9
Zingone et al. 2010	On GFD	Self-report measure	0.07	-0.02	0.16	2.9
van Hees et al. 2012	On GFD	Self-report measure	0.12	0.11	0.13	3
Overall Depression						
Dana et al. 2020	Mixed GFD	Self-report measure	0.03	0.007	0.04	3
Siniscalchi et al. 2005	Mixed GFD	Self-report measure	0.17	0.11	0.23	2.9
Stone et al. 2012	Mixed GFD	Self-report measure	0.26	0.23	0.30	3
Addolorato et al. 1996	Not on GFD	Self-report measure	0.69	0.46	0.91	2.2
Addolorato et al. 2004	Not on GFD	Self-report measure	0.67	0.43	0.91	2.1
Longarini et al. 2018	Not on GFD	Self-report measure	0.58	0.41	0.74	2.5
Addolorato et al.2008b	Not on GFD	Self-report measure	0.40	0.15	0.65	2.1
Parker et al. 2022	Not on GFD	Self-report measure	0.27	0.22	0.31	3
Hallert & Derefeldt, 1982	On GFD	Case Note Review	0.12	0.02	0.22	2.8
Ludvigsson et al. 2007a	On GFD	Case Note Review	0.03	0.02	0.03	3
Briani et al. 2008	On GFD	Clinician Assessment	0.06	0.003	0.11	3
Addolorato et al. 2004	On GFD	Self-report measure	0.60	0.35	0.85	2.1
Passananti et al. 2013	On GFD	Self-report measure	0.39	0.29	0.49	2.8
Addolorato et al. 2001	On GFD	Self-report measure	0.46	0.29	0.62	2.5
Zingone et al. 2021	On GFD	Self-report measure	0.31	0.22	0.39	2.9
Addolorato et al. 2008a	On GFD	Self-report measure	0.38	0.31	0.45	2.9
Addolorato et al. 2008b	On GFD	Self-report measure	0.60	0.41	0.79	2.4
Alharbi et al. 2017	On GFD	Self-report measure	0.43	0.34	0.52	2.8
Arigo et al. 2011	On GFD	Self-report measure	0.37	0.30	0.44	2.9
Barratt et al. 2013	On GFD	Self-report measure	0.15	0.10	0.19	3
Ciacci et al. 1998	On GFD	Self-report measure	0.32	0.22	0.41	2.8
Dorn et al 2010	On GFD	Self-report measure	0.08	0.03	0.13	3
Guedes et al. 2020	On GFD	Self-report measure	0.35	0.25	0.45	2.8
Hauser et al. 2006	On GFD	Self-report measure	0.06	0.04	0.08	3
Nachman et al. 2010	On GFD	Self-report measure	0.15	0.05	0.25	2.8
O'Shaughnessy et al. 2022	On GFD	Self-report measure	0.05	-0.08	0.17	2.7
Parker et al. 2022	On GFD	Self-report measure	0.044	0.03	0.06	3
Zylberberg et al. 2017	On GFD	Self-report measure	0.08	0.02	0.14	3
Ramirez-Cervantes et al. 2015	On GFD	Self-report measure	0.60	0.49	0.71	2.8

A random effects models was calculated using the generic inverse variance method and a forest plot of this is shown in Figure 3. The random effects model suggested a weighted average prevalence rate of 0.12 (95% CI 0.11 to 0.13) for major depressive disorder and a weighted average prevalence rate of 0.28 (95% CI 0.21 to 0.36) for overall depression. Therefore, the weighted average prevalence for those with CD was 12% for major depressive disorder and 28% for overall depression.

The difference between the prevalence rates for major depressive disorder and overall depression were statistically reliable (X^2 = 17.63, p < 0.01). Whilst this difference was observed, it is unclear of the distinctness of the 'major depressive disorder' group vs the 'overall depression' group. This is due to the way in which studies report depression and how this may have changed over time, with the changing of diagnostic labelling. It is not clear whether studies that report 'depression' as a single construct, may actually be reporting the prevalence of 'major depressive disorder'. The 'major depressive disorder' group is also a relatively small number of studies and contains a number of older studies, thus less robust and giving an older estimate of prevalence. Therefore, due to lack of clarity in this, for further analyses these groups have been combined and no distinction is made between types of depression that studies are reporting.

Figure 3

Forest Plot of the Prevalence of Depression in Coeliac Disease



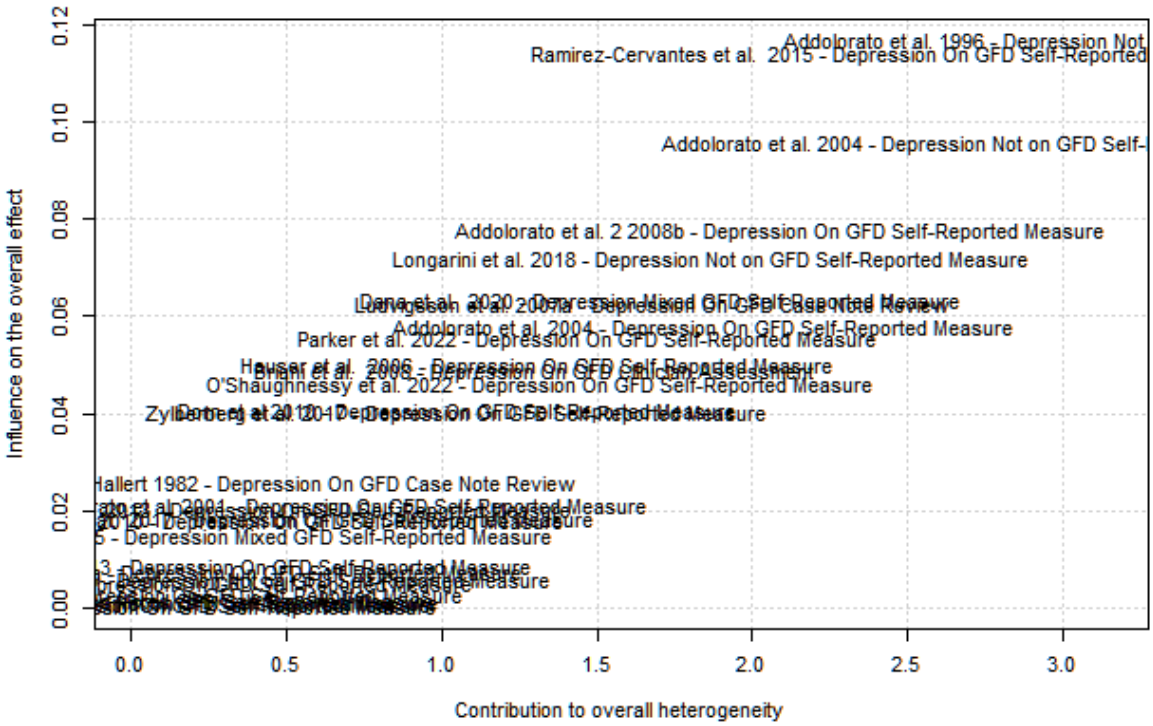
For overall depression, a high level of heterogeneity between studies was observed (tau^2 = 0.033, Higgin's I^2 = 97%; $p < 0.01$), suggesting that the estimates of prevalence rates in the included studies may be biased by the presence of uncontrolled or confounding factors. Therefore, the focus of the subsequent analyses will be upon the identification of the sources of heterogeneity between the estimates of prevalence. As previously stated, for subsequent analyses there is no distinction between 'major depressive disorder' and 'overall depression', they are combined.

The Impact of Influential Primary Studies

The impact of disproportionately influential studies was assessed using a "leave-one-out" analysis, in which the random effects model was calculated with each of the primary studies removed in turn, and change in weighted average effect size (i.e., influence) and the change in heterogeneity (i.e., discrepancy) was recorded. The result of this "leave-one-out" analysis is presented on the Baujat plot (Baujat et al., 2002) in Figure 4. This calculation was performed for all 32 primary studies (major depressive disorder and overall depression combined).

Figure 4

Baujat Diagnostic Plot of Sources of Heterogeneity



Note. The vertical axis reports the influence of the study on the overall effect and the horizontal axis reports the discrepancy of the study with the rest of the literature.

As can be seen from Figure 4, three studies (Addolorato et al., 1996; Addolorato et al., 2004; Ramirez-Cervantes et al., 2015) were in the area of the Baujat plot (top right) that is associated with influential studies reporting results discrepant from the rest of the literature.

The random effects model was recalculated with each of the three studies showing disproportionate influence removed. The corrected random effects models are reported in Table 8. As can be seen, there was little change (relative to the overall pooled estimate) in the random effects model when omitting studies showing disproportional influence and there was no substantive difference in conclusion from omitting any of these studies.

Table 8

The Impact of Removing Studies Showing Disproportional Influence

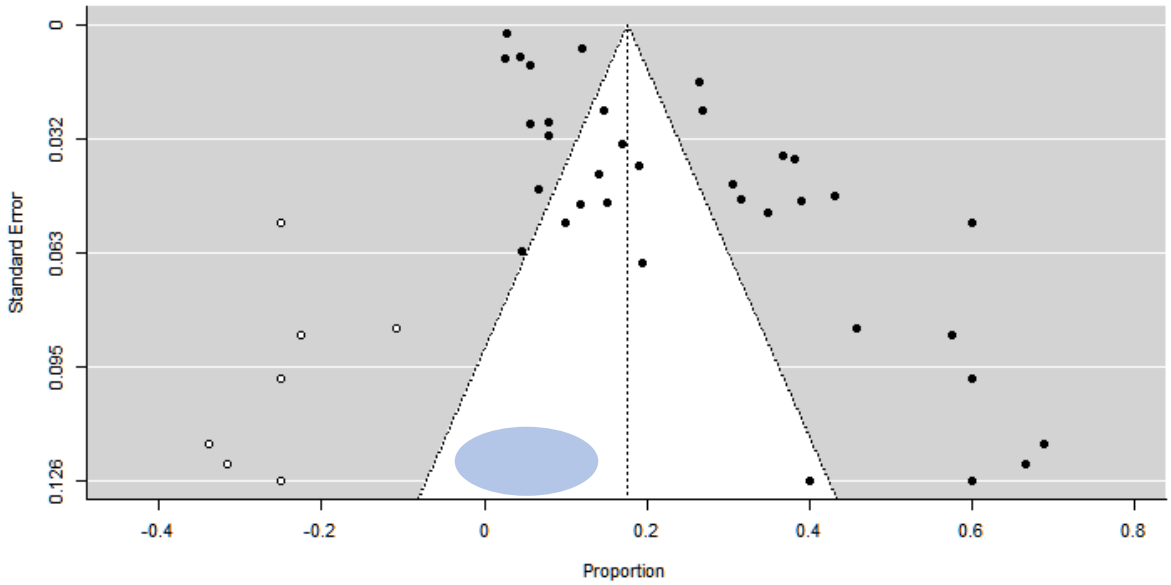
Study Omitted	PR	95%-CI	*p*-value	Tau^2	tau	I^2	% Change
Omitting Addolorato et al. 1996	0.26	0.19 - 0.34	< 0.01	0.04	0.19	97.30%	4.50%
Omitting Addolorato et al. 2004	0.27	0.19 - 0.34	< 0.01	0.04	0.19	97.30%	4.07%
Omitting Ramirez-Cervantes et al. 2015	0.26	0.19 - 0.34	< 0.01	0.04	0.19	97.10%	4.46%
Pooled estimate	0.28	0.20 - 0.35	< 0.01	0.04	0.20	97.30%	

The Impact of Publication and Small Study Biases

Publication bias is caused by the tendency for statistically significant results to be published and the reticence to publish papers with non-significant results. Small study bias is the tendency for studies with smaller sample sizes to show greater variability in their measurement of prevalence rates. These biases can be identified in a funnel plot, which plots the magnitude of a study's prevalence rate (i.e., the importance of the study in the synthesis) against the precision of the measurement (i.e., the study's sample size). If there is an absence of publication bias, the effects from the studies with small sample sizes which show greater variability, will scatter more widely at the bottom of the plot compared to studies with larger samples at the top which will lie closer to the overall meta-analytic effect, creating a symmetrical funnel shape. If there is an absence of studies in the area of the plot associated with small sample sizes and non-significant results (marked in blue on Figure 5), then it is likely there is some publication bias leading to an overestimation of the true effect. The funnel plot of depression prevalence rates is presented in Figure 5.

Figure 5

A Funnel Plot of the Prevalence of Depression in CD



Note. The 95% confidence interval of the expected distribution of depression is shown as an inverted "funnel". The white point are studies imputed by the trim and fill procedure (Duval & Tweedie, 2000). The area marked in blue is the area of the funnel plot this is associated with null effects in small studies.

As can be seen from Figure 5, there is evidence of publication bias in the distribution of prevalence rates. The effect of publication bias was simulated using a trim and fill procedure (Duval & Tweedie, 2000). The trim and fill procedure builds on the assumption that publication bias would lead to an asymmetrical funnel plot. The trim and fill procedure iteratively removes the most extreme small studies from the side of the funnel plot associated with positive effects, re-computing the effect size at each iteration until the funnel plot is symmetric about the (corrected) effect size. While this trimming yields the adjusted effect size, it also reduces the variance of the effects, resulting in biased and narrow confidence intervals. Therefore, the original studies are returned into the analysis, and the procedure imputes a mirror image for each on the side of the funnel plot associated with negative effects. The trim and fill procedure yielded a corrected random effects model of 0.18 (95% CI 0.14 - 0.21). The corrected random effects model evidences an approximately 31% decrease relative

to the uncorrected estimate of depression point prevalence (0.28), so the depression prevalence estimate is lower than original analyses when corrected for this bias.

The Effect of Risk of Bias in the Primary Studies

In order to assess the impact of study level risk of bias upon heterogeneity, a series of subgroup analyses were conducted on the prevalence rates for the risk of bias ratings of "low risk" and "any risk" (i.e., unclear risk and high risk of bias combined) for each of the six types of methodological bias (Table 9). Statistically significant difference estimates of prevalence were highlighted for selection bias, statistical bias and reporting bias.

Table 9

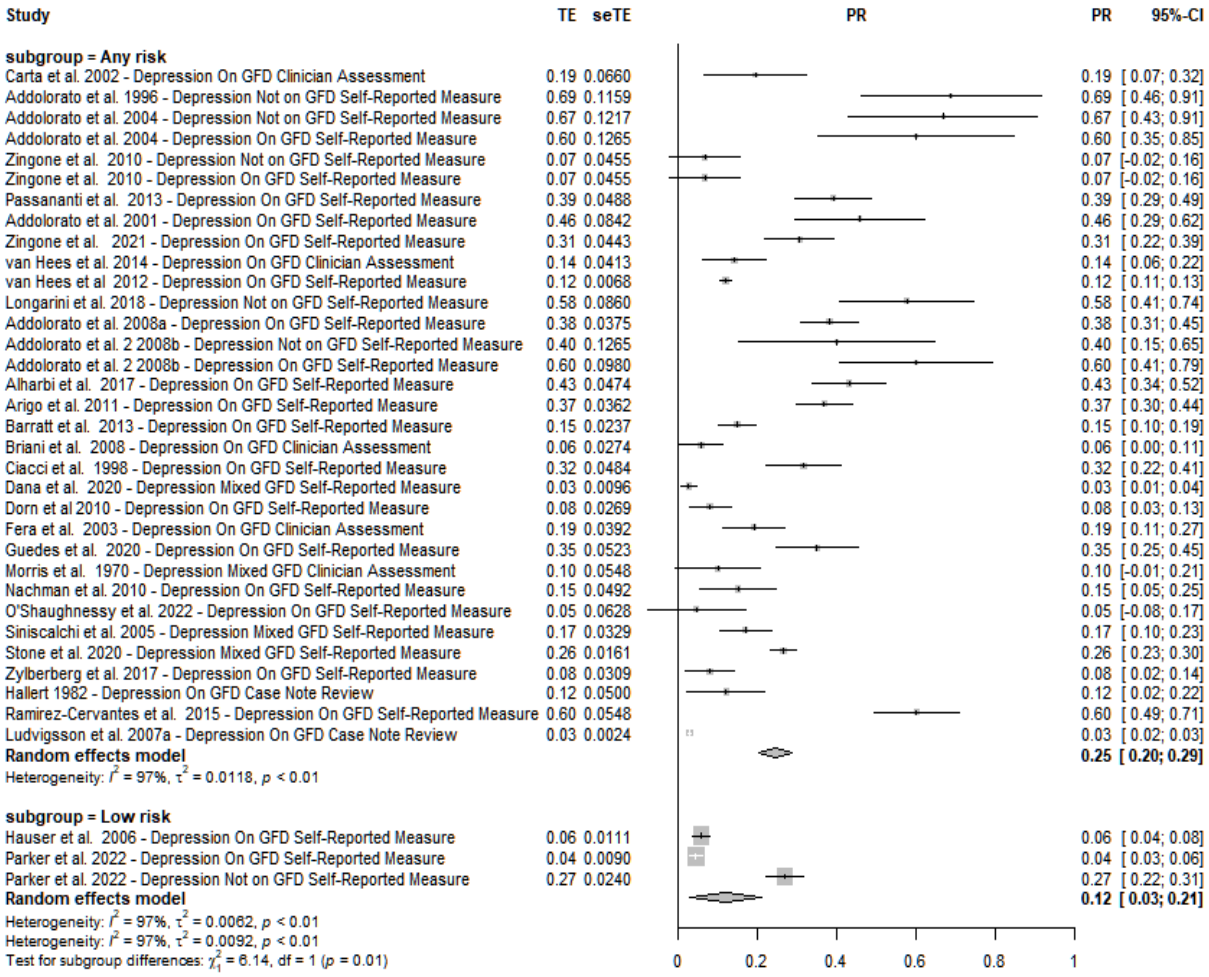
The Impact of 'Low Risk' and 'Any Risk' upon the Prevalence Rates (PR) of Depression

Type of Bias	Low Risk			Any Risk				
	PR	95% CI	*k*	PR	95% CI	*k*	X^2	*P*
Selection bias	0.12	0.03 -0.21	3	0.25	0.20 - 0.29	33	6.14	0.01
Performance bias	-	-	-	0.23	0.19 - 0.26	36	-	-
Detection bias	0.23	0.19 - 0.27	31	0.21	0.03 - 0.40	31	0.03	0.86
Statistical bias	0.28	0.22 - 0.33	22	0.17	0.12 - 0.21	14	9.25	0.002
Reporting bias	0.32	0.24 - 0.41	17	0.18	0.14 - 0.22	19	8.62	0.003
Generalisability bias	0.21	0.18 - 0.25	26	0.32	0.18 - 0.47	10	2.17	0.14

Selection bias showed statistically significant difference estimates of prevalence (see Figure 6), with lower levels of bias being associated with lower estimates of prevalence. This suggests that inclusion of studies that are at risk of selection bias may increase the estimate of the depression prevalence.

Figure 6

The Effect of Selection Bias on the Estimate of Depression Prevalence



Statistical and reporting biases evidenced statistically significant difference estimates of prevalence (Figure 7 and 8 respectively), with lower levels of bias being associated with higher estimates of prevalence. This suggests that inclusion of studies that are at risk of statistical and reporting biases bias may decrease the estimate of the depression prevalence.

Figure 7

The Effect of Statistical Bias on the Estimate of Depression Prevalence

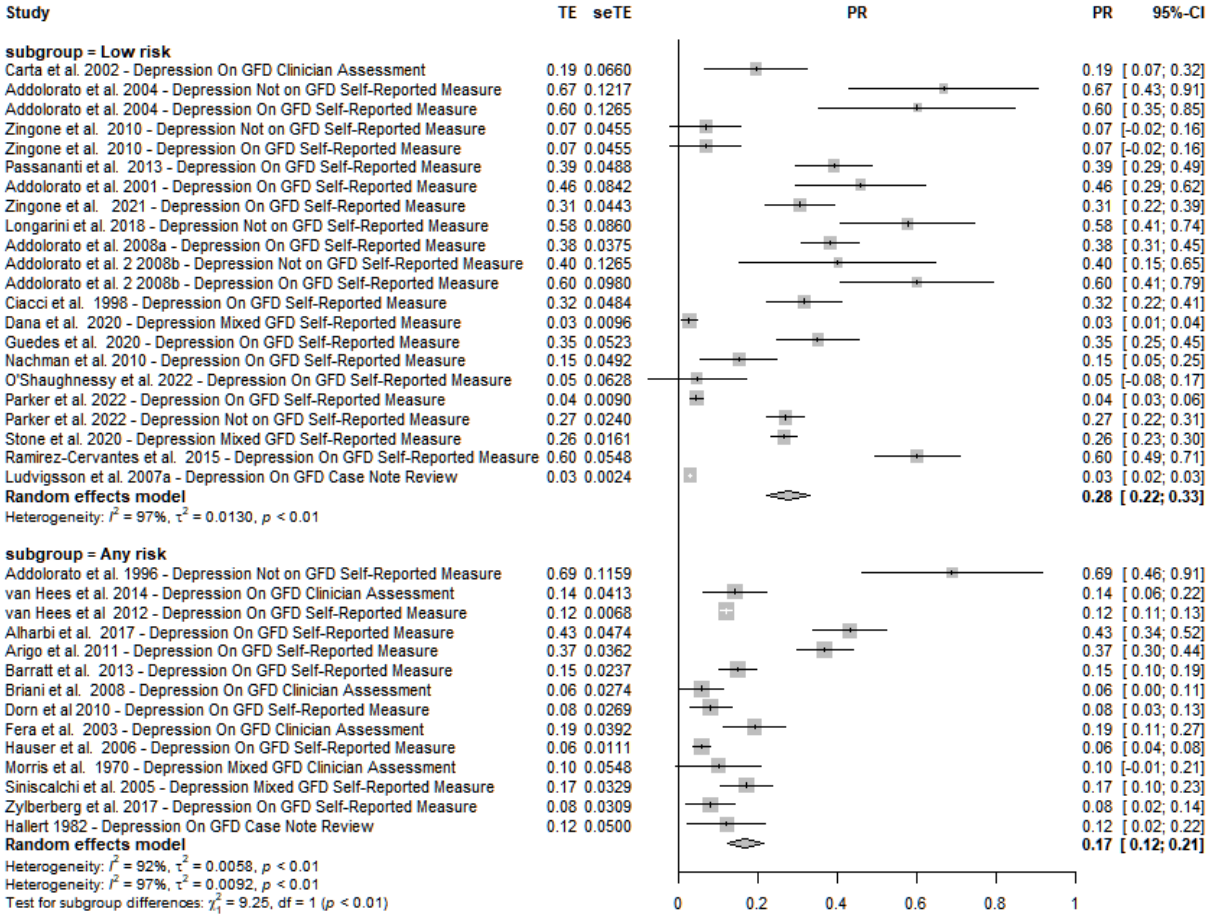
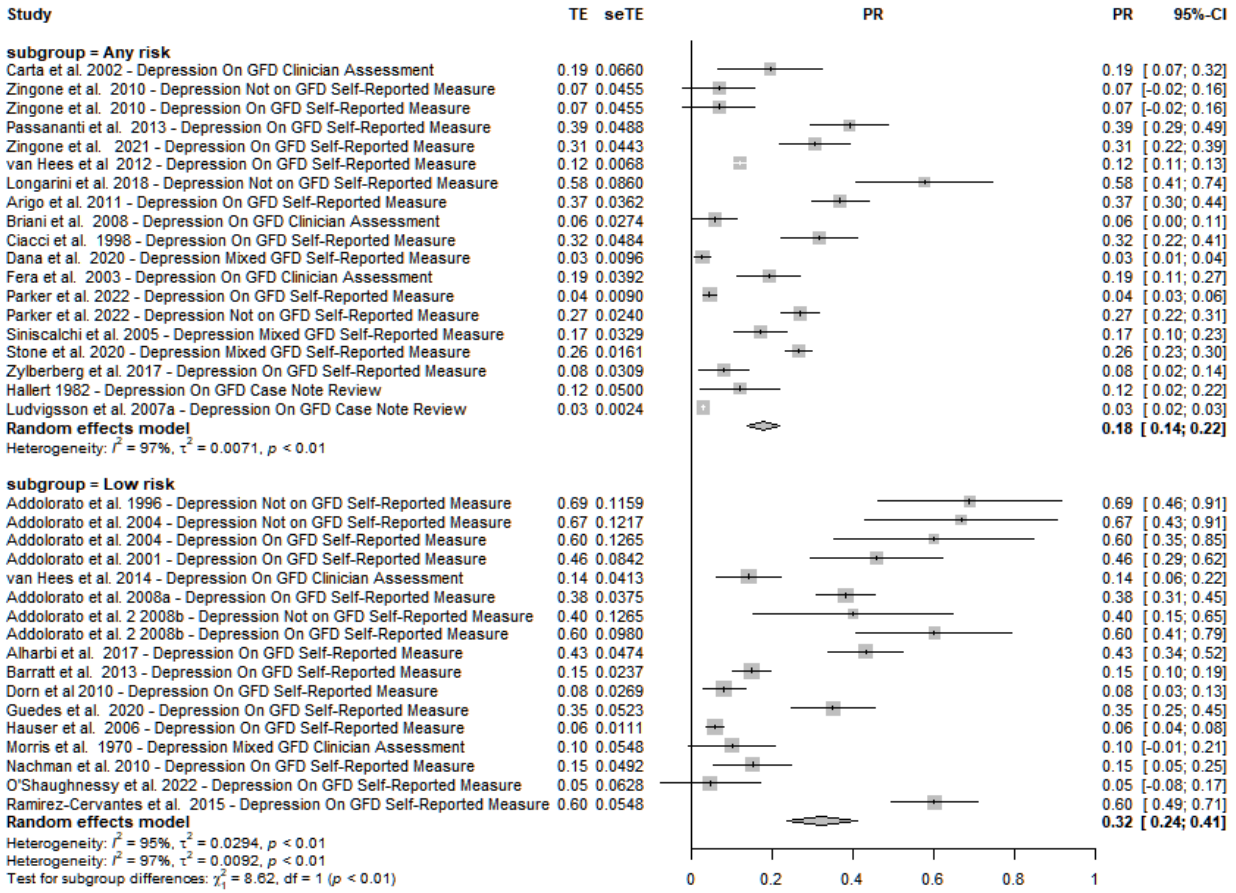


Figure 8

The Effect of Reporting Bias on the Estimate of Depression Prevalence



The Difference Between Point Prevalence and Lifetime Prevalence

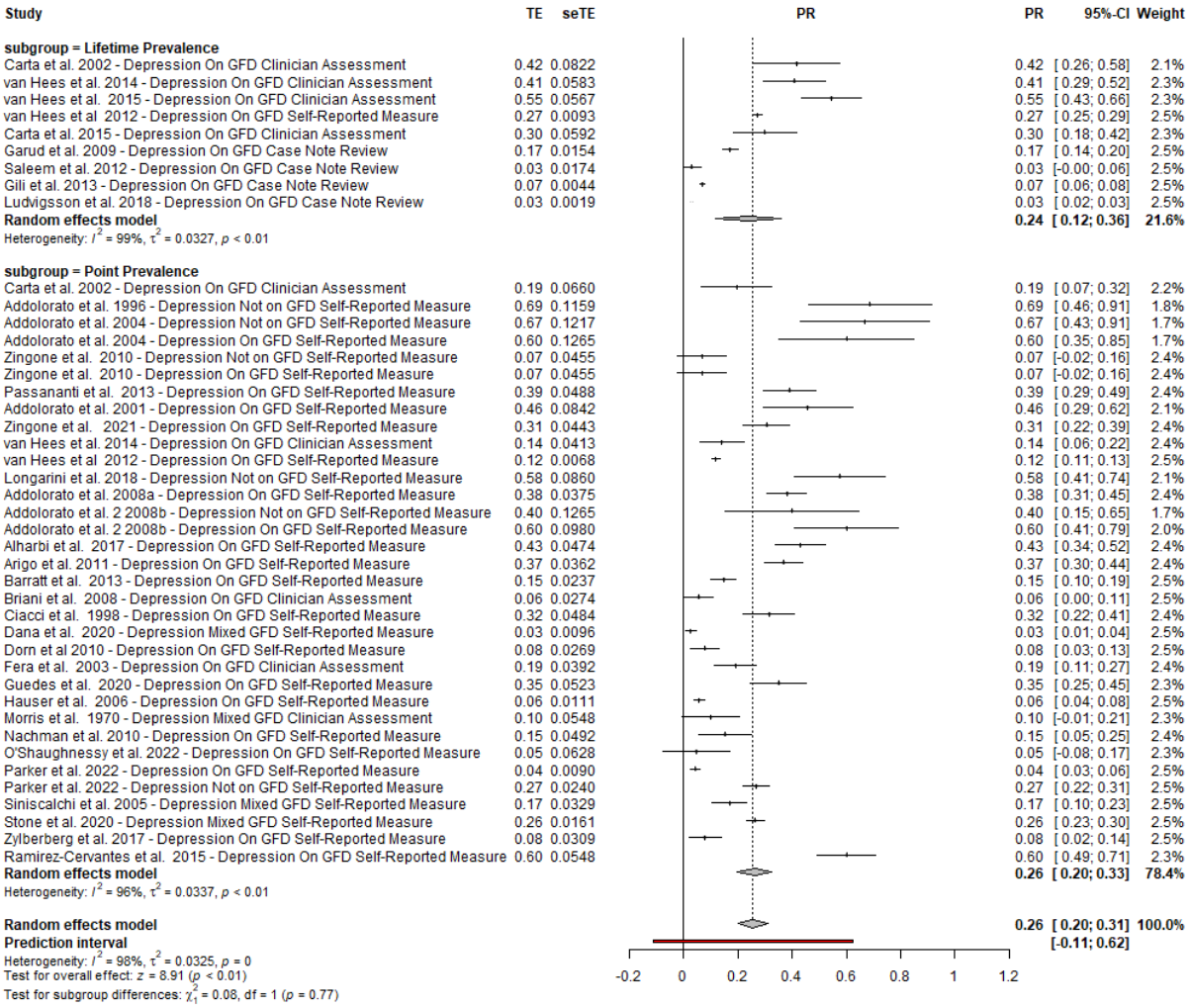
A sub-group analysis was undertaken to explore the difference between estimates of point prevalence and lifetime prevalence of depression (see Figure 9). Based upon previous risk of bias analyses, no studies were excluded and therefore this analysis was performed on all studies reporting depression in individuals with CD. This was important to investigate as many of the studies presenting lifetime prevalence data did not explicitly state when diagnosis or measurement of depression had occurred, which means that depression may have been identified in childhood and this meta-analysis has a focus upon depression in adults with CD. Therefore, it is not possible to state whether the

prevalence estimates are contaminated with childhood data. Hence, the decision to use point prevalence data as the 'primary' studies and compare this to lifetime prevalence data.

There was no significant difference (X^2 = 0.08, p = 0.77) between the point prevalence estimate of depression (0.26, 95% CI 0.20 to 0.33) and the lifetime estimate of depression prevalence (0.24, 95% CI 0.12 to 0.36). Therefore, despite the above identified issues with lifetime prevalence data, no significant differences in prevalence estimates were identified.

Figure 9

The Comparison of Prevalence Rates between Point and Lifetime Prevalence Rates of Depression

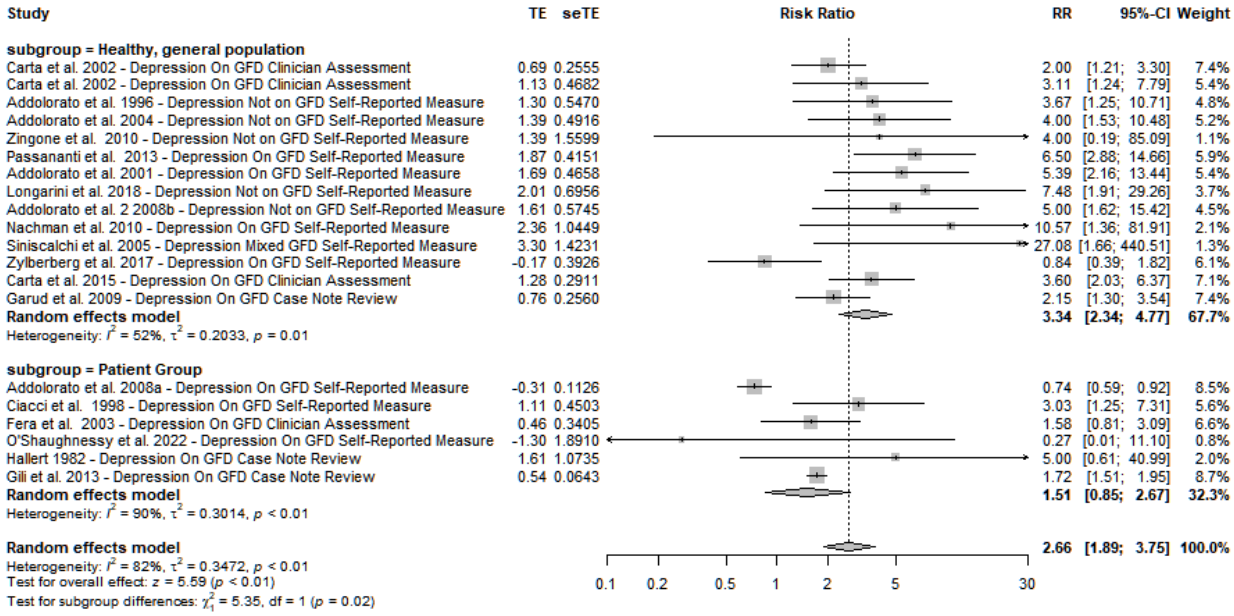


The Relative Risk of Depression

Studies that included estimates of the prevalence of depression in a CD sample and estimates of the prevalence of depression in a contrast group were used to estimate the relative risk of depression (see Figure 10). All calculations were performed on the log transformed relative risk however this was converted back into relative risk ratios for reporting in Figure 10. Studies that reported depression rates in other chronic conditions (such as diabetes, irritable bowel disease, hypertension and hepatitis C) were included in the comparison as a patient group. There were 12 studies that reported data on depression for a healthy, general population sample and 6 studies that reported data for a patient sample. Study labels (such as GFD status and measurement) type refer to only the CD status of the study's sample, and not to the patient group, and were used to easily distinguish effects in this meta-analysis, so are to be disregarded in this analysis.

Figure 10

The Relative Risk of Depression in the General and a Patient Population in Comparison to Individuals with CD



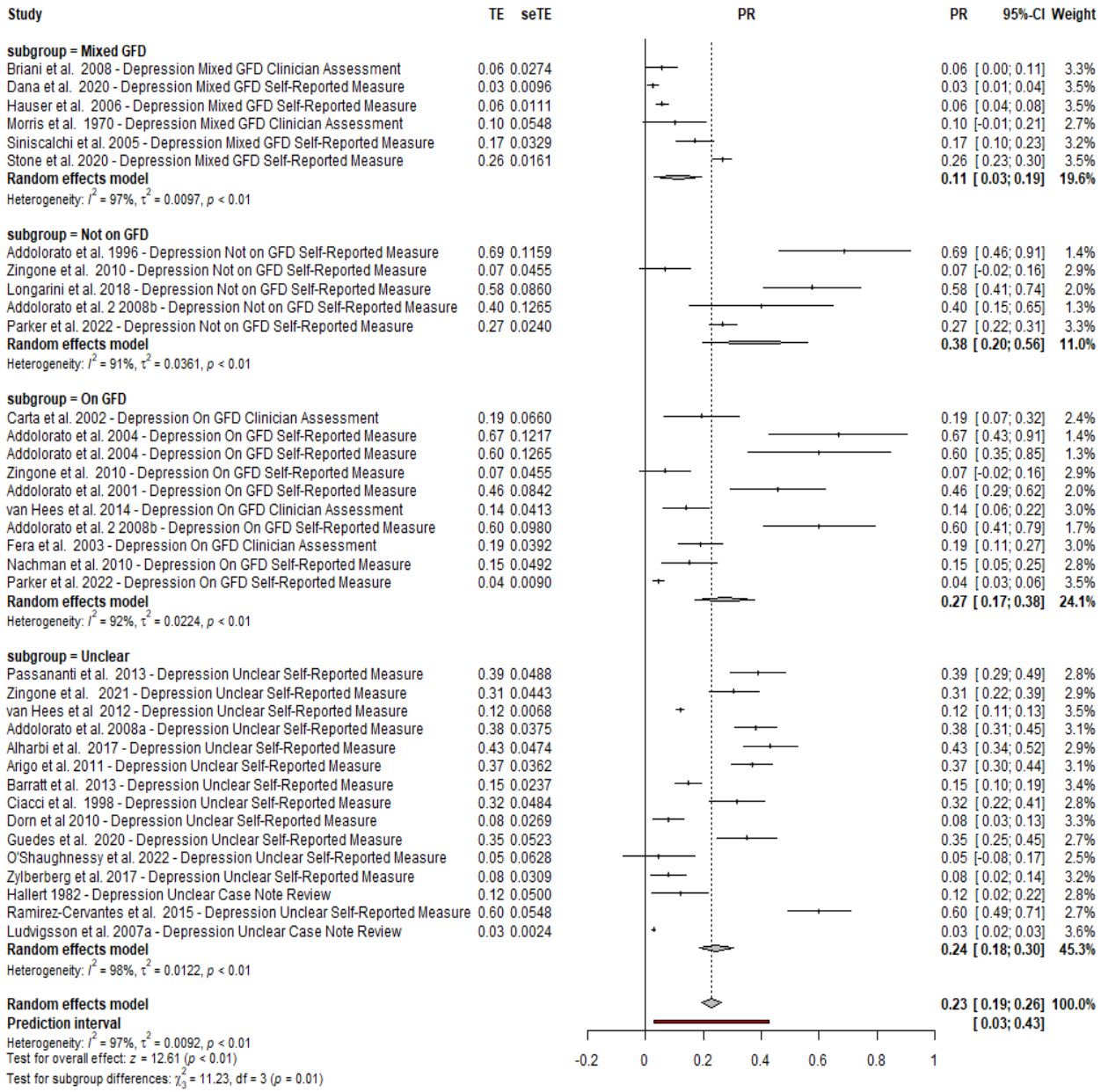
An increased relative risk (RR) of depression was observed when individuals with CD were compared with the general population (RR = 3.34, 95% CI 2.34 to 4.77). There was a significant difference (X^2 = 5.35, p = 0.02) in the relative risk of depression in the CD condition when compared to the general population or patient group. Whilst the overall relative risk of depression for individuals with CD was 1.51 when compared to the patient group, 95% confidence intervals span around 1 (.85 to 2.67). Therefore, it is uncertain whether there is a true difference in risk, or the result is due to chance. Based on the confidence intervals, it can only be concluded that there is likely no statistically significant difference in the relative risk of depression between those with CD and other patient groups.

The Effect of a Gluten Free Diet on Rates of Depression in CD

A subgroup analysis was undertaken comparing the prevalence of depression based upon the GFD status of the samples. GFD status was categorised into four groups from study descriptions: those on a GFD (labelled - on GFD), those not on a GFD (labelled - not on GFD), samples that stated that some participants were on a GFD and some were not (labelled - mixed GFD) and finally, samples that the study did not state the GFD status for (labelled - unclear). A significant difference (X^2 = 11.23, p = 0.01) was observed between groups, with the highest prevalence level reported for those not on the GFD (n = 5) compared to on the GFD (n = 9), mixed GFD (n = 6) and unclear GFD status (n = 15). (Figure 11). Therefore, not being on the GFD was associated with the highest prevalence level of depression. However, there was high heterogeneity within all groups and each group contained a small number of studies. Furthermore, it cannot be deduced the composition of the 'unclear' and 'mixed GFD' groups, therefore these estimates need to be interpreted with caution and may change upon clarification of this and the publication of further studies.

Figure 11

The Comparison of Depression Prevalence Estimates Between GFD Status



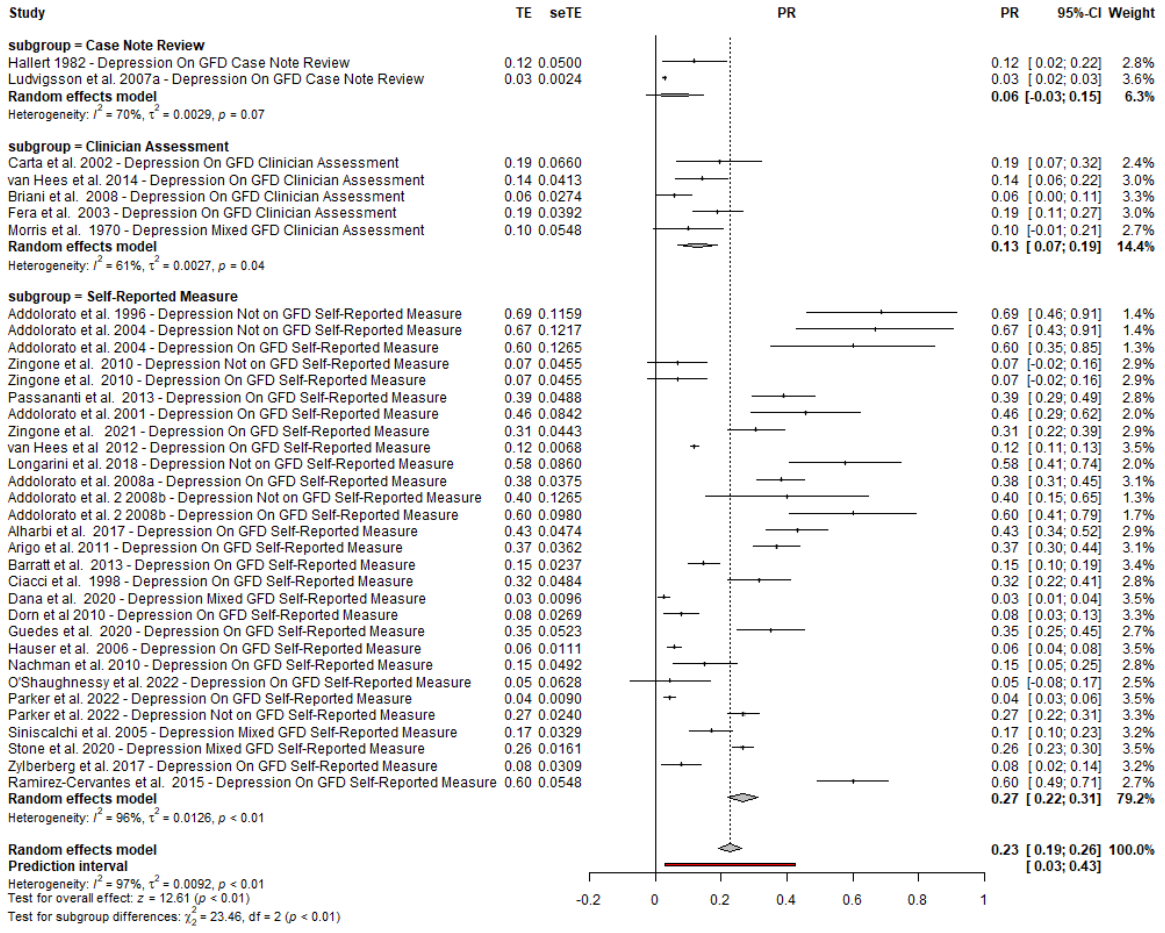
The Effect of Measurement Type on the Rates of Depression in CD

A subgroup analysis was undertaken comparing the ways in which depression was measured across studies – through self-report measures (such as the Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith, 1983) and the Patient Health Questionnaire (PHQ-9) (Kroenke & Spitzer,

2002), standardised clinician assessment and through identifying disorder through a case note review. A statistically significant difference (X^2 = 23.46, p < 0.01) was observed between groups, with a higher prevalence level being reported for studies using self-report measures (n = 25) compared to clinician assessment (n = 5) and case note reviews (n = 2) (Figure 12). Therefore, a self-report measurement of depression is associated with a higher level of depression prevalence. However, only two studies were included for case note review and only five for clinician assessment, therefore these estimates should be interpreted with caution and may change with the publication of further studies.

Figure 12

The Comparison of Depression Prevalence Estimates Between Measurement Types



Discussion

Summary of Findings

The main aim of this meta-analysis was to describe and evaluate the current literature estimating the prevalence of depression in adults with a diagnosis of CD. This review expanded upon previous literature reviews by including a larger number of studies, evaluating person and study characteristics, searching multiple databases, and including studies that identified depression in various ways including through self-report measures, clinician assessment and through case note reviews. Overall, this meta-analysis estimated a point prevalence of depression of 26% and lifetime prevalence of 24% in individuals with CD, which contrasts with an estimated global depression prevalence of 5% of adults in the general population (IHME, 2019). There was no significant difference between the point and lifetime prevalence estimates of depression. This may suggest that for some with CD, depression may be persistent, reoccurring, or pervasive. However, many of the studies included in this meta-analysis give no information on the persistence or reoccurrence of depressive symptoms nor the timing of depressive symptoms; whether it was prior to CD diagnosis, or related to other significant events, for example. Given that the definition of lifetime prevalence is simply the proportion of a population who, at some point in life has ever had the characteristic, the only conclusions that can be taken from the studies presenting lifetime prevalence in this meta-analysis is that clinical depressive symptoms have occurred at least once in the research sample's lives, which could have been before adulthood and that the prevalence of previous events is similar to point prevalence rates. A recent study on this topic found that there was a significant improvement in the depression, anxiety and quality of life scores from diagnosis to 24 months post diagnosis, for individuals with CD, and multivariate analyses revealed that adherence to the GFD was the most influential factor in this improvement, compared to age, gender and type of CD (Canova et al., 2021). Other, more dated research has suggested that depression may persist over time in CD; Addolorato et al. (2001) found that when comparing between newly diagnosed and one year on the GFD, whilst

state anxiety significantly decreased over this time period, there was not a significant decrease in trait anxiety or depression. Due to this mixed picture, to analyse the persistence and reoccurrence of depression in CD, further data needs to be evaluated with this question as a focus. This has clinical importance in the mental health service planning for individuals with CD, such as in the use of screening programmes, intensity of interventions and level of support that might be needed in helping to manage their CD. Research in other populations with long term health conditions, such as Hepatitis C, has shown a significantly higher rate of recurrent brief depression (RBD) over time in comparison to controls (Carta et al., 2012) whereas for Type 2 Diabetes, 66% of a sample who initially met the criteria for depression on the Edinburgh Depression Scale (de Cock et al., 2011), experienced reoccurring or persistent depressive symptoms over a 3 year period (Nefs et al., 2012; Pouwer et al., 2020). Therefore, CD may follow a similar course.

In addition, this meta-analysis explored the heterogeneity between studies, which was found to be high between primary studies, suggesting that estimates of depression prevalence may be biased by the presence of uncontrolled and confounding factors. Whilst there was no substantive difference in overall conclusions when the impact of influential studies was evaluated, it was revealed that there was likely some publication bias leading to an overestimation of the true effect. When corrected for publication bias, a prevalence rate of 18% was estimated for depression in individuals with CD compared with a 28% uncorrected score for the point prevalence of depression. Therefore, true depression prevalence rates may be lower than the literature suggests when accounting for biases. Furthermore, the analysis revealed that those studies with higher selection bias were associated with higher estimates of depression prevalence, and studies with higher statistical and reporting bias was associated with lower estimates of depression prevalence. This is important to consider when understanding the literature and designing future studies.

A further finding of the initial analyses revealed that there was a significant difference in the prevalence rates of depression between studies reporting 'major depressive disorder' (12%) to studies reporting simply 'overall depression' (28%). This finding may be important in understanding the patterns and presentation of depression in CD. Across diagnostic manuals such as the DSM-5 (5th ed.; DSM-5; American Psychiatric Association, 2013), 'major depressive disorder' is generally understood to be a severe form of depression with a significant impact. 'Overall depression', whilst not a diagnostic term, may be assumed to be a broader category, encompassing milder forms of depression. However, diagnostic criteria for 'major depressive disorder' or similar diagnoses such as 'major depressive episode', have evolved and changed over time, as has the use of diagnostic language in clinical practice, research and society. Therefore, it was unclear how the terms 'major depressive disorder' and 'depression' were used and understood across the studies, and the terms could have been used interchangeably. This led to a lack of clarity about the distinctness between the 'major depressive disorder' group and 'overall depression' group. Thus, there is uncertainty in that those studies reporting 'depression' may also have included participants with symptoms that would meet 'major depressive disorder' criteria. Therefore, to remove this ambiguity and to meet the aims of this meta-analysis, which focused on the factors influencing the prevalence of depression, rather than types of depression alone, the groups were combined for all further analyses. However, due to the significant difference found between groups, an alternative approach could have been to explore prevalence rates within these two groups further, which would have clinical implications for the types of intervention that individuals with CD may require, as initial analyses suggest that 'overall depression' is more prevalent than more severe depression. This would require clarification of the specific definitions of 'major depressive disorder' and 'overall depression'.

Findings in Context

The findings of this meta-analysis can be considered within the wider existing literature. A recent meta-analysis by Sharma et al. (2021) found that depression was 1.55 times more likely in

individuals with CD than controls. This is in comparison to this meta-analysis, estimating that individuals with CD are 3.34 times more likely to develop depression compared to the general population and probably at a similar risk rate to other patient populations with chronic conditions. One reason for the discrepancy in this risk rate is that Sharma et al. (2021) included only five studies in their analysis. Similarly, Clappison et al. (2020) found that the odds of having depression was significantly higher for those with CD; however, they found a pooled prevalence of depression in CD of 4%. Furthermore, another meta-analysis found that the depression rate in CD is similar to that of other chronic or autoimmune conditions (Smith & Gerdes, 2012).

The findings that those not on the GFD show higher depression rates relative to those on the GFD is in line with existing literature (Cossu et al., 2017; Sainsbury & Marques, 2018). This reflects an important factor in understanding the association between CD and depression, with important clinical implications. Research generally accepts that there is a bidirectional relationship, in that depression may make it more difficult to adhere to the GFD, and that lower levels of adherence to the GFD may lead to increased depression (Cossu et al., 2017). Whilst there are many suggested factors that may make it harder for an individual to adhere to the GFD, such as poor education from health professionals about the GFD, low motivation and the financial cost, it is also suggested that regular dietetic reviews are associated with higher adherence (Abu-Janh & Jaana, 2020; Hall et al., 2009). Therefore, embedding these into medical services may not only increase adherence to the GFD, and reduce the health complications associated with untreated CD, but also reduce levels of depression. In terms of the possible causal mechanisms for depression in those with CD, these findings may provide support for the hypotheses that mental health disorders may be related to elements of the GFD, such as resulting from nutritional deficiencies (Campagna et al., 2017) or from the direct effect of gluten ingestion upon neurotransmitters or the CNS (Cossu et al., 2017; Kukla et al., 2015).

Another interesting finding relates to how depression was measured across the studies; it was found that studies that used self-report measures of depression and report the number of participants above a clinical cut off score, such as the HADS (Zigmond & Snaith, 1983) and PHQ-9 (Kroenke & Spitzer, 2002), were associated with higher estimates of depression prevalence. This may be expected given that self-report can be biased in leading to a substantial overestimation of the prevalence of depression than those who might meet depression diagnostic criteria through a clinician assessment (Thombs et al., 2018). However, measurement by clinician assessments can be costly in terms of resources such as time and people, and therefore is not always feasible in collecting data of large quantities. Therefore, alternative methods have been proposed of calculating prevalence estimates from self-report measures, such as 'back calculation', which involves adjusting the percentage above a cut-off threshold by existing estimates of sensitivity and specificity (Leeflang et al., 2013; Thombs et al., 2018).

Strengths and Limitations

This review had strength in synthesising the breadth of literature reporting an association between CD, depression, and other mental health disorders, and strengthening the conclusion that CD and depression are associated. The review identified the prevalence of mental health disorders, and not just the presence of any symptomatology. Identifying clinical levels of these disorders is important, as this is where psychological support is likely to be focused. The findings from this review have important implications for those designing and administering services to individuals with CD; it suggests that mental health screening and intervention should be an essential part of CD care, particularly focused on helping individuals maintain a GFD. A further strength of this review was the use of a wide, inclusive search strategy which meant that a large number of studies were able to be reviewed, increasing the robustness and validity of the findings.

However, the inclusive search meant that some differences or variables that may have implications for the estimated prevalence rates of depression and other mental health difficulties were not controlled for within the search strategy. For example, in requiring a study to only include participants who have a CD diagnosis via duodenal biopsy, to report on any historical mental health disorders or to specify a certain study design, as in Sharma et al., 2021. Therefore, there may be factors that were uncontrolled for that have influenced the prevalence rate estimates revealed by this meta-analysis, which may include study quality as well as participant characteristics. A further limitation of this review is that studies were included in which the primary aim of the research may not have been to measure depression and other mental health disorders. These studies may not have been optimised to detect mental health disorders and therefore prevalence rates may differ across studies, based on whether it was their primary or secondary aims to measure mental health disorders in a CD population.

Future Research

In terms of future research, future research and reviews would benefit from assessing mental health disorders over time for those with CD, starting at pre-diagnosis. Due to a minimal number of studies exploring this, this was not able to be analysed as part of this meta-analysis, however previous research has suggested that anxiety and depression may be a feature pre-diagnosis, and that anxiety may then reduce following the GFD but depression remains (Addolorato, 2001). In addition, changes in the identification and diagnosis of mental health disorders over time should be considered. As part of the inclusive search, the meta-analysis included older studies, such as Morris et al. (1970), however over time DSM and ICD codes for the included mental health disorders have changed, as well as the way in which they are recorded and reported. This may have implications for prevalence rates and could be further investigated. Furthermore, based on the increased risk of eating disorders and bipolar disorder revealed in the meta-analysis for those with CD, further exploration of this association could have important clinical implications in supporting individuals

with CD. When conducting the search for this meta-analysis, there were many studies that were relevant and appeared beneficial to this exploration, however the results were presented in a format that meant that event rates of depression or other mental health disorders could not be established, such as only presenting means and standard deviations (e.g., Barberis et al., 2019). Therefore, the prevalence estimates from this meta-analysis are based on studies that provided results in an appropriate form and may change through inclusion of these studies. This has implications for other researchers in presenting their data.

Conclusion

To conclude, this meta-analysis used an inclusive approach to provide current prevalence estimates of depression in CD and confirms previous literature suggesting increased risk for those with CD. The aim now is to continue understanding the mechanisms and direction of this relationship in order to implement the appropriate support within healthcare services to minimise the occurrence of depression.

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3. Empirical Research Paper:

Understanding the Experience of 'Brain Fog' in Coeliac Disease: An Interpretative Phenomenological Analysis

Abstract

Coeliac disease (CD) can present with a wide variety of symptoms, both intestinal and extra-intestinal. 'Brain fog' is an extra-intestinal symptom that whilst commonly reported anecdotally by the CD community and in some of the literature, may not always be associated with CD by health professionals or organisations such as Coeliac UK. This study aimed to qualitatively explore the lived experiences of 'brain fog' for the first time in individuals with recently diagnosed CD. Seven participants with CD who reported having experienced 'brain fog' were recruited through social media and took part in an online semi-structured interview. Interviews were analysed using interpretative phenomenological analysis (IPA). Four Group Experiential Themes (GETs) emerged from the data, 'The Course of Brain Fog', 'Physical Symptoms Take Priority', 'Lost in the Fog' and 'The Gluten Free Diet isn't Always a Magic Cure'. Overall, varied cognitive symptoms were reported including difficulties in memory, language, and attention. Furthermore, participants described significant and widespread social, work and emotional impacts of 'brain fog' and for some, the symptoms continue despite introduction of the gluten free diet (GFD). Findings from this study align with previous existing literature and contribute to recognising 'brain fog' as a formal symptom of CD by health professionals. Furthermore, the findings also suggest that a multi-disciplinary team approach, including psychological input, may have benefit for CD services by providing screening, monitoring and support for 'brain fog' related difficulties.

Introduction

Around 1% of the worldwide population are estimated to be affected by coeliac disease (CD), a chronic, inflammatory autoimmune condition which results in intestinal damage following the consumption of gluten, a protein that is present in wheat, barley and rye (Singh et al., 2018). Currently, the only recommended treatment is a lifelong gluten free diet (GFD). Untreated CD has been linked to multiple long-term health consequences such as cardiovascular disease, and cancers, including those outside of the gastrointestinal tract such as breast cancer, uterine cancer, and head and neck cancer (Kårhus, 2020).

CD Symptoms

There are a range of gastrointestinal and extraintestinal issues that are associated with CD, however the clinical presentation of CD can be extremely variable, and this can make diagnosis challenging (Lindfors et al., 2019). Widely recognised gastrointestinal symptoms include diarrhoea, steatorrhea, unexplained weight loss and growth failure (Croall et al., 2020a; Ludvigsson et al., 2013). Whilst some people have these symptoms, often termed 'classical CD', others do not; they may present without the signs and symptoms of malabsorption, such as with bloating, constipation, and abdominal pain (non-classical CD) or even with no symptoms at all (asymptomatic CD) (Lebwohl et al., 2018; Ludvigsson et al., 2013). Extraintestinal symptoms may include tiredness and headaches as well as neurological and psychiatric manifestations, such as gluten ataxia, peripheral neuropathy, anxiety, depression and chronic fatigue (Durazzo et al., 2022; Pinto- Sánchez et al., 2015). Furthermore, CD is recognised to be a systemic disorder, and is associated with other problems such as anaemia, osteoporosis, liver disease, reproductive disorders, and skin conditions (Croall et al., 2020a; Elwenspoek et al., 2021; Leffler et al., 2015; Pinto-Sánchez et al., 2015; Salmi et al., 2022).

‘Brain Fog’: An ‘Unofficial’ Symptom

There are other symptoms that, whilst are largely reported anecdotally by the CD population, are distinctly underrepresented within the research literature. Cognitive impairments, first highlighted by Kinney et al. in 1982 are a group of such symptoms and can be variable in severity and duration (Durazzo et al., 2022). Using UK Biobank data, Croall et al. (2020b) found that, in comparison to healthy controls, individuals with CD displayed significant deficits in reaction time, a higher proportion of self-reported anxiety, depression, thoughts of self-harm and health related unhappiness as well as displaying white matter changes on brain imaging. This provides evidence that CD is associated with neurological and psychological consequences. A mild form of cognitive impairment, which is often referred to as ‘brain fog,’ is commonly reported and characterised by subtle impairments in the cognitive functions of memory, attention, executive function, language, and speed of cognitive processing (Makhlouf et al., 2018; Yelland, 2017). Whilst the exact pathophysiological mechanisms responsible for ‘brain fog’ are not fully understood, most recent hypotheses include the idea that systemic and cerebral inflammation caused by CD leads to increased circulating cytokine levels, which have been linked to changes in behaviour, mood and cognition, and therefore leads to cognitive impairment (Makhlouf et al., 2018). Another hypothesis attributes the ingestion of gluten leading to a reduction in brain serotonin levels as a causal factor for cognitive difficulties (Choi et al., 2009; Makhlouf et al., 2018). At a broader level, these hypotheses have relevance for more recent developments in the literature, such as the theory of the gut-brain connection, also known as the gut-brain axis (GBA). This refers to the bidirectional communication system between the enteric nervous system (ENS) (the gut and the gastrointestinal tract) and the central nervous system (CNS) (the brain and the spinal cord). Communication between the two can occur through various pathways such as neuroendocrine signalling pathways, hormones, inflammatory processes and immune systems (Mayer et al., 2022). There is evidence to suggest that the above pathways are under the influence of the gut microbiome; microorganisms including

bacteria, viruses, and fungi within the gastrointestinal tract, and can contribute to the structure, function and development of the brain through the GBA. In the GBA, it is suggested that the brain and the gut communicate together to maintain homeostasis (the body's ability to maintain a stable internal environment) (El Aidy et al., 2015; Lerner et al., 2017; Martin et al., 2018). Whilst exploration of the GBA in CD remains limited, a disruption in this homeostasis, such as in CD, may lead to the cognitive impairments as understood under the term 'brain fog'. Interestingly, a recent review of the literature suggested that cognitive impairments may be more likely in individuals who present with gastrointestinal symptoms of CD (Makhlouf et al., 2018). However, 'brain fog' is not exclusive to CD and has been associated with other conditions such as traumatic brain injuries, psychiatric conditions, menopause and hypothyroidism, suggesting that 'brain fog' may not just related to gluten ingestion or the GBA (Bell et al., 2023; Jaff & Maki, 2021; McWhirter et al., 2023; Samuels & Bernstein, 2022).

Evidence for the above hypotheses of causal mechanisms of 'brain fog' in CD is supported by research suggesting that adherence to the GFD can lead to improvements in 'brain fog' symptoms. Lichtwark et al. (2014) found that for individuals reporting 'brain fog' pre-diagnosis, after 12 months of strict GFD adherence, participants displayed a significant improvement on neuropsychological tests measuring verbal fluency, attention, and motor function, and this was strongly correlated with participants' intestinal healing. In other research, a significant improvement in the cognitive abilities of reasoning, problem solving, and cognitive flexibility was observed after 6 months on the GFD (Cassisi et al., 2020). However, older research such as Hu et al. (2006) found that only three of their thirteen patients improved or stabilised cognitively after starting the GFD. However, their results should be interpreted cautiously given that the sample also included multiple individuals aged above 60 years old who were presenting with more severe cognitive impairments and who are more at risk of developing a progressive dementia (Anstey et al., 2019). Moreover, many were diagnosed with CD later in life, suggesting that substantial internal damage may have occurred over time. Therefore, for

those with more severe forms of cognitive impairment and more severe intestinal damage, the GFD may not have the same positive impact.

Aims and Objectives

To date, whilst there is research highlighting an association between CD and 'brain fog', there has been no explorative qualitative investigation of this association, leading to it still being poorly understood and unrecognised as a symptom of CD (Croall et al., 2020b). Without understanding the phenomenology of 'brain fog' in CD, there is no shared understanding of what the experience is like and thus there is the risk that researchers may be describing different experiences altogether, all under the same 'brain fog' term. Furthermore, without understanding how 'brain fog' presents and its impact upon functioning, studies using measurement of cognitive functions, such as those studies described above e.g. Lichtwark et al. (2014), may not be measuring domains that are most important or pertinent to measure. Additionally, although there have been qualitative investigations of 'brain fog' within other patient populations, such as those suffering from the long-term effects of COVID-19 (Callan et al., 2022), it may be that the experience and mechanisms involved differ for those with CD. Whilst this study does not aim to provide information on causal links or mechanisms, the understanding of the GBA helps to provide a context in which this qualitative study is framed, and the results understood.

Studies of 'brain fog' in other conditions such as hypothyroidism, suggest that it could have a significant, widespread impact on an individual's everyday functioning, quality of life and treatment adherence (Haskard-Zolnierek et al., 2022; Samuels & Bernstein, 2022). Therefore, further understanding of this experience will contribute to the evidence base and recognise that this is a real, significant symptom of CD; this in turn will support diagnosis and identification of individuals without 'typical' CD symptoms, by highlighting the symptoms that clinicians should be aware of. It also has

implications for clinical services and the support that might be offered for those with CD, which might include mental health support and strategies to support difficulties in cognitive functioning.

Thus, using qualitative methodology, this study aims to answer the research question: How do individuals with recently diagnosed CD experience and make sense of 'brain fog'? Using a sample of individuals with CD diagnosed within the last six to eighteen months will offer a closer connection to the 'brain fog' experience pre-diagnosis, as well as any changes they may have experienced once diagnosed and following the GFD. In addition, the present study will aim to understand the specific symptoms that participants experience, the onset and progression of the difficulties as well as its impact and the sense they make of their difficulties, especially before they received a CD diagnosis.

Method

This study uses an interpretative phenomenological analysis (IPA) methodology, using updated terminology as described by Smith et al. (2021). IPA uses a phenomenological and double hermeneutic approach; it is predominantly concerned with how individuals make sense of their lived experiences, and the researcher plays an active role in interpreting these experiences (Pietkiewicz & Smith, 2014; Smith & Osborn, 2008). To meet the aims of the research, it was felt that IPA offered the best process to understand the unique experiences of individuals with CD who experience 'brain fog', through analysis of semi-structured interviews.

Participants

Seven eligible participants (6 females, 1 male) were included in this study. Participants were recruited using a purposive sampling method via an advertisement, which was placed upon various social media sites including Facebook, Instagram and Twitter (See Appendix C). Demographic information for all participants is displayed in Table 1. Based on an emerging link between the long-term effects of COVID-19 and 'brain fog' (Jennings et al., 2022), participants were also asked if they had been diagnosed with this, for information about possible contributing factors. All inclusion and

exclusion criteria for the study are outlined in Table 2. The participant journey and procedure for this study is detailed under the 'Procedure and Interview Development' section.

Table 1

Participant Demographic Data

Participant Pseudonym	Age	Ethnicity	Occupation and/or Sector	Time Since CD Diagnosis	Long Covid diagnosis?
Frankie	42	White British	Teacher (Education)	9 months	No
Taylor	33	White British	Accounts Assistant	7 months	No
Alex	50	White British	-	7 months	No
Ashley	49	White British	Technology	14 months	No
Charlie	35	White British	Programme Manager	15 months	No
Rowan	25	White British	Higher Education	17 months	No
Sam	59	White British	Retired	17 months	No

Note. Two of the sample reported recently diagnosed perimenopause or menopause. In addition, participants reported taking a range of medications including vitamin supplements (including B12), Insulin (for Type-1 Diabetes), Lisinopril (for high blood pressure) and Estradiol (hormone replacement therapy (HRT) for perimenopause).

Table 2

Study Inclusion and Exclusion Criteria

	Criteria	Rationale
Inclusion Criteria	- Have experienced or be experiencing 'brain fog' or mild cognitive difficulties. - Received a diagnosis of CD by a healthcare professional in the past 6-18 months and this will be self-reported by the participant. - Aged between 18 and 60 years old - Following the GFD and this will be self-reported by the participant.	Participants must have lived experience of 'brain fog' and be able to articulate their experience. Participants who have been diagnosed within 6-18 months should have access to more recent memories and therefore are likely to be able to describe their experiences with more detail and accuracy. It also enables a period of time adherent to the GFD, hopefully leading to healing and improvements. This age group is in line with previous studies; it has recently been suggested that adults over 60 years with CD may have a higher chance of experiencing dementia-type symptoms and so this age-group will be excluded from the sample (e.g., Ching & Lebwohl, 2022). Based on the literature, participants on the GFD will hopefully see an improvement in their 'brain fog' symptoms and be able to reflect on this.
Exclusion Criteria	- Diagnosis of CD received a less than six months ago or more than 18 months prior to recruitment. - A diagnosed neurological disorder, condition, or a history of a brain injury - A diagnosis of any current, mental health difficulties - A history of, or current substance misuse difficulties - Another health condition newly diagnosed within the last six months.	All excluded conditions and difficulties may also cause 'brain fog' like symptoms or cognitive difficulties. Whilst all causative factors cannot be fully controlled for in this study, main conditions and difficulties were identified in an attempt to limit the influencing factors upon the participant's difficulties, to aim for an understanding of 'brain fog' in relation to CD specifically.

Ethics

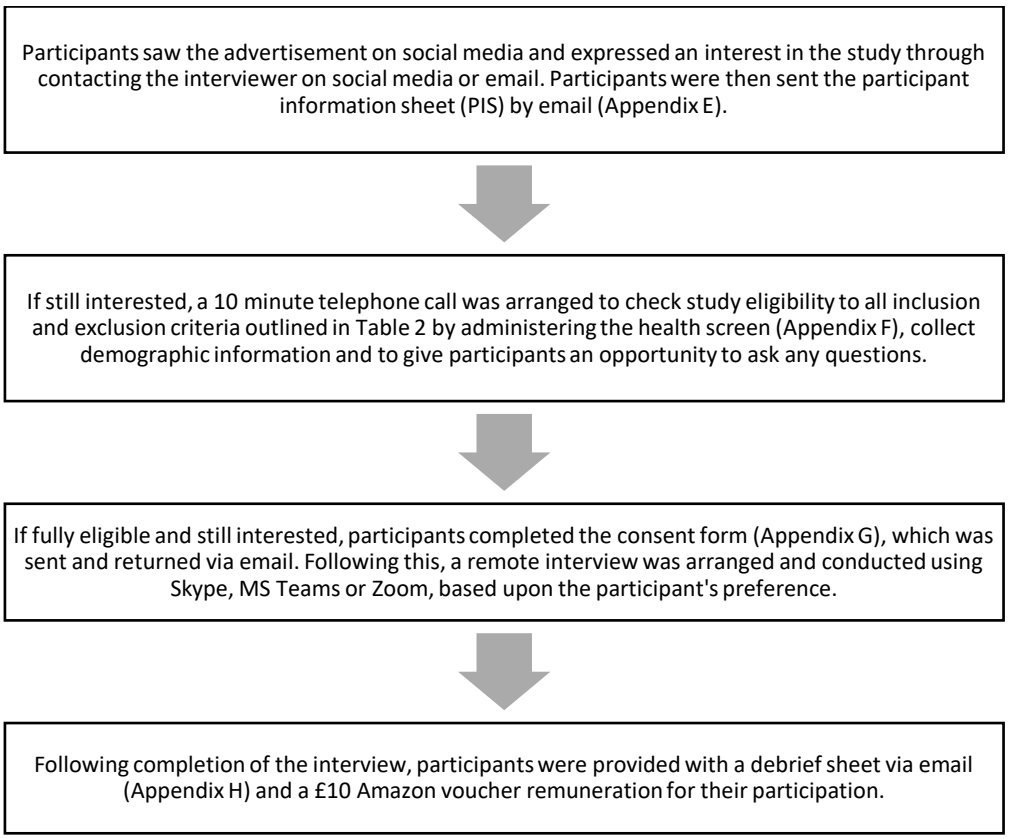
Full ethical approval for this study was gained from the University of Birmingham's Ethics Committee (Appendix D). Participants were remunerated with a £10 Amazon voucher following completion of the interview. A data management plan was created and followed, in which all data collected from participants was stored on the University's secure BEAR Research Data Store (RDS). Participant anonymity and confidentiality was protected using gender neutral pseudonyms within this thesis. Due to the sensitive nature of the interviews, participants distress levels were monitored throughout interviews by the interviewer; however, there were no occasions in which it was deemed necessary to pause or terminate any interviews.

Procedure and Interview Development

The detailed procedure the participant followed throughout this study is outlined in Figure 1 and all related documents can be found in Appendices F to J. Data was collected between October 2022 and March 2023. In total, 25 individuals expressed an initial interest in the study and were sent the Participant Information Sheet (PIS). Of these, 10 individuals were willing and eligible for the initial telephone eligibility check. One individual cancelled the scheduled telephone call and did not want to proceed. One more completed the telephone call, then was unable to complete the interview. Therefore, in total eight individuals were interviewed; however, only seven of these interviews were analysed and included in this study, as one, which was the first interview, was deemed insufficient in length and depth for analysis. This interview, however, was useful in piloting and developing the interview schedule. All participants who were not eligible but had dialogue with the researcher, were signposted to Coeliac UK resources and to other research opportunities. The decision to end data collection was made in March 2023 in conjunction with project supervisors, based on perceived sufficient homogeneity across the sample to provide understanding of the 'brain fog' experience (Alase, 2017) and was based on the capacity to complete the project within the timescale of the doctoral programme.

Figure 1

Study Procedure



A semi-structured interview schedule was developed in conjunction with two project supervisors. This was based upon the research question and was grounded in the current literature on 'brain fog' in people with CD (see Appendix I). Each interview followed the same semi-structured schedule and interview length ranged between 34 and 47 minutes, with a mean length of 41 minutes. The semi-structured format to the interview allowed for a flexible and responsive approach to the content of the participant's interview. Prior to each interview, time was spent rapport building and when appropriate rapport had been established, the interview began.

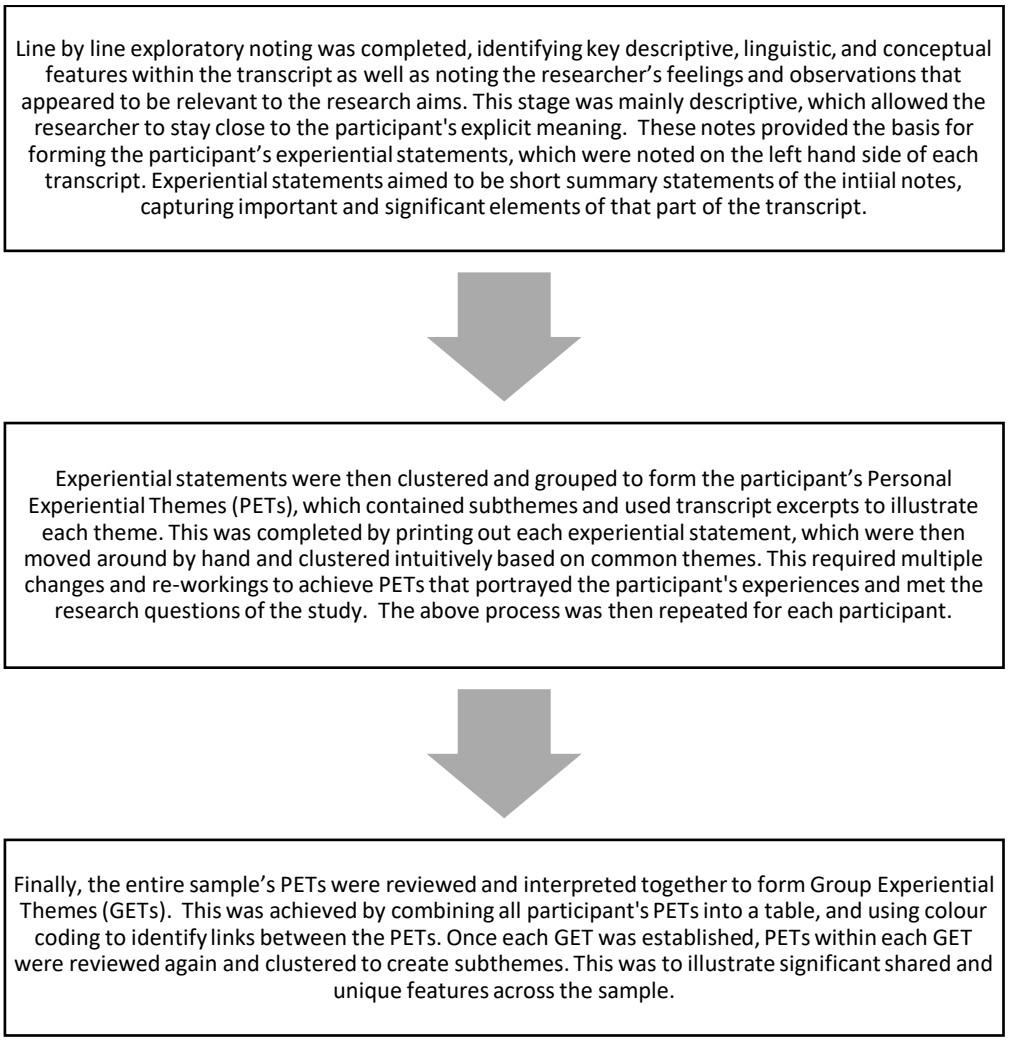
Analysis

The interviews were recorded using an encrypted dictaphone and transcribed verbatim by the researcher. Transcripts were read and re-read by the researcher to familiarise herself with the

content before being analysed using the IPA procedure stated in Smith et al. (2021). The analysis process is described in Figure 2.

Figure 2

Analysis Process



Transcripts were annotated, highlighting key descriptive, linguistic, and conceptual features. Below describes each type of noting and example quotes from participant's transcripts:

- **Descriptive** noting identified important content of what the participant was saying in relation to CD, 'brain fog' and their experiences. It highlighted key elements of the transcript which gave information that furthered understanding of the 'brain fog'

experience in individuals with CD. For example, “I was able to look back and see the symptoms I was having that I didn’t know I was having” (Rowan, line 23-24).

- **Linguistic** noting identified parts of the transcripts where the researcher perceived that language was used in a way that was interesting, unusual, or felt significant in understanding the participant’s experience. Attention was also given to pauses, laughter, repetition, tone, and the purpose of which language was used. For example, “It really feels like that, it’s like a mist. Something about feeling slow in my brain…” (Charlie, line 10-12).
- **Conceptual** noting identified excerpts in which the participant’s illustrated their sense making of their experiences, or provided information on their overarching understanding of what was happening. An example of a conceptually coded quote is: “Well, I was absolutely convinced it was my thyroid, or I’d had covid and I didn’t know, you know, like long covid or something, but yeah, I was absolutely convinced it was my thyroid. I knew I was anaemic, and my protein was low” (Frankie, line 217-220).

Validity and Quality

To aim to achieve validity and quality, different tools were used in designing, completing, and writing up the present study. Individual supervision with project supervisors and peer supervision was utilised at all stages of the research process, and particularly in the interpretation of the data and the development of themes. Levitt et al.’s (2018) journal article reporting standards for qualitative research (JARS-qual) were used to provide a structure in designing and writing up of this study. In addition, Nizza et al.’s (2021) four markers of a high-quality IPA studies gave guidance and aspirations for this study. The four quality indicators are:

- Constructing a compelling, unfolding narrative

- Developing a vigorous experiential and/or existential account
- Close analytic reading of participants' words
- Attending to convergence and divergence

Reflexivity

Due to the double hermeneutic nature of IPA, it is important for a researcher to consider their personal influence upon the research process and analysis. This was achieved through keeping a reflective diary following each interview and reflecting in project supervision on the process. In terms of my influence, I am a 28-year-old, British, female Trainee Clinical Psychologist. I am of mixed white British and Asian ethnicity. I am in good health and I have a diagnosis of irritable bowel syndrome (IBS), meaning I could relate to some of the physical symptoms that participants were describing. Fortunately, I have no immediate family members who have experienced chronic illnesses; however, I do have some family friends with a diagnosis of CD. Despite this connection, I was shocked by my naivety around some of the experiences within CD and learnt a huge amount through the process of conducting the interviews. Being a first-time qualitative researcher and also this as my first research project on the topic of CD, I found it hard initially to take a more neutral stance when interviewing, rather than the approach I take within my clinical work which involves lots of validation, paraphrasing and offering of hypotheses. Therefore, I found I was initially a little conflicted between the two positions I was having to hold, and the interviews felt unnatural and unsatisfying. Through supervision and as interviews progressed however, I felt I was able to strike a balance that felt conducive to gaining in depth information and maintaining rapport whilst not leading the interview, by adjusting my interview style and using questions that seem to work well for previous participants. Being witness to the significant impact that the GFD and 'brain fog' has on individuals evoked empathy and an emotional connection to the participants and interviews. By recognising and considering my influence upon the research, this helped to ensure that the results and

interpretations are grounded in the data. I noticed that throughout the course of interviews, the strongest emotive and verbal responses were elicited from participants when discussing the GFD and I interpreted this to signify that whilst all participants found their 'brain fog' hard, they found the GFD element of CD harder and that is where their attention and energy may be focused. This high level of distress related to the GFD is echoed in the research literature, in studies such as Satherley et al. (2022).

Results

Results Overview

A summary of Group Experiential Themes (GETs) and subthemes is displayed in Table 3. When considering the results of the analysis, it is important to highlight that whilst participants can all be considered 'recently' diagnosed with CD (within 6-18 months prior to interview), they are all at different stages in their CD and 'brain fog' journey in terms of knowledge and improvement. Therefore, the different dimensions of participants' experiences have been captured in this overview. Further examples of the IPA process and product of analysis can be found in the appendices. This includes:

- An excerpt of an annotated transcript with exploratory noting and experiential statements (Appendix J)
- A visual illustration of the process undertaken to find connections across participants to form the GETs (Appendix K)
- A master table of all GETs and participant quotes contributing to each theme (Appendix L)

Table 3

Summary of Group Experiential Themes (GETs) and Subthemes

Group Experiential Theme		Subtheme	Participants Contributing to Theme
1.	**The Course of 'Brain Fog'**	1.1 A gradual "creep"	All participants
		1.2 A range of "foggy" difficulties	All participants
		1.3 "Bigger than a little fog": impact and severity	All participants
		1.4 "It is all so alien": making sense of the symptoms	All participants
2.	**Physical Symptoms Take Priority**	2.1 Overshadowing of 'brain fog': From the unconscious to the conscious	All participants but Frankie and Taylor
		2.2 "I guess I was in denial about them": the (possible) stigma around "mental" symptoms	All participants but Ashley and Sam
3.	**Lost in the Fog**	3.1 "A shell of myself": loss of their 'normal' self	All participants
		3.2 "You're there, you're awake but you're not 'there'": loss of presence and time	All participants but Frankie and Taylor
		3.3 "No one's ever mentioned coeliac disease and 'brain fog' as something that exists together": feeling lost and alone in the 'brain fog' journey	All participants but Frankie and Sam
4.	**The GFD isn't Always the Magic Cure**	4.1 "Will I be me?": improvement is not just about symptom reduction	All participants
		4.2: "Owning it": navigating the 'brain fog' symptoms	All participants

Group Experiential Themes

1. The Course of 'Brain Fog'

One of the aims of the present study was to understand what 'brain fog' feels like for people with CD and to understand the specific parts of cognition that may be affected. Participants generally reported a gradual onset to their 'brain fog' and described specific cognitive difficulties widely understood under the 'brain fog' umbrella, as well as associated co-morbid problems such as tiredness and mood changes. Participants described varying levels of impact upon their everyday life, and all made sense of their difficulties within their context.

1.1 A Gradual "Creep". Participants tended to describe their 'brain fog' developing in a slow, gradual way. When asked to describe how their symptoms started and what was noticed first,

Charlie stated "…it was so gradual it's quite hard to separate it and it was kind of all going together" (line 63-64). Frankie echoed this, describing the onset of symptoms was like a slow "creep" (line 163) and said: "It was difficult to notice it because it all happened so gradually, so it wasn't just like one day where I just couldn't remember anything, it was more that it slowly and surely got worse" (line 154-157). These accounts could be interpreted to suggest that identifying which symptoms started first was difficult for participants and therefore further accounts of the 'brain fog' experience may be limited by this. The language which is used such as "gradual", "creep" and "slowly" suggests that the onset of 'brain fog' may not have felt really significant or impactful for participants.

Participants differed in reporting when they perceived their 'brain fog' symptoms to have started. For Alex, Charlie, Rowan and Frankie, their symptoms started very much prior to their CD diagnosis. Rowan noticed a significant change over a year prior to their CD diagnosis:

> …cause I was always really bright in school and everything, very organised, very motivated, umm and for about a year, eighteen months before I was diagnosed that all just started to trail off and I became a bit more away with the fairies at times. (line 11-15)

Here, Rowan's account, like others, further suggests that their symptoms were progressive and changed some of the fundamental qualities about them in a negative or hindering way.

Whereas other participants including Taylor, Ashley and Sam, felt that their 'brain fog' symptoms mainly started following their CD diagnosis and starting on the GFD. Taylor reported symptoms starting around two months prior to interview, with their CD diagnosis being six months before the interview. Taylor stated, "You think with the gluten free diet your symptoms would improve, but I've kind of gone the other way" (line 57-59).

For many of the participants, it is only when looking back following an improvement that they were able to identify they were experiencing 'brain fog' symptoms. Rowan said, "I was able to look back and see the symptoms I was having that I didn't know I was having" (line 23-24) as well as

Sam stating, “Looking back, there are occasions then I must have had it, and I had it before I was diagnosed, and I didn’t realise it was part and parcel of what it was” (line 482-484). Due to the slow, gradual nature of the ‘brain fog’ progression, participants may have not been able to notice the small changes that were happening to them. Furthermore, these more recent realisations may be due to increased attention to the symptoms or increased knowledge of the ‘brain fog’ and CD association following diagnosis.

1.2 A Range of “Foggy” Difficulties. Participants’ accounts suggest that they found it difficult to exactly describe and name the specific cognitive symptoms that they were experiencing, likely due to the vague and non-tangible nature of ‘brain fog’ – the experience of it is within the name: foggy. Participants also described not experiencing ‘brain fog’ symptoms in isolation – they were often also experiencing physical symptoms related to CD, with Rowan summarising:

> It’s so hard to pin down, I can pin down my physical symptoms easier than I can pin down the ‘brain fog’, cause it’s, the physical symptoms are the obvious, but ‘brain fog’ is, when you are feeling a bit foggy, cause you are so foggy, you don’t even realise, you don’t think, its only afterwards you realise. (line 445-449)

In this quote, Rowan points to the hidden or invisible nature of ‘brain fog’, and this contributes to the wider narrative of how ‘brain fog’ appears to be hard to articulate and understand from a participants’ perspective.

This difficulty in ‘pinning down’ the symptoms appeared to make it hard for participants to provide consistent accounts of their symptoms and there were contradictions observed within accounts. Sam initially stated that their ‘brain fog’ meant that they were fixated on the specific task they were doing at the time, and unable to think about anything else. They said:

> So you get focused on like one task, so you tend to just do what you're doing and not be able to focus on anything else. So, I might be in the car and won't talk to my . . . [partner] for 40 minutes because I'm just concentrating on the driving. (line 50-53)

Then later, Sam stated that their mind tends to be thinking about everything else, but the task they are currently doing, which is discrepant from their earlier account. They said:

> …everything, you tend to think about other things, the road, you tend to think about things that are going on, things that are going on that day, things you gotta prioritise, you tend sort of, uh, think of everything that's going on, that's ahead of you, rather than what's going on at the moment. (line 374-378)

Interestingly, as seen above, participants Sam and Alex talked about their symptoms largely from a second person perspective, using the pronouns 'you'. This might suggest that they feel their experience is representative of the general CD population that experience 'brain fog' rather than their individual perspective.

However, as a collective, the sample described several cognitive difficulties which included difficulties in memory, language, concentration, attention, executive functioning, confusion, distractibility, and information processing. Charlie description of the experience of 'brain fog' could be interpreted as being like a bidirectional impermeable barrier in which they cannot process information nor give information out. Charlie said: "…it was sort of like a mist that doesn't allow things in or sort of doesn't really allow them out and sort of slows, like things would get lost in between" (line 19-21). Rowan also experienced this 'barrier' which lead to a disconnect, stating "…it's like my mouth and brain weren't connected" (line 184-185). In describing their 'brain fog', Taylor said:

> I'd say like memory loss as well, I don't know whether this is all part of brain fog but memory loss, is probably the thing that I suffer with the most, still. I forget words that I need to say, I'll forget mid-sentence and I don't know what I need to remember. I'll just stop and not know

> what to say, and it'll take me a couple of seconds for me to kind of think, what do I need to say next. Um, so yeah, that's, that's probably one of the main things that I really suffer from with the brain fog, and the confusion in the memory loss as well. (line 25-33)

Whereas Alex stated:

> I just knew that I was struggling for words, to try and articulate what I wanted to say to people and to remember, like, the most, like, it's really like, you have a memory for places you've been and people you've seen but you don't have a memory for like, recent stuff and sort of current things. (line 6-11)

Participants also described other symptoms that they interpreted as being both a part of their 'brain fog' and a consequence of it. These included altered mood, irritability, tiredness, lack of motivation and headaches. Taylor stated that:

> And also, just the agitation, and I think the agitation comes from probably being so confused and forgetting words and things like that. And again, the tiredness and things like that, whether that's related to the stress of everything that's going on with like brain fog and the confusion. (line 33-37)

1.3. "Bigger Than a Little Fog": Impact and Severity. An important feature of all participants' accounts was just how impactful, worrying and significant their 'brain fog' symptoms eventually were in their everyday life activities. Charlie's account suggested that the term 'brain fog' minimised the impact and severity of the symptoms, they said:

> It makes a lot of sense, it's so clear, like I said, the word fog really encapsulates what it is, and you say it and you can understand it but there's something a bit colloquial about it which doesn't get the impact or the severity of it across. Because I think it is severe or can be

> severe. If it's making you think you have early onset dementia, like I feel it's bigger than a little fog, you know. (line 591-597)

All participants described significant disturbances to their everyday functioning in some way, whether that was at work, home or socially. Alex, when talking about CD and 'brain fog', said "So, it completely impacts your life, completely impacts your whole life, on every level" (line 440-442). This suggests a debilitating, widespread impact on functioning levels for individuals. Taylor further described this; had to give up the college course they were studying, and it impacted their ability to complete the job they were so familiar with doing. Taylor then had to take sick leave from their job, due to the severity of symptoms. Their account gives a sense of feeling lost in the experience:

> I couldn't remember anything I'd just learnt so I kind of had to stop doing my college work because of that. And then it was my work, so I was sat there at work one day and it got to the point where my manager asked me to do something, and I sat there and was like, I literally don't know what I'm doing, I've got no idea. (line 15-20)

Frankie found that they were no longer able to function as a teacher as effectively as previously and ended up moving to a non-classroom-based role. Thinking spontaneously and problem solving appeared to be difficult for Frankie, which likely then lowered their confidence in their abilities. They said:

> I'm a teacher and I've always had outstanding lesson observations, I got an unsatisfactory lesson observation, like the activity the kids were doing didn't relate to the learning objective very well, and I just wasn't bringing the learning together for the kids, so I could plan a lesson, and I could plan an activity but if I had to get up and sort of, the kids, the kids let you know they didn't understand, I then found it really hard to like, you know, scoop them up and put them on the right track again. (line 169-177)

Another area that was reported to be significantly affected were in social settings and the skills required to function in these settings. Participants not only described significant social impacts of the GFD, but also of the 'brain fog' they were experiencing. For example, Alex said:

> I don't like going out. I feel very, kind of, isolated, because although you've got the brain fog, you feel like you've got a lot of noise around in, you don't want to make a decision, like I would hate to be out without knowing the people I'm with would look after me. Like if I went out without my [partner], I couldn't guarantee that I will, like know, where I am, what I'm doing, where I'm going. (line 144-151)

Here, Alex shows how they doubted themselves and their own abilities due to the 'brain fog' symptoms. Their account can be interpreted to suggest that 'brain fog' not only has specific cognitive impacts, but the symptoms may also culminate into an isolating and overwhelming experience. There is almost a sense of being childlike in Alex's words; in a lack of ability to be independent and relying on others to look after them to ensure their safety.

Participants all agreed that the 'brain fog' and associated difficulties had a significant impact on others around them – it wasn't just affecting them individually. For Charlie and Frankie, a significant area of impact was their ability to parent and be engaged with their children. When asked about what the 'brain fog' impacted the most, Charlie said:

> … it impacted, er, my ability to parent and be present with him and that really felt like a struggle, which makes me feel quite sad, because when I look, I think at the time I kept thinking I'm just a terrible parent, what, like I just can't get on a level with him, I can't. There was bodily fatigue I was experiencing as well, but fatigue in my body and fatigue in my brain so I just can't…like all I could do was basically sit on the sofa and watch him play and any time he tried to get me involved I just like couldn't do it. Like I just felt exhausted in every way. (line 186-195)

Charlie here describes feeling inadequate or defective in the words “I’m just a terrible parent”, suggesting, like others, that at the time, ‘brain fog’ was unable to be perceived as specific, isolated difficulties, for example, a difficulty in concentration. Instead, ‘brain fog’ was perceived to be a fault with their fundamental selves and the roles that they held. In the way Charlie spoke about their symptoms above, there was a sense of regret and mourning for the time with their child that they will never regain.

In addition, ‘brain fog’ had significant personal and emotional impacts, which is discussed further in Theme 3: Lost in the Fog.

1.4. “It is all so Alien”: Making Sense of the Symptoms. Before understanding that their ‘brain fog’ might be linked to their CD, participants made sense of their symptoms as best they could within their current context and making sense of it appeared to feel containing. Many were initially confused about what was happening; Alex said, “it is all so alien” (line 179). Most recognised that there could be multiple contributing factors to their symptoms, for example, with Ashley stating, “There’s probably lots of things brain fog can be attributed to…” (line 478-479) and Alex alluding to the idea that anything could be causing it:

> I just sort of thought I was going to mad, and I thought it was, I just didn’t know, I wasn’t sure if it was . . . or to do with some kind of change, like anything really, cause you just don’t know. (line 86-89)

For some, their symptoms occurred during the worst period of the COVID-19 pandemic, so they attributed their symptoms to stress and being furloughed[1]. Others identified vitamin deficiencies, ‘baby brain’, menopause/perimenopause, psychological causes such as depression, going “mad”, other physical health conditions, busy work and life as well as general aging as possible

[1] To furlough means to suspend a worker on paid or unpaid leave, whilst keeping them on the payroll and not making them redundant. It was used during the COVID-19 pandemic when companies were unable to operate or provide work for staff.

causes. When asked what they thought was causing their 'brain fog' at the time, Ashley said: "I've kind of put that down to not really enjoying work, but it could be a combination of them both if that makes sense [as in 'brain fog' related to CD]" (line 31-33) and "so getting older . . . It was busy a time when I first noticed things" (line 107-108). Frankie thought their symptoms had a more physical cause:

> Well, I was absolutely convinced it was my thyroid, or I'd had covid and I didn't know, you know, like long covid or something, but yeah, I was absolutely convinced it was my thyroid. I knew I was anaemic, and my protein was low. (line 217-220)

Charlie, Sam and Alex worried that what they were experiencing was due to dementia. This signifies just how severe and impactful the symptoms were to them, to consider such a significant diagnosis. On the possible causes of their symptoms, Alex said: "It's an awful condition, it kind of makes you feel like you've got dementia, that's the only way I can put it, like you're in the early stages of a dementia" (line 24-27).

Most described a change in their ideas about causation over time, recognising the link between CD and 'brain fog'. Attributing their symptoms to this seemed to contain their worry and catastrophising about what might be causing the symptoms. Demonstrating this, Charlie, when reflecting on the changes in her 'brain fog' over time said: "I no longer think I have early onset dementia (laughs) and it really doesn't stop me anymore" (line 346-348).

2. **Physical Symptoms Take Priority**

Participants often discussed the physical symptoms of CD in conjunction with the 'brain fog' symptoms. The accounts were interpreted to suggest that all factors involved in having CD such as physical symptoms, adjustment to the diagnosis and coping with the GFD are very much entwined and must be considered when understanding the experience of 'brain fog'. Often, physical symptoms were the focus of attention and priority for participants, rather than the 'brain fog' symptoms.

2.1. Overshadowing of the 'Brain Fog': From the Unconscious to Conscious. In their interviews, many participants described how often it is only when looking back that they are able to identify that they were experiencing 'brain fog'. One possible explanation for this is due to the gradual, slow onset of symptoms it may have become their new normal. Sam described originally being unaware of their symptoms, saying: "you tend to sort of, erm, sort of do something unconsciously" (line 58-59). Another explanation is that due to their significant physical symptoms they were experiencing prior to diagnosis, and then possibly the impact of the lifestyle changes required by starting the GFD, 'brain fog' goes unnoticed or is not the focus of attention, meaning it was much harder to identify it at the time. For example, Rowan stated "But something like brain fog, is like a hidden symptom, it's not the obvious one, so when you've got like violent diarrhoea happening, you don't always think about other symptoms" (line 499-502). When asked about the impact of 'brain fog' on their social life, Ashley said they found coping with the GFD more difficult than the 'brain fog': "…I think being Coeliac is more difficult [than 'brain fog'], like going for dinner. I think that's impacting social life more so" (line 309-310).

Participants also suggested that the result of other elements of having CD may lead to 'brain fog' symptoms themselves. For example, Rowan hypothesised that their worry and anxiety about their physical CD symptoms, such as diarrhoea and stomach pain, may contribute to increased levels of 'brain fog':

> …whereas now it's more if I'm feeling ill [physically], I will worry about it and stress about it and get quite anxious about it, so that's where my brain is focused than on the tasks I'm meant to be doing, so that's where the fog comes in, so it might be linked in that way. (line 610-614)

Here, Rowan points to a causal link between the emotional distress that the physical symptoms of CD bring, and 'brain fog'. Alex further speaks about this idea, suggesting that stress related to their CD is linked to their levels of 'brain fog':

> …that's another way to describe it, someone who stutters or has Tourette's or has an affliction, and when they feel calmer about it, it almost becomes easier, so someone who is calm or confident around somebody, so for instance someone with Tourette's or a stutter or something, if they are not in an environment which is going to cause them stress, then they are less likely to have that. Whereas a time where they are feeling stressed about something, it makes their stutter worse, and that's exactly how 'brain fog' feels for me. (line 353-362)

2.2. "I Guess I was in Denial About Them": The (Possible) Stigma around "Mental" Symptoms. Another important distinction between physical and 'brain fog' symptoms that was interpreted from participants' accounts, was related to societal stigma attached to mental symptoms. This appeared to have affected participants in different ways, for some it meant they did not seek help. Others appeared to have denied their symptoms to themselves and others. Therefore, it may be that the 'brain fog' symptoms may not have only been hidden by other parts of CD, such as the physical symptoms, but also due to possible shame and stigma around their symptoms. For example, participants used words like "mad" and "mental" at times. Alex said, "I thought I was going a bit mad really" (line 52). For some, like Rowan, it appeared that stigma and cultural norms meant that they found it hard to talk about and felt less able to seek help for their 'brain fog' symptoms than their physical symptoms. Rowan said:

> I think I come from a family background that doesn't openly talk about mental stuff or doesn't go get checked out about something that's mental. So, I probably just didn't pay attention to it as much as I probably could have done to it. (line 135-138)

Charlie described a similar experience when asked whether help had been sought for their 'brain fog'. They described feeling like 'brain fog' symptoms were easier to put to the side than physical symptoms. This is possibly because physical symptoms are easier to seek help for or may have more perceived importance or urgency. Charlie said:

> I think it's like, um, and this is probably common in lots of people but it was like your brain, feelings and emotions can be sort of like put off, it will resolve, whereas if it's a bodily or physical pain it's like, Oh, I need that treated. (line 230-234)

Furthermore, Charlie described how they declined support offered from work, as this hurt their ego. There was a sense that accepting help would mean admitting something was 'wrong'. For example, Charlie said:

> . . . but you know, there were just like, they'd have meetings and be like, what is going on? Do you need support here or support there? And that would bruise my ego a bit so I would never accept any support . . . (line 442-447)

It may be that this perceived stigma and shame around having 'mental' symptoms may be one of the reasons why many participants talked about their difficulties in such a self-critical way. When describing examples of how 'brain fog' had impacted everyday life, Frankie used language that implied both high expectations and critique of herself, describing how they "couldn't remember like really obvious details, that I should know" (line 24-25) and "and you're like, come on, get it together" (line 103). Alex when talking about wondering whether it was dementia or going 'mad', said: "I guess I was in denial about them" (line 34). It may be that the denial was linked to the previously discussed stigma and shame around 'mental' symptoms.

3. Lost in the Fog

Loss was a prominent theme running through the stories participants told in relation to 'brain fog'. The accounts suggested that loss took on multiple forms; for some this was loss of who they felt they previously were due to the negative emotional impact of 'brain fog', for some this involved loss of time, experiences, and memories, whilst for others this involved feeling 'lost' in their post diagnostic journey in relation to CD, but particularly if they continue to experience 'brain fog' symptoms.

3.1. "A Shell of Myself": Loss of Their 'Normal' Self.

'Brain fog' caused, and still causes, emotional turbulence for all participants leading to negative emotions and views about the self, which included feelings of depression and low mood, anxiety, stress, embarrassment, inadequacy as well as loss of confidence, trust in self, feeling useless and like a hindrance. In relation to the impact of their 'brain fog' at work, Alex said: "it makes you feel really inadequate and really awful" (line 121-122). Charlie, when asked how the symptoms impacted them emotionally, portrayed a sense of emptiness, they said:

> Mmm, yeah, I think I just felt, I looked at myself in a not very favourable light, it was like a real feeling of being like useless and not having any skills at all, having nothing at all in any area of life and feeling sort of like a hindrance and that I made, with the mistakes I was making, it wasn't just feeling useless like I wasn't able to help, it was as if I was making things worse for other people. So, yeah, I wasn't thinking positively about myself, at all. I just sort of reinforced this idea that I had nothing to offer. (line 472-480)

The symptoms tended not to be viewed as just specific difficulties individuals were experiencing; it was almost that the difficulties became part of who they were, their identity and reflected their value, so that for some, 'brain fog' and its impact meant they felt they had lost their

'old' self. Taylor, when describing hitting a 'crisis' point with their 'brain fog' and had to take sick leave from work, said "I just had no hope, I had nothing, I was empty" (line 196) and then went on to say:

> I just felt like I'd really lost myself, like a shell of myself basically because I couldn't do anything, I had no energy to do anything, I had nothing in my brain to do anything, so yeah I guess that's just how I felt with that. (line 204-207)

The language used by Taylor, "a shell of myself", feels really significant in understanding the impact of 'brain fog' on an individual's identify and self-perception. Although previously alluded to, this highlights how 'brain fog' can be life changing on a number of different levels and recognises the loss that participants in this study felt. With loss, of course, comes grief, and possibly some of distress and emotional impacts that were described from participants were part of this grief process.

Others reported that their 'brain fog' had changed who they were, leading to negative self-evaluations. Alex described 'brain fog' as a force that changes how they were to others, they said: "you're not the person that you're kind of being portrayed to be [by the brain fog]" (line 36-37) then Alex goes onto say: "I'm just not the person I was, I'm not the happy go lucky person, who feels confident and ease at [themselves]. I don't like myself that much, because I don't like the person I am towards other people" (line 192-195). As a consequence, some participants also worried about how their symptoms were perceived by others. Rowan said: "[the brain fog] …made me quite self-conscious about that. I still am quite self-conscious about it" (line 211-212). Whilst Taylor said:

> Um, I know that I'm getting stressy, and I know I'm getting agitated, so I feel a little bit embarrassed about it sometimes. And obviously, I don't, some people might not understand so I don't want them to think I'm being a cow about it I suppose, or I'm being an idiot, so it makes me worry about what other people think about me. More than anything it feels embarrassing as I just can't control it. (line 163-169)

In this account, Taylor highlights another experience reported by many participants, of others not understanding or 'getting it'. This provides support for how 'brain fog' was previously described as isolating. There is a sense of fear linked to these experiences, of uncontrollable symptoms, of others' reactions and of what is happening to their bodies.

Sam also reported changes to their personality, using a Jekyll and Hyde metaphor, which was interpreted to have been used to show the extent of their contrasting personalities, in possibly unpredictable ways. They said:

> I've found more now if I don't eat, you know, you get the brain fog, you get, not aggressive but you're thinking style changes. You tend to become a bit Jekyll and Hyde-y, you tend to become a bit of a different person. (line 595-598).

Frankie described significant perceived loss of themselves and their abilities, with their partner having to take on some responsibilities as Frankie could no longer manage them, saying: "My . . . [partner] said [they] was sort of, like [they] had an extra child, because [they] was having to remember everything for me" (line 128-130). Frankie went onto say:

> I just couldn't trust myself or rely on myself. Things like, if there was a change to my routine, or to my family routine, you know I couldn't be trusted, I couldn't be trusted to pick the kids up from school. (line 81-85)

Here, Frankie talks about the experience in a very matter of fact way. However, their words describe, an extremely confusing and emotive time, in which the repetition of narratives around "trust", from others and themselves, emphasises how they perceived they were unable to hold the responsibilities of an adult and a parent. This self-doubt and self-judgement led to further distress.

Upon improvement of their symptoms, Frankie said it felt like "woaaaah I'm back!" (line 352), which reflects how they felt the 'brain fog' symptoms were part of their whole self and only on

improvement did they feel their 'normal' self had returned. Unfortunately, even for those that the 'brain fog' symptoms had improved, there was lasting emotional impacts of their difficulties; for example, Charlie said:

> Um, but there is, I feel like I'm still a little bit burned by the lack of confidence I had when I still had brain fog, so I'm still a little bit of that mindset like "Oh I can't do this" and so on. (line 411-414)

3.2. "You're There, You're Awake but You're not 'There'": Loss of Presence and Time.

Another theme of 'loss' identified by many participants, was the idea that due to 'brain fog' they felt they were unable to be 'present', and therefore the accounts from participants suggested that they encountered missed time, opportunities and memories, with not being able to be an active agent in their lives. There are a number of factors that may have contributed to this, including memory difficulties, the emotional impact of the symptoms and the 'foggy' feeling meaning they were unable to 'see' and engage properly within their lives. Alex summarised this as: "you're there, you're awake but you're not 'there'" (line 103-104), with Ashley saying, "I feel like it's more absent mindedness" (line 60-61). Rowan described feeling like 'brain fog' distanced them from experiencing everyday life: "…because brain fog becomes like you're distanced from what's going on" (line 241-242). Alex described their experience as "just getting kind of vacant is the only way I can describe it" (line 60).

Charlie described being unable to recall periods of time, because the 'brain fog' impacted on their ability to process and retain information: "And actually, there is a whole chunk of time now that I just don't, like I know I watch films a lot, and I don't remember them so it's sort of like, it's sort of like completely blocked out" (line 27-30).

In contrast, Sam described being unable to be present in a different way to other participants. Sam described being so pre-occupied on future tasks and thoughts, that they are unable to focus on the present moment:

> So like I could be cutting the grass and half way through the lawn I'd be thinking about emptying the shed out and all that sort of thing, and you're thinking well I'm cutting the grass. And you cut the grass and all you want to do is do the shed, and you get to the shed and then you think about, cleaning the mower and it's all, sort of, you tend to, you're thinking style of what you've got to do changes, it's kind of like you're focused on getting things done in a certain way. (line 464-472)

3.3. "No One's Ever Mentioned Coeliac Disease and 'Brain Fog' as Something That Exists Together": Feeling Lost and Alone in the 'Brain Fog' Journey. All participants described either a lack of information or support, pre and post CD diagnosis, in relation to both CD and their 'brain fog'. Participants described health professionals not informing them that 'brain fog' might be associated with CD. Ashley said, "no one's ever mentioned coeliac disease and 'brain fog' as something that exists together" (line 118-120) and for some, this link was only thought about after seeing the advert for the present study. This has implications for understanding the participants' experiences collectively, as it shows that participants were all at different stages of their understanding of the 'brain fog' experience in CD and therefore articulated this differently. Thus, understandings across participants may not be comparable.

Due to this lack of recognition of an association between 'brain fog' and CD, it may be that some had delayed diagnoses of CD, if 'brain fog' was a significant part of their presentation without the 'typical' gastrointestinal symptoms, leading health professionals to consider other diagnoses rather than CD. Rowan found that they had to be self-resourceful in finding other avenues outside of the NHS and Coeliac UK to learn more about the association between the two: "…but what Coeliac UK aren't very good at it is going into the mental health side of things, the mental things, the mood symptoms, so I got a lot of that from Instagram" (line 394-397). Upon reflecting on their journey to

diagnosis, Charlie wonders about how the journey may have been different if more questions about cognition had been asked:

> I suppose when I went to the GP about my bloating, not even he, he was just like why don't we put coeliac on the blood test, why not, that sort of thing. Almost like if I'd been asked questions at the time, I was asked loads of physical questions like how often I went to the toilet, that sort of thing but I was never asked about my brain function, you know? About how that was going. (line 552-559)

Participants who then continue to experience 'brain fog' following starting the GFD, describe feeling unsupported in attempting to discover the causation of their ongoing 'brain fog', leading to frustration and ongoing emotional distress. Ashley, when discussing their ongoing battle with physical and 'brain fog' symptoms said: "So I'm just frustrated and annoyed. I'm not under any specialist or anything for this, so it's all, I feel very unsupported by my GP, if I'm honest" (406-408). This may also suggest that GPs find 'brain fog' difficult to work with; maybe it is not perceived as serious enough to be referred to a specialist. Maybe it is hard to assess due to its intangibility and therefore causes difficulties in understanding what the most appropriate support might be.

For Taylor, highlighting of a possible link from their doctor seems to have helped them emotionally when coping with the unknown ('brain fog'):

> I thought that, I thought that I had some sort of illness, it sounds stupid. I thought there was something wrong in my brain basically, and that caused me to panic, and yeah, I started googling about what it could be, I did notice that coeliac was on there, but I still didn't connect the two, no one told me that, I wasn't really given much information when I was diagnosed. (line 436-441)

4. The Gluten Free Diet isn't Always a Magic Fix

Not all participants within the study noticed an improvement in their 'brain fog' following the introduction of the GFD, as the literature may suggest. Across participants, improvement has not been linear, and some continue still to experience variable 'brain fog' symptoms, which may be for a variety of reasons. In light of continued symptoms, participants have found their own ways to manage the symptoms and the difficulties associated with them.

4.1 "Will I be me?": Improvement is not Just About Symptom Reduction. For some, starting the GFD rapidly improved their symptoms. Particularly for Frankie, Charlie and Rowan, significant improvements were noticed after starting the GFD. Frankie noticed a stark improvement in their symptoms very quickly. Frankie said: "Oh well it started getting better after a week, after two weeks it was, ahh like a million times better, really was, it was just like, it was like a light was back on, I felt 20 years younger" (line 345-348). Frankie's words "I felt 20 years younger" could be interpreted as expressing some of the associated mental and physical qualities of being younger, such as more energy, better physical health, less stress and responsibility, as well as an increased sharpness cognitively, to name a few. The phrase is also often used to express a sense of happiness or rejuvenation. Those who did notice a difference following the GFD, described the feeling of improvement with words like 'lifting' and 'clearing', just like a physical fog would. Charlie said:

> . . . but as soon as I started the GFD, like it just cleared so quickly and it wasn't, it did feel like depression, it did feel like depression, and it's hard to pinpoint what was a depression and what wasn't but it did magically disappear once I'd gotten on the gluten free. (line 39-42)

For these individuals, they feel there is a direct link between ingesting gluten and their 'brain fog' symptoms, as when they have been 'glutened' (when gluten is accidentally ingested and symptoms are experienced), they have noticed an increase in their symptoms. Rowan, on times they think they have been 'glutened' said: "…as my symptoms come back all in a rush" (line 470-471).

Unfortunately, for others, despite being on the GFD, they continue to experience 'brain fog' symptoms. Sadly, Ashley feels their 'brain fog' symptoms have deteriorated since being on the GFD. For Taylor, Alex and Sam, whilst they feel their symptoms are improving, it is not as consistent or as quick as they would have hoped. Taylor portrayed a sense of feeling let down and disappointed by the GFD:

> You think with the gluten free diet your symptoms would improve, but I've kind of gone the other way, um, and they've probably got worse for a little bit and now they're easing off but they're still there and you would expect it not to be with the gluten free. (line 57-61)

For those who symptoms continue, grappling with the unknown of when or how their symptoms might improve appeared to be very difficult for them, Alex said:

> I just don't know, know how long, I hate to say it but I just don't know when I'll be well. So you kind of think to yourself, is this the best I'm going to be? Will I be 'me'? (line 416-419)

In contrast, Sam continues to experience 'brain fog' symptoms, but very clearly feels that the symptoms happen when they are not intaking the correct nutrients or eating regularly:

> I'll tell you when I do get it more, when I don't eat properly and I miss meals, if I don't get any nutrients, I tend to end up being a bit like that. I also get really tired and I yawn a lot, and again, I know when I'm not right, what I'd call it a bit like diabetes where you get unbalanced and you don't have enough nutrients in your body, and I tend to eat something and erm, to kind of, to make me feel a little bit better. (line 86-92)

Whilst Rowan notices a link between ingesting gluten and 'brain fog', like other participants, has hypotheses about other influencing factors upon their 'brain fog', saying: "And I feel like sometimes, feeling down can encourage the brain fog to come on" (line 592-593). This highlights that participants

recognise that there could be multiple causal factors involved in their 'brain fog' and lots is still unknown for them.

Most importantly, when talking to participants, it was felt that whilst symptom reduction was important to them, this was not the true marker of 'improvement'. Instead, it was their ability to now be present, engage, contribute, and enjoy life again. It was also apparent that it was hard to really measure 'improvement' in the sense of 'brain fog', as the experience of 'brain fog' is closely entwined with other elements of having CD, such as coping with the GFD, symptoms and adjustment to the diagnosis. Frankie described a change from finding everyday activities a chore, to actually wanting to do them: "So just like a day out with the kids stopping being like arrrgghh and it was like yay come on guys get in the car we're going out!" (line 369-371). Charlie further agreed, stating:

> I can interact in book club now, I can finish the book, I can have a proper conversation about it. I can watch films again, I enjoy them and I can remember what happens in them. Like going to the theatre again, like all these things, I feel I have the capacity to absorb and enjoy. I think enjoy is an important word as I feel I didn't have the capacity to enjoy anything and now I do. (line 421-427)

4.2. "Owning it": Navigating the 'Brain Fog' Symptoms. Throughout their 'brain fog' journey, participants were self-resourceful in finding ways to cope and manage their 'brain fog', which appeared to be a way in which to gain some control over their experiences within an uncontrollable situation. For some, this helped to compensate for the cognitive difficulties that they were experiencing, for others this helped to deal with the emotional impact of the experience. Coping strategies included communicating with others, further research and awareness about 'brain fog', acceptance of the symptoms and changing of some lifestyle factors. Many participants also used practical memory strategies, such as phone reminders and lists. Sam on helping them remember where their belongings are in the house said: "So what I tend to do now is that everything goes in its

place, so I put things in the same place, the wallet, the keys" (line 141-143). Alex, as well as using lists, initially felt the need to disguise or justify their difficulties to others, alluding to a sense of trickery in their actions. They said:

> You have to try and be really clever, like you write lots of notes down to try and remember, and if you don't know or remember, you try and brush it off like "oh it's my age" or whatever or "I've got loads of things on". Like I've got two children and I'll be like "oh I've got loads of things on my mind at the same time" and it is literally just trying to blag it really. (line 129-135)

However, at the point of interview, Alex had found some acceptance by "owning" their symptoms. This acceptance stage may also be linked to the loss and grief process previously discussed in an earlier theme. In this case, the acceptance made them feel less embarrassed, more equipped to cope with the symptoms and reduced the emotional impact of their symptoms. In addition, it seems to have led to an increased sense of control over how others may perceive the symptoms and certain situations. Alex said:

> And also, like, my awareness of it, I will tell people now, I'm not as embarrassed as I was, like I've said to my boss, "I'm really sorry, I'm just not getting it, can you go through it again, my brain is not understanding it". So, it's almost like I'm just owning it now, which makes it easier as its kind of like, more of a reality of what you've got, like you can't just, you're not accepting it, but there's an acceptance… [unrelated speech] … like if I don't own it, and I'm not, don't tell people, you're almost allowing people to have an assumption about what you're going through anyway. Whereas actually, sometimes it feels like an excuse and I don't want it to be excuse, I want it to be a reason. And that's the only way it's got easier really, through just owning it. (line 325-332)

Many participants additionally talked about the support and guidance they had received through CD social media support groups. Many said it helped them to understand their 'brain fog' symptoms in the context of CD and helped them feel less isolated, Taylor said:

> As I didn't know this was down to coeliac in the beginning, and at the start, it's seeing people comment on the groups and on the Facebook I'm in and I was like oh my god I have the same symptoms. And you talk to people about it and it helps you feel that you're not the only one. (line 421-425)

Participants all agreed that increased knowledge and awareness of 'brain fog' was helpful for both them and others in navigating and coping with 'brain fog'. Rowan even associated increased knowledge with an improvement in their symptomatology:

> Umm, and because it was gradual and there was no one day where I was like "wow I'm better" so it's really hard to say, but I would say it was between 3 to 6 months where like I didn't have to worry about the toilet as much. It was probably about then that I knew all I could know about coeliac disease without going to study it academically. (line 436-441)

This suggests that increased awareness and understanding of 'brain fog' is important and helpful for those experiencing it to cope and manage their symptoms.

Discussion

The aim of the study was to explore how individuals with recently diagnosed CD experience the phenomenon of 'brain fog'. This was achieved using IPA methodology to analyse seven semi-structured interviews. The analysis demonstrated that the experience is complex, but most importantly has significant impacts upon many elements of individual's lives and sense of self. Four group experiential themes emerged from the data: 1) The Course of 'Brain Fog', 2) Physical Symptoms Take Priority, 3) Lost in the Fog and 4) The GFD isn't Always the Magic Cure.

Findings in Context

Many of the findings from this study align with findings from existing literature, such as the specific areas of cognition participants reported to be affected like memory, attention, executive functioning, and speed of processing (Yelland, 2017). Furthermore, the themes that emerged closely map onto qualitative investigations of 'brain fog' in other health conditions, such as that by Callan et al. (2022) in relation to the long-term effects of COVID-19, in which the emerging themes such as 1) psychosocial impact: guilt, shame and stigma, 2) hypothesising mechanisms to inform self-management and 3) navigating healthcare, map onto the present study's themes. This may suggest that the findings from the present study are reflective of others' experiences and that 'brain fog' may be a universally similar experience, with smaller complexities and nuances at a diagnosis or person level. In relation to COVID-19, the context in which participants were experiencing 'brain fog' was during and immediately after the COVID-19 pandemic, which may give a framework to understand some of the experiences reported, for example, how some individuals were unable to recognise their symptoms at the time or unable to recognise any social impacts due to the pandemic restrictions in place.

When making sense of their cognitive difficulties, participants were generally initially worried about their symptoms and tried to make sense of them with plausible explanations. This links to Leventhal's common-sense model of health and illness (Leventhal et al., 2003) which is a theoretical framework for understanding how individuals conceptualise their illness and respond to it. Individuals have their own, unique beliefs about their illness which are thought to fall under specific categories including perceptions about the symptoms, cause, consequences, and level of control (Rivera et al., 2019). Research has suggested that those who have more understanding and answers regarding their illness, and believe in the effectiveness of their treatment, hold more positive and helpful beliefs (Law et al., 2014; Leventhal et al., 2003). This was observed in participants in this study; once participants had contextualised their 'brain fog' to be related to CD, their level of worry and catastrophising

appeared to be relieved and they were able to talk about 'brain fog' and coping in a much more hopeful way. This may be due to feeling contained by a specific cause and having regained control over what was happening to them. Additionally, participants mostly conceptualised their difficulties within a medical model, considering causes such as dementia and vitamin deficiencies. This is likely due to the context in which the sample are situated; they are an exclusively white British sample, living in the UK, in which the 'biomedical model' is dominant (Farre & Rapley, 2017). Sense making of these experiences may be very different in other cultures and countries.

Participants reported varied improvements in their 'brain fog' after adherence to the GFD. This is in line with existing research which has reported mixed findings on the impact of the GFD on cognitive impairments (e.g., Hu et al., 2006). Croall et al. (2020a) found no significant differences in cognitive performance between those with established CD on a GFD and established CD not on a GFD. However, from further analyses found that cognitive deficits were present when newly diagnosed with CD, but then the deficits appear to stabilise following adherence to the GFD, except for visuoconstructive abilities, which may still decline. There are various possible reasons why participants may continue to experience 'brain fog' symptoms. Lichtwark et al. (2014) suggested, in a small sample, an association between 'brain fog' symptoms and intestinal (mucosal) healing. Research suggests that intestinal healing can take many years on the GFD and is not always fully achievable; Newnham et al. (2016) found that after one year on the GFD, 37% of their sample had achieved mucosal healing to normal histology levels, and by five years, 50% had. Therefore, incomplete intestinal healing may explain some of the persistent 'brain fog' symptoms experienced. They may also still be unknowingly ingesting gluten, through a lack of knowledge about the GFD, or have a type of CD called refractory CD (RCD) in which symptoms persist despite a strict GFD for more than 12 months. Estimates suggest up to 20% of those with CD may have RCD (Lebwohl et al., 2018; Leffler et al., 2007). Alternatively, the proposed mechanisms by which gluten ingestion is linked to 'brain fog' may be incorrect, or that there are other causal factors involved in an individual's 'brain

fog'. These could range from lack of sleep to poor nutrition (Kverno, 2021). Despite the exact mechanisms of 'brain fog' in CD being unknown, the results of the present study point towards phenomenological evidence of the GBA in CD, especially for those that experienced an improvement in their 'brain fog' and psychological symptoms following starting the GFD. The findings from this study further support the proposed bidirectional link; that a disruption in the gut or gut microbiome may cause 'brain fog' and other psychological symptoms through the GBA. Participants then described how they felt their increased stress and anxiety about their 'brain fog' and CD may have increased their gut symptoms. This then continues the cycle of dysregulation in the body. Whilst this conclusion is based upon a very small number of participants, the findings of this study provide a basis and rationale for further exploration of the GBA within CD and point towards where the points of intervention should be focused.

In an alternative line of interpretation, mental health difficulties should also be considered in relation to 'brain fog'. The experiences described in this study such as feelings of depression and isolation, align with findings in the existing literature that CD is associated with higher levels of mental health difficulties (e.g., Clappison et al., 2020) and there is evidence to suggest that mental health difficulties, such as depression, are associated with 'brain fog' or cognitive dysfunction (e.g. Atique-Ur-Rehman & Neill, 2019; Pan et al., 2019). Furthermore, some of the sample reported they were experiencing menopause or perimenopause and were prescribed HRT medication for this. Whilst those participants felt that their menopausal symptoms were not a main causal factor in their 'brain fog', nonetheless cognitive difficulties and 'brain fog' are associated with this condition (Jaff & Maki, 2021; Zhu et al., 2022). This may also the case for Type 1 Diabetes which one participant had a diagnosis of (Li et al., 2017). Therefore, there may be other contributing factors to 'brain fog' and this is likely to always be the case given CD is associated with other co-morbidities and long-term health consequences (Del Prete et al., 2020; Kaukinen, 2021).

Strengths and Limitations

There are various strengths and limitations to be considered in this study. The study had strength in using a rigorous IPA methodology to be the first study to qualitatively investigate the experience of 'brain fog' within a sample of people with CD. Whilst previously, 'brain fog' was understood as a concept with related cognitive impairments, this study furthers this understanding at a more personal level and describes some of the significant and distressing impacts of the cognitive symptoms which were not previously known. Therefore, this study not only contributes to the literature which suggests that, for some, 'brain fog' is a symptom of CD and should be increasingly recognised as such, but also the findings help to guide understanding of what support and interventions might be needed at a clinical level. Furthermore, the study gained narratives from a range of ages and occupations; this had benefit in gaining a breadth of experiences from varying perspectives, including different health systems and personal contexts. The semi-structured interview method allowed for flexibility within the interview, enabling participants to elaborate on any question and the researcher to be guided by what was important for the participant (Alamri, 2019). Due to the varying perspectives gained, this study demonstrated that there are complexities to 'brain fog' when associated with CD, and therefore it appears important to consider each presentation of 'brain fog' on an individual level.

However, whilst the exclusion criteria aimed to limit any other difficulties that can cause 'brain fog', as discussed there may have been other factors contributing to participants' experiences that are unknown; however, the aim of this study was not to develop a causal relationship between 'brain fog' and CD, rather to understand the lived experience. Furthermore, the sample contained mostly female participants, with one male, and all participants were from a white British ethnic background, and therefore findings should be considered within the context of these limitations. For this study, experiences were reported similarly across genders. However, based on the very small sample it cannot be concluded that the experience is universally similar for both males and females

and further research must be completed to establish this. The white British sample brings other considerations, including possible lack of diversity in participants' sense making of their 'brain fog', so conclusions are based only on this perspective. It also raises considerations regarding the barriers to engagement in research for individuals who are not white British. They may be at initial diagnostic stage, in not being diagnosed appropriately in the first place, through to post diagnostic support. Given this study's sample was recruited through social media support groups, it may be that forums such as these are less accessible for individuals who are not white British. Future research should aim to represent the UK's diverse population to ensure services developed for those with CD are appropriately designed (Redwood & Gill, 2013).

A further important limitation of this study is that it used remote, online methods for all stages of the research process. Whilst this increased accessibility to participants geographically, was a necessary practicality for the timescale of the study and was based on ongoing COVID-19 restrictions for face-to-face research within higher education, this excluded those who may not have the equipment to participate in the study, access to the internet or have the required digital literacy to be part of social media groups, use email and video conferencing software (Lo Iacono et al., 2016). Furthermore, interviews were relatively short in length which may have limited the depth gained however the researcher felt that all interviews were terminated when participants had reached saturation in their experiences.

Clinical Implications

In contrast to much of the literature that suggests that the cognitive impairments that characterise 'brain fog' are 'mild', 'subtle' and 'slight' (Durazzo et al., 2022; Lichtwark et al., 2014; Yelland, 2017), the participants in this study described significant difficulties which had debilitating impacts at different levels of their lives. Whilst this small sample limits the scope of generalisations, nevertheless it highlights that 'brain fog' can be significantly impactful and should be treated as such

within the literature and clinically. This increased understanding of 'brain fog' has utility pre-CD diagnosis in being a symptom that health professionals should consider when confronted with patients who may not have the 'classic' CD symptoms. There is also utility post-diagnosis, in designing services for individuals with CD; firstly, in providing individuals with detailed information about 'brain fog' and secondly in screening, monitoring and providing support for individuals. Many of the sample did not realise they were experiencing 'brain fog' at the time, so regular cognitive screening may have benefit in identifying symptoms leading to appropriate interventions, such as a review of their GFD with a dietician in case of accidental gluten ingestion or psychological support in coping or making adjustments to function with the impairments. Therefore, a multidisciplinary approach to CD diagnosis and management may have benefit, with integrated psychology input for both cognitive and psychological screening and intervention. This would have implications for the economic status of health services, to possibly reduce the burden of those who may develop long term physical and mental health consequences of CD and in particular untreated CD (Kårhus, 2020; Kaukinen, 2021), by taking a preventative rather than reactive approach.

Future Research

This study examined individual's experiences at the beginning of their CD journey. All participants were at different stages, in terms of improvement, knowledge and awareness, making sense of their experiences and adjustment. Therefore, there may be utility in replicating a similar study in those further along in their journey, with more time to have made sense of their experiences. Furthermore, this study used one source of data: semi-structured interviews. Given that the 'brain fog' experience described by participants was vague and hard to articulate, triangulation of data, as advised by Larkin and Thompson (2011), may have benefit, using methods such as symptom and food diaries. Finally, further investigation of the mechanisms and contributing factors involved in CD related 'brain fog' would have clinical utility in supporting individuals with the experience. Cognitive assessments, considering in particular the cognitive difficulties described in this study and

the wider ‘brain fog’ literature at various time points in the CD journey may help to achieve this further understanding.

Conclusion

To conclude, this study increases understanding of ‘brain fog’ within a CD context; all participants in this study highlighted the importance of increased knowledge and awareness in understanding their symptoms, in reducing stress and embarrassment and in moving forward with their diagnosis and management of CD. Therefore, this provides a clear rationale for further exploration on this topic – to alleviate individual’s distress and enable better functioning.

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3. Press Release for the Literature Review

Risk of Depression 3 Times More Likely in Those with Coeliac Disease

Adults with coeliac disease are estimated to be 3.34 times more likely to develop depression than the general population. These findings add further support for the notion that mental health screening and support should be an integral part of coeliac disease healthcare.

The study, carried out in October 2022, reviewed findings across 36 research studies, all measuring depression in adults with coeliac disease – an autoimmune condition that causes gut damage when gluten is eaten. Gluten is found in wheat, barley and rye, which are widely used to make all sorts of commonly eaten foods such as bread, pasta and pizza. The study found that across all people with coeliac disease, over 21% had clinical levels of depression. This is a much higher rate than in the general population – the World Health Organisation estimates that around 5% of adults globally have depression. Levels of depression were different depending on how well people were following their gluten free diet – the only treatment for the condition currently. People who followed the diet well were less likely to experience depression than people who still consumed gluten.

Emily Ahmed, Trainee Clinical Psychologist at the University of Birmingham, said: *"This study used an inclusive approach to show us that depression may be a significant problem for people with coeliac disease. There are several reasons why this might be; it might be that there is a biological cause for the depression, such as vitamin deficiencies or from chemical imbalances within the brain. Individuals with coeliac disease also face daily struggles managing the burden of a chronic health condition and strict gluten free diet, which often impacts them emotionally, and could lead to mental health difficulties."*

Further research to understand the causes of depression and other mental health difficulties will be important in developing services and processes to support people with coeliac disease. It has

been suggested that mental health screening and support should be a routine part of healthcare services for people with coeliac disease. Having depression may mean it is harder to maintain a gluten free diet, and therefore increased support could not only reduce mental health difficulties but also increase long-term physical health, reducing the burden on the NHS.

END

4. Press Release for the Empirical Research Paper

Lost In the Fog: 'Brain fog' a Distressing 'Hidden' Symptom of Coeliac Disease

A recent study has shone a light on a 'hidden' symptom of the autoimmune condition, coeliac disease - a condition that causes gut damage following the consumption of gluten. Gluten is found in wheat, barley, and rye, and used widely in staple foods such as bread, pasta and pizza. New research reveals that this symptom, commonly referred to as "brain fog", can be severe and can have a significant impact on all areas of life.

'Brain fog' leads to difficulties in brain activity such as memory, language, and concentration. Some people with 'brain fog' have described feeling like their brain is 'fuzzy' and that they cannot think properly. Because of this people find it harder to function in their everyday life – they may forget what they need from the shops or they may struggle to concentrate for long periods of time, such as when reading a book or trying to work. Most will have heard of 'brain fog' in relation to the Menopause or Long Covid, but not much is known about this difficulty in coeliac disease.

Emily Ahmed, Trainee Clinical Psychologist at the University of Birmingham, said: *"Previously, 'brain fog' hasn't really been recognised as an 'official' symptom of coeliac disease, yet so many people within the coeliac disease community have reported that they suffer from it. There has been previous research that connects coeliac disease and 'brain fog' together, but we were still unsure about what the experience is like for people. This study enhances our knowledge and understanding of what 'brain fog' feels like for people with coeliac disease and shows us just how debilitating it can be".*

The study, by researchers at the University of Birmingham, interviewed seven people who had been diagnosed with coeliac disease within the last 6 to 18 months, and who felt they had experienced or continue to experience 'brain fog'. Researchers found that people reported a wide

variety of symptoms that impacted on their everyday life. Some people were no longer able to do their jobs, whilst others had to rely on their families to pick up their children up from school. Most worryingly, some people said that the 'brain fog' had knocked their confidence, made them feel anxious, depressed and embarrassed, and that they were no longer the same person that they used to be.

Previous research has suggested that 'brain fog' is quite a mild condition, however the people interviewed in this study would disagree. Before realising their 'brain fog' might be linked to their coeliac disease, people thought the problems were due to their busy, stressful life, the COVID-19 pandemic, other physical and mental health problems or even dementia. One interviewee in the study said: *"If it's making you think you have early onset dementia, like I feel it's bigger than a little fog".* Whilst there were only seven people interviewed, and so a small study, it certainly shows a growing picture that for some, the symptoms can be severe and can have a significant impact on life.

It is estimated that around 1% of the worldwide population have coeliac disease, however it is believed that only around a quarter of those with coeliac disease have actually been diagnosed. One of the reasons for this is that there is so much variability in the symptoms that people with coeliac disease can present with, meaning that making a diagnosis can be challenging. Some interviewees in the study felt that when being diagnosed, the focus was only on their physical symptoms, such as diarrhoea and bloating, and there was very little, if any, discussion from health professionals about some of the 'brain fog' symptoms they were experiencing. Some believed that, had their 'brain fog' been recognised as a possible symptom, they would have been diagnosed sooner, and therefore they would have experienced less distress. Emily Ahmed concludes: *"Our hope is that further recognition and understanding of this symptom of coeliac disease can aid health professionals and services in not only recognising this symptom during diagnosis but also in ongoing*

support – being given information and guidance was really important for people in this study to feel in control of what was happening to them".

END

B. Appendices

Appendix A

List of all Studies Included in the Meta-Analysis by Mental Health Disorder

Table A1

List of all Studies Included in the Meta-Analysis by Mental Health Disorder

Mental Health Disorder	Study Name	
Depression	Carta et al.	2002
	Addolorato et al.	1996
	Addolorato et al.	2004
	Zingone et al.	2010
	Passananti et al.	2013
	Addolorato et al.	2001
	Zingone et al.	2021
	van Hees et al.	2014
	van Hees et al.	2015
	van Hees et al	2012
	Longarini et al.	2018
	Addolorato et al.	2008a
	Addolorato et al. 2	2008b
	Alharbi et al.	2017
	Arigo et al.	2011
	Barratt et al.	2013
	Briani et al.	2008
	Ciacci et al.	1998
	Dana et al.	2020
	Dorn et al	2010
	Fera et al.	2003
	Guedes et al.	2020
	Hauser et al.	2006
	Morris et al.	1970
	Nachman et al.	2010
	O'Shaughnessy et al.	2022
	Parker et al.	2022
	Siniscalchi et al.	2005

Mental Health Disorder	Study Name	
	Stone et al.	2012
	Zylberberg et al.	2017
	Carta et al.	2015
	Hallert & Derefeldt	1982
	Ramirez-Cervantes et al.	2015
	Garud et al.	2009
	Saleem et al.	2012
	Gili et al.	2013
	Ludvigsson et al.	2007a
	Ludvigsson et al.	2018
Anxiety	Carta et al.	2002
	Addolorato et al.	1996
	Addolorato et al.	1996
	Addolorato et al.	2004
	Zingone et al.	2010
	Passananti et al.	2013
	Addolorato et al.	2001
	Ciacci et al.	2021
	Zingone et al.	2021
	Addolorato et al.	2008a
	Addolorato et al. 2	2008b
	Barratt et al.	2013
	Dana et al.	2020
	Fera et al.	2003
	Guedes et al.	2020
	Hauser et al.	2006
	Lebovits et al.	2022
	O'Shaughnessy et al.	2022
	Parker et al.	2022
	Rostami-Nejad et al.	2020
	Carta et al.	2015
	Hallert & Derefeldt	1982
	Ramirez-Cervantes et al.	2015
	Garud et al.	2009
	Ludvigsson et al.	2018
	Lebwohl et al.	2021

Mental Health Disorder	Study Name	
	Addolorato et al.	2004
Eating Disorders	Passananti et al.	2013
	Arigo et al.	2011
	Satherley et al.	2016
	Marild et al.	2017
	Fink et al.	2022
	Garud et al.	2009
	Lebwohl et al.	2021
Bipolar Disorder	van Hees et al.	2014
	Carta et al.	2015
	Garud et al.	2009
	Saleem et al.	2012
	Ludvigsson et al.	2007a
Psychotic Disorders	West et al.	2006
	Garud et al.	2009
	Ludvigsson et al.	2007b
	Lebwohl et al.	2021
Obsessive Compulsive Disorder	Fera et al.	2003
	Hallert & Derefeldt	1982
	Garud et al.	2009

Appendix B

Comparison with Other Mental Health Disorders

As part of the search strategy, studies measuring other specific mental health disorders were collated, including anxiety (*n* = 26), eating disorders (*n* = 7), bipolar disorder (*n* = 5), psychotic disorders (*n* = 4), and OCD (*n* = 3). Some studies reported multiple outcomes. The comparison of depression prevalence rates with the prevalence rates of other mental health disorders in individuals with CD is reported in Table A1. A forest plot of this subgroup analysis is presented in Figure B1. A statistically significant difference in prevalence rates was observed for the different mental health conditions (X^2 = 804.63, p < 0.0001). The analysis shows that the estimated prevalence of depression in individuals with CD was 21%, anxiety was 30%, eating disorders 4%, bipolar disorder 2%, psychotic disorders 0.4% and OCD 9%.

Table A1

The Prevalence Rates (PR) of Other Mental Health Conditions for Individuals with CD

Mental Health Disorder	*k*	PR	95%-CI
Depression	45	0.21	0.19 to 0.24
Anxiety	44	0.30	0.27 to 0.33
Eating Disorder	9	0.04	0.027 to 0.05
Bipolar Disorder	6	0.02	0.004 to 0.03
Psychotic Disorders	5	0.004	0.002 to 0.006
OCD	3	0.09	-0.013 to 0.20

Studies that included estimates of the prevalence of the various mental health disorders in a CD sample and in a contrast healthy, general population group were used to estimate the relative risk of all mental health disorders (Table A2). There were 13 studies that reported this data for depression, 9 for anxiety, 3 for eating disorders, 2 for bipolar disorder, 1 for OCD and 1 for psychotic disorders. A forest plot of this subgroup analysis is presented in Figure B2. There was an increased risk of depression (RR = 3.34, 95% CI 2.34 to 4.77), anxiety (RR = 2.15, 95% CI 1.67 to 2.78) and eating disorders (RR = 5.50, 96% CI 3.09 to 9.78). Bipolar disorder carried a relative risk of 3.22 (95% CI 0.93 to 11.15) in individuals with CD relative to the general population. As the 95% confidence intervals

span around 1, no conclusions can be made regarding risk and there is likely no difference in risk. In contrast, there was a decreased rate of OCD (RR = 0.67, 95% CI 0.12 to 3.61) and psychotic disorders (RR = 0.08, 95% CI 0.009 to 0.74) in persons with CD relative to the general population. Once again, for OCD the 95% confidence intervals span around 1 and should therefore be interpreted with caution. For OCD and psychotic disorders, estimates were derived from a single study and should be treated with caution as they are likely to change with the publication of further studies.

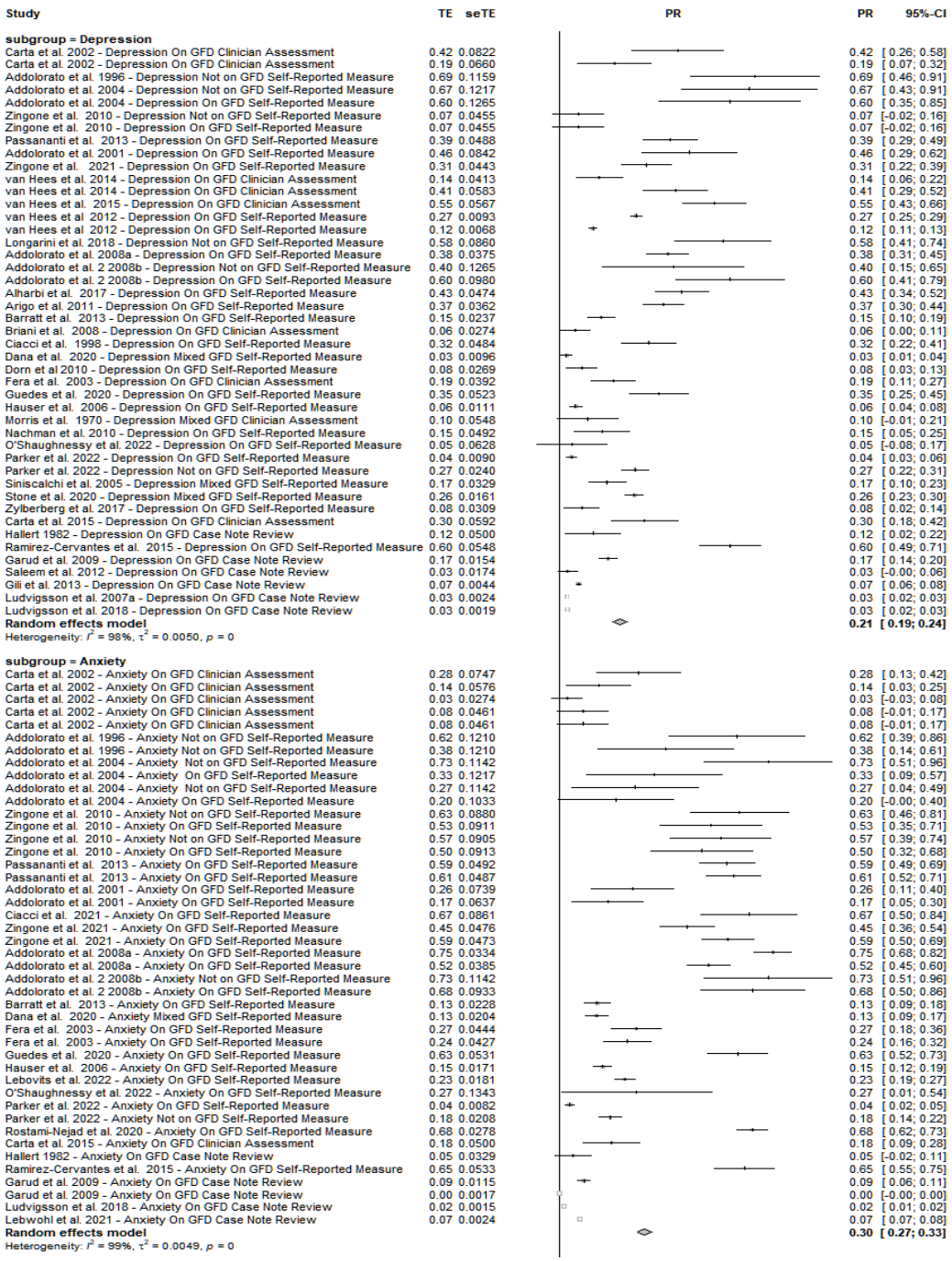
Table A2

The Relative Risk (RR) of Other Mental Health Conditions for Individuals with CD Compared with the General Population

Mental Health Disorder	*k*	RR	95%-CI
Depression	14	3.34	2.34 to 4.77
Anxiety	19	2.15	1.67 to 2.78
Eating Disorders	5	5.50	3.09 to 9.78
Bipolar Disorder	3	3.22	0.93 to 11.15
OCD	1	0.67	0.12 to 3.61
Psychotic Disorders	1	0.08	0.009 to 0.74

Figure B1

Forest Plots of the Prevalence Rates of Various Mental Health Disorders in Individuals with CD Compared to the General Population



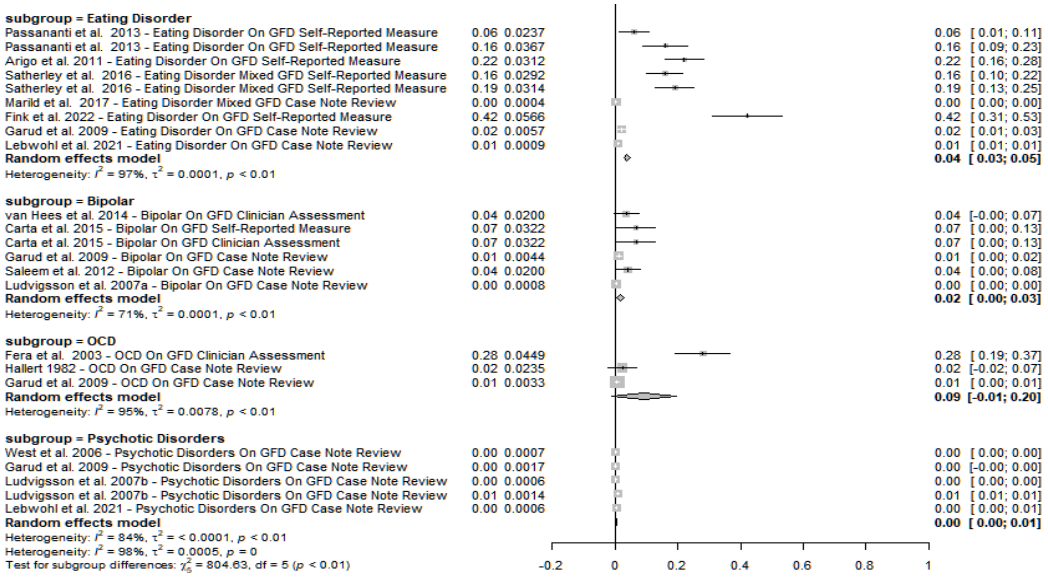
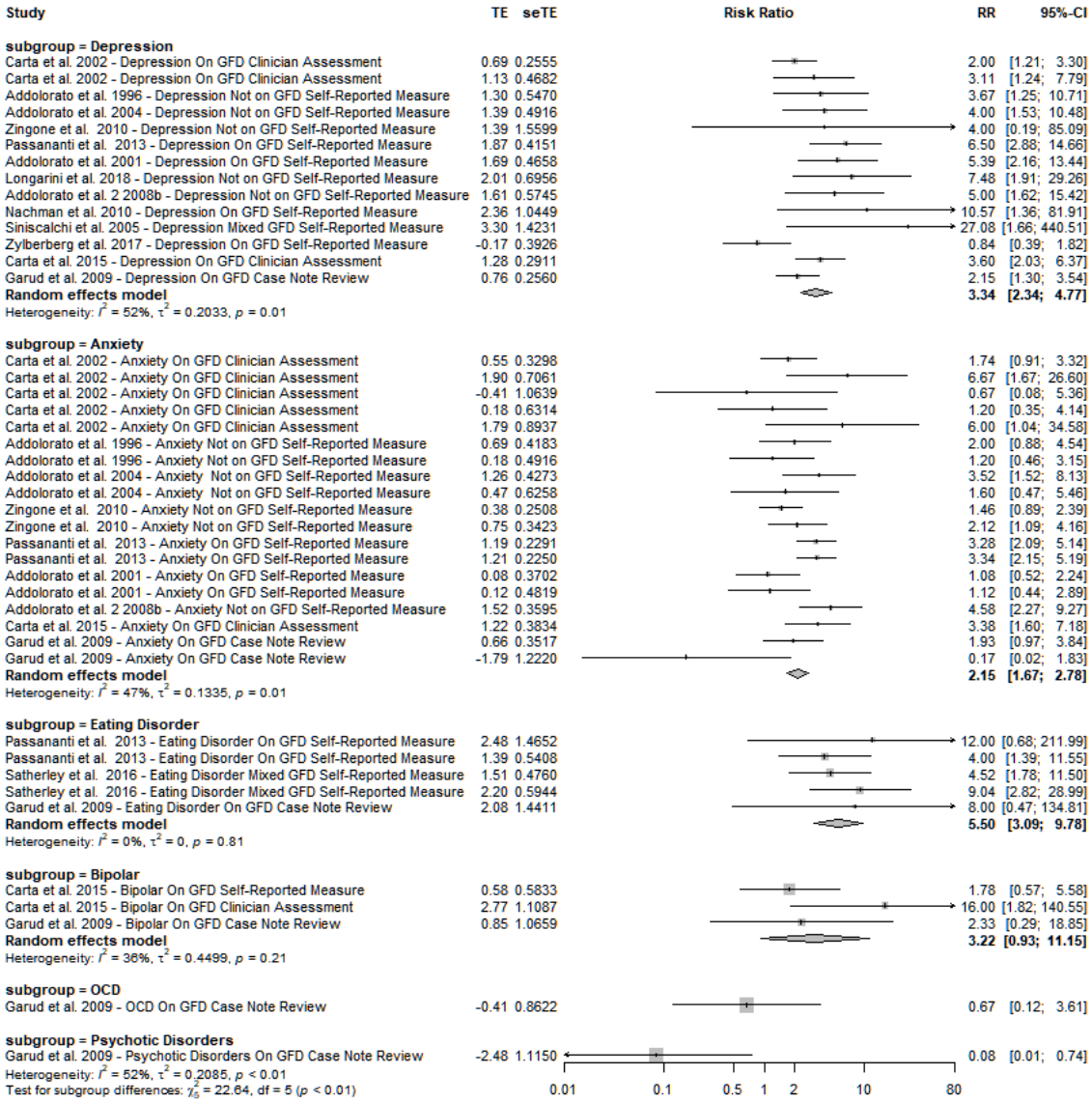

subgroup = Eating Disorder
Passananti et al. 2013 - Eating Disorder On GFD Self-Reported Measure 0.06 0.0237 0.06 [0.01; 0.11]
Passananti et al. 2013 - Eating Disorder On GFD Self-Reported Measure 0.16 0.0367 0.16 [0.09; 0.23]
Arigo et al. 2011 - Eating Disorder On GFD Self-Reported Measure 0.22 0.0312 0.22 [0.16; 0.28]
Satherley et al. 2016 - Eating Disorder Mixed GFD Self-Reported Measure 0.16 0.0292 0.16 [0.10; 0.22]
Satherley et al. 2016 - Eating Disorder Mixed GFD Self-Reported Measure 0.19 0.0314 0.19 [0.13; 0.25]
Marild et al. 2017 - Eating Disorder Mixed GFD Case Note Review 0.00 0.0004 0.00 [0.00; 0.00]
Fink et al. 2022 - Eating Disorder On GFD Self-Reported Measure 0.42 0.0566 0.42 [0.31; 0.53]
Garud et al. 2009 - Eating Disorder On GFD Case Note Review 0.02 0.0057 0.02 [0.01; 0.03]
Lebwohl et al. 2021 - Eating Disorder On GFD Case Note Review 0.01 0.0009 0.01 [0.01; 0.01]
Random effects model 0.04 [0.03; 0.05]
Heterogeneity: I^2 = 97%, τ^2 = 0.0001, p < 0.01
subgroup = Bipolar
van Hees et al. 2014 - Bipolar On GFD Clinician Assessment 0.04 0.0200 0.04 [-0.00; 0.07]
Carta et al. 2015 - Bipolar On GFD Self-Reported Measure 0.07 0.0322 0.07 [0.00; 0.13]
Carta et al. 2015 - Bipolar On GFD Clinician Assessment 0.07 0.0322 0.07 [0.00; 0.13]
Garud et al. 2009 - Bipolar On GFD Case Note Review 0.01 0.0044 0.01 [0.00; 0.02]
Saleem et al. 2012 - Bipolar On GFD Case Note Review 0.04 0.0200 0.04 [0.00; 0.08]
Ludvigsson et al. 2007a - Bipolar On GFD Case Note Review 0.00 0.0008 0.00 [0.00; 0.00]
Random effects model 0.02 [0.00; 0.03]
Heterogeneity: I^2 = 71%, τ^2 = 0.0001, p < 0.01
subgroup = OCD
Fera et al. 2003 - OCD On GFD Clinician Assessment 0.28 0.0449 0.28 [0.19; 0.37]
Hallert 1982 - OCD On GFD Case Note Review 0.02 0.0235 0.02 [-0.02; 0.07]
Garud et al. 2009 - OCD On GFD Case Note Review 0.01 0.0033 0.01 [0.00; 0.01]
Random effects model 0.09 [-0.01; 0.20]
Heterogeneity: I^2 = 95%, τ^2 = 0.0078, p < 0.01
subgroup = Psychotic Disorders
West et al. 2006 - Psychotic Disorders On GFD Case Note Review 0.00 0.0007 0.00 [0.00; 0.00]
Garud et al. 2009 - Psychotic Disorders On GFD Case Note Review 0.00 0.0017 0.00 [-0.00; 0.00]
Ludvigsson et al. 2007b - Psychotic Disorders On GFD Case Note Review 0.00 0.0006 0.00 [0.00; 0.00]
Ludvigsson et al. 2007b - Psychotic Disorders On GFD Case Note Review 0.01 0.0014 0.01 [0.01; 0.01]
Lebwohl et al. 2021 - Psychotic Disorders On GFD Case Note Review 0.00 0.0006 0.00 [0.00; 0.01]
Random effects model 0.00 [0.00; 0.01]
Heterogeneity: I^2 = 84%, τ^2 = < 0.0001, p < 0.01
Heterogeneity: I^2 = 98%, τ^2 = 0.0005, p = 0
Test for subgroup differences: χ^2_5 = 804.63, df = 5 (p < 0.01)
-0.2
0
0.2
0.4
0.6
0.8
1

Figure B2

Forest Plots of the Relative Risk of Various Mental Health Disorders in Individuals with CD Compared to the General Population



Appendix C

Social Media Advertisement

UNIVERSITY OF BIRMINGHAM

Do you have Coeliac Disease

AND

Have you experienced 'brain fog' or 'fuzzy thinking'?

We are looking for individuals with Coeliac Disease to share their experiences of 'brain fog' with us.

You can participate if:

- You have experienced in the past or currently experience 'brain fog' or cognitive difficulties such as problems with your memory, concentration, and attention.
- You have been diagnosed with Coeliac Disease by a healthcare professional within the last 6- 18 months.
- You are aged 18 -60 years old
- You are following the gluten free diet
- You do not have any recent diagnosed mental health, substance use or neurological difficulties
- You have not had any other health conditions newly diagnosed within the previous six months

If you participate:

- You will take part in one interview, remotely using a video communication program such as Zoom or Skype.
- You will be able to withdraw up to 14 days after receiving a transcript of your interview
- The data stored for this study will not contain any personal identifiable information
- As a token of appreciation, you will be given a **£10 amazon voucher** upon completion of your interview

If interested in participating or for more information, please contact Emily Ahmed: [redacted]

Appendix D

Ethical Approval

Dear Dr Gary Law,

Re: "Investigating 'Brain fog' in Newly Diagnosed Coeliac Disease: A Multiple Case Study"

Application for amendment ERN_21-1398A

Thank you for the above application for amendment, which was reviewed by the Science, Technology, Engineering and Mathematics Ethical Review Committee.

On behalf of the Committee, I can confirm that this amendment now has full ethical approval.

I would like to remind you that any substantive changes to the nature of the study as now amended, and/or any adverse events occurring during the study should be promptly brought to the Committee's attention by the Principal Investigator and may necessitate further ethical review. A revised amendment application form is now available at https://intranet.birmingham.ac.uk/finance/accounting/Research-Support-Group/Research-Ethics/Ethical-Review-Forms.aspx . Please ensure this form is submitted for any further amendments.

Please also ensure that the relevant requirements within the University's Code of Practice for Research and the information and guidance provided on the University's ethics webpages (available at https://intranet.birmingham.ac.uk/finance/accounting/Research-Support-Group/Research-Ethics/Links-and-Resources.aspx) are adhered to and referred to in any future applications for ethical review. It is now a requirement on the revised application form (https://intranet.birmingham.ac.uk/finance/accounting/Research-Support-Group/Research-Ethics/Ethical-Review-Forms.aspx) to confirm that this guidance has been consulted and is understood, and that it has been taken into account when completing your application for ethical review.

Please be aware that whilst Health and Safety (H&S) issues may be considered during the ethical review process, you are still required to follow the University's guidance on H&S and to ensure that H&S risk assessments have been carried out as appropriate. For further information about this, please contact your School H&S representative or the University's H&S Unit at healthandsafety@contacts.bham.ac.uk.

If you require a hard copy of this correspondence, please let me know.

Kind regards,

Ms Sam Waldron (she/her)

Research Ethics Officer
Research Strategy & Services Division

University of Birmingham

Appendix E

Participant Information Sheet (PIS)

Understanding the Experience of 'Brain Fog' in Coeliac Disease

Participant Information Sheet

My name is Emily Ahmed and I am a Trainee Clinical Psychologist studying at the University of Birmingham. I am conducting this research as part of the requirements of the Clinical Psychology Doctorate course I am enrolled upon.

I would like to invite you to take part in a research study around an experience sometimes called 'brain fog' that has been reported by some people with Coeliac disease (CD). This experience includes symptoms such as confusion and difficulties with short-term memory, concentration, and attention, and is often experienced alongside fatigue. Please read this information sheet before you decide whether you would like to take part. Feel free to talk to other people about this study before you decide whether you would like to take part. It should take no more than 10 minutes to read.

What is the purpose of the study?

This study is being carried out as a postgraduate student research project that will make up part of an educational qualification (ClinPsyD). The main purpose of this study is to understand people's experience of 'brain fog' in CD. Symptoms are reported by some people with CD before they have started a gluten free diet (GFD) or if they have been accidentally exposed to gluten once they are following the diet.

What will you ask me to do?

The study will involve:

An Interview: There will be an interview carried out **remotely through an online video platform such as zoom or skype**. The interview will be recorded. During the interview you will be asked about your experience of 'brain fog', your symptoms, the impact on your life and how concerned you are about it. This will last up to an hour.

I would like to recruit around 7 people for this study. You will not be required to make any changes to the way you manage your CD to participate in the study; we assume that anyone taking part will continue to follow the gluten-free diet.

The interviews will be analysed using qualitative methods to understand individuals' lived experiences of brain fog and to see whether there are any commonalities across experiences. I will not use your real name for this to protect your identity. All transcripts will be assigned a pseudonym.

Who can take part?

You must:	**You must not:**
Have experienced 'brain fog' prior to your diagnosis or still be experiencing it now	Have a diagnosed neurological disorder or history of brain injury.

Have a diagnosis of Coeliac disease, made by a health professional within the last 6 to 18 months Be following the gluten free diet (GFD)	Have diagnosis of a current mental health difficulty Have a history of, or current substance misuse difficulty. Have another health condition newly diagnosed within the last six months

What are the benefits and risks of taking part?

The main benefit of the study is that you will be contributing to research that has important implications for the future of CD understanding. Taking part in this study will not affect the outcome of your treatment in any way. You will be given a £10 high street voucher for participating in the study.

There are no disadvantages or risks posed to you as a result of taking part in this study. However, the interview could be quite tiring; we will take breaks if needed.

COVID-19 Precautions

The interviews will be conducted remotely using a video platform such as zoom or skype. Therefore, there are no COVID-19 related risks posed as a result of this research.

Do I have to take part?

Taking part in this study is completely voluntary and greatly appreciated. If you do take part, you have the right to withdraw without giving a reason. If you wish to withdraw you should contact the researcher, Emily Ahmed or her supervisor (detailed at the bottom of this document) and ask for your data to be withdrawn. You will have up to 7 days after your interview to withdraw.

What if I am worried about my 'brain fog' or Coeliac symptoms?

If you are worried, we suggest that you talk to your GP about your symptoms or contact the Coeliac Uk Helpline on **0333 332 2033. The helpline is staffed by dieticians and food experts and is open to call** from 10am to 4pm Monday to Friday.

Will my taking part in the study be kept confidential?

Yes. The records of this study will only be accessible by the research team on this project. You will not be able to be identified from the information in the report. All data that identifies you (your name, etc.) will be destroyed 3 months after the study has finished in line with University of Birmingham research guidelines. The audio data from the interviews will be transcribed either by myself or by a professional transcription service. There will be no personal identifying data in the audio files so no one will know who you are.

Will my data be kept secure?

The data from this study will be stored on password protected files on the University of Birmingham system during the research process. In accordance with GDPR, all data collected will be relevant and necessary. Your data will be used solely for this research project and no one else will have access to it.

What will happen after I have taken part?

You will be provided with a full debrief at the end of your interview and be given a debrief sheet. Participants will also be sent an electronic summary of the full project if they wish once the research has been completed. You will also receive a £10 high street voucher following your second appointment, as a token of appreciation.

If you have any questions or concerns before, during or after your participation in this research my contact details, and those of my supervisors, are on the bottom of this form.

Thank you for considering participating in this research project.

Contact Details

Chief Investigator:

Emily Ahmed

Doctorate in Clinical Psychology

E-mail: [redacted]

Research Supervisors:

Dr Gary Urquhart Law Email: [redacted]

Appendix F

Health Screen and Background Information

Understanding the Experience of 'Brain Fog' in Coeliac Disease

Background Information & Health Screen

Name:

Phone:

Email:

Screening Questions (conducted via initial telephone call)

1. **Do you currently have a diagnosis of Coeliac disease? YES/NO**

   If no, participant is not eligible to take part in the study.

   - When was this diagnosis made?

2. **Have you previously experienced or currently experience 'brain fog' or cognitive difficulties e.g. difficulties with concentration, memory, attention etc? YES/NO**

   If no, participant is not eligible to take part in the study.

3. **Are you currently following the gluten free diet? YES/NO**

   If no, participant is not eligible to take part in the study.

   If yes, when did you start this?

4. **Do you have any diagnosed neurological conditions or disorders? YES/NO**

   If yes, what is the diagnosis and when was this diagnosed?
   ……..

5. **Have you ever experienced a brain injury? YES/NO**

   If yes, what was the diagnosis and when did this occur?
   ……..

6. **Do you have a history of, or current difficulty with substance misuse? YES/NO**

If yes, please give further details
……..

7. **Do you have a current diagnosed mental health difficulty? YES/NO**

If yes, please give further details
……..

8. **Do you have another health condition newly diagnosed within the last 6 months? YES/NO**

If yes, please give details – undergoing investigations for some symptoms

Covid? Long covid?

9. **Please give details of any current medication** –

Demographics

Gender:
Age:
Ethnicity:
Occupation:

Appendix G

Consent Form

Understanding the Experience of 'Brain Fog' in Coeliac Disease

Consent Form

Participant pseudonym for this trial:

Name of Researcher: Emily Ahmed

Please initial box:

1. I confirm that I have read the participant information sheet for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	
2. I understand that my participation is voluntary and that I am free to withdraw up to 14 days following receiving a transcript of my interview, without giving any reason, without my medical care or legal rights being affected.	
3. I understand that the information collected about me may be used to support other research in the future and may be shared anonymously with other researchers.	
4. I understand that if I have any concerns about my symptoms, I should discuss any concerns with my G.P.	
5. I understand that the information I give as part of this research will be confidential and will be viewed by Emily Ahmed and her academic supervisors. I give permission for these individuals to have access to this information.	
6. I agree to voluntarily take part in the above study.	

Name of Participant	Date	Signature
_____	_____	_____
Name of person taking consent	Date	Signature
_____	_____	_____

Appendix H

Participant Debrief Sheet

Understanding the Experience of 'Brain Fog' in Coeliac Disease

Debrief Sheet

Thank you for participating in this research study.

The aim of this study is to explore and understand the experience of 'brain fog' related to Coeliac disease (CD).

'Brain fog' or cognitive symptoms such as difficulties with memory, concentration and attention are well known in the CD community, but in the research literature the focus has been more on the neurological effects of gluten, such as a condition called gluten ataxia, which causes difficulties with coordination and movement, sometimes with slurred speech and jumpy vision. In recent years this is beginning to change, and this study will add to this developing knowledge.

The interview you took part in focussed on your experience of 'brain fog' over time, what symptoms you were aware of and how this impacted your day-to-day life. You were able to recount when you started to experience these symptoms and how severe they were as well as discussing your ideas about the causes of the 'brain fog'.

Results

The data from your interview will be analysed along with other participant's data to look for themes and to further understand what 'brain fog' is like for people with CD. You have the option of receiving an electronic summary of the full project when it is completed, please inform the researcher if this is something that you would like.

Right to Withdraw

Following your interview, you will be given the option to review a transcript of the interview to ensure it is a true reflection of the interview. You will have 14 days to review this transcript, make any comments or withdraw your data by contacting the researchers on the below details. If no contact is made by the end of this time period, we will assume the transcript is correct and your data will be included in the study. You will then no longer be able to withdraw.

Further Information and Support

- Please be reminded that if you have any concerns or questions regarding your symptoms or Coeliac disease, please contact your G.P.
- If you would like further information on CD Coeliac UK is an excellent source of information and support: www.coeliac.org.uk.
- Being diagnosed with a health condition can be an extremely stressful time. If you would like help and support with your mental health, please contact your G.P. Alternatively, there are multiple self-help resources and support options detailed on the following websites www.mind.org.uk, www.rethink.org.uk and www.coeliac.org.uk.

Contact Details:

Emily Ahmed
Doctorate in Clinical Psychology
Email: [redacted]

Research Supervisors:
Dr Gary Urquhart Law
Email: [redacted]

Dr. Ruth Howard

Appendix I

Study Interview Schedule

Interview Topic Guide

Initial Experience of 'Brain Fog'

1. **Tell me about the 'brain fog' that you have experienced.**

2. **Tell me about your first experiences of 'brain fog'.** When did you first notice it?

3. **Specific symptoms**. What symptoms did you first notice? When did it happen? Did you notice any patterns with the symptoms? When did they feel better or worse?

4. **Perceived causes.** What do/did you think was causing the symptoms? What meaning did you make of the 'brain fog' and what was happening? E.g for how you felt about and viewed yourself? What did you think was happening?

5. **Impact**. How did it affect life? What did other people notice? Did it stop or limit you doing anything? What was it like at its best/ worst? Out of 10 (with 1 being not at all, 10 being worst possible) – how much did the brain fog impact your life?

6. **Level of concern.** Any concern about these symptoms at the time? How did you feel about it?

Coeliac Diagnosis and Gluten Free Diet

7. **Coeliac Diagnosis.** When were you diagnosed with Coeliac disease?

8. **Gluten Free Diet.** When did you start following the gluten free diet? What is it like following the diet? Easy/ difficult?

'Brain Fog' Over Time

9. **Description of the brain fog now.** Any change to "brain fog" symptoms? Tell me about how your brain fog has been over time? How are things now? What is better/worse? Same and different?

10. **Following starting the GFD.** Did you notice any changes following being gluten free? What did you notice?

11. **Description of how specific symptoms have changed.** Are some areas better/worse/same? Have you noticed any improvement or decline?

12. **Timing.** If changes were noticed, at what time point were they observed? What do you think caused these changes? Any patterns noticed?

13. **Knowledge of 'brain fog' now.** Has your knowledge of brain fog increased since you first noticed it?

14. **Any remaining concerns.** Is there anything that concerns you?

15. **Impact now.** Any remaining impact? Have others noticed any differences? Out of 10 (with 1 being not at all, 10 being worst possible) – how much does the brain fog impact your life?

16. **Any other relevant information.** Is there anything you think I haven't asked about that is relevant?

Appendix J

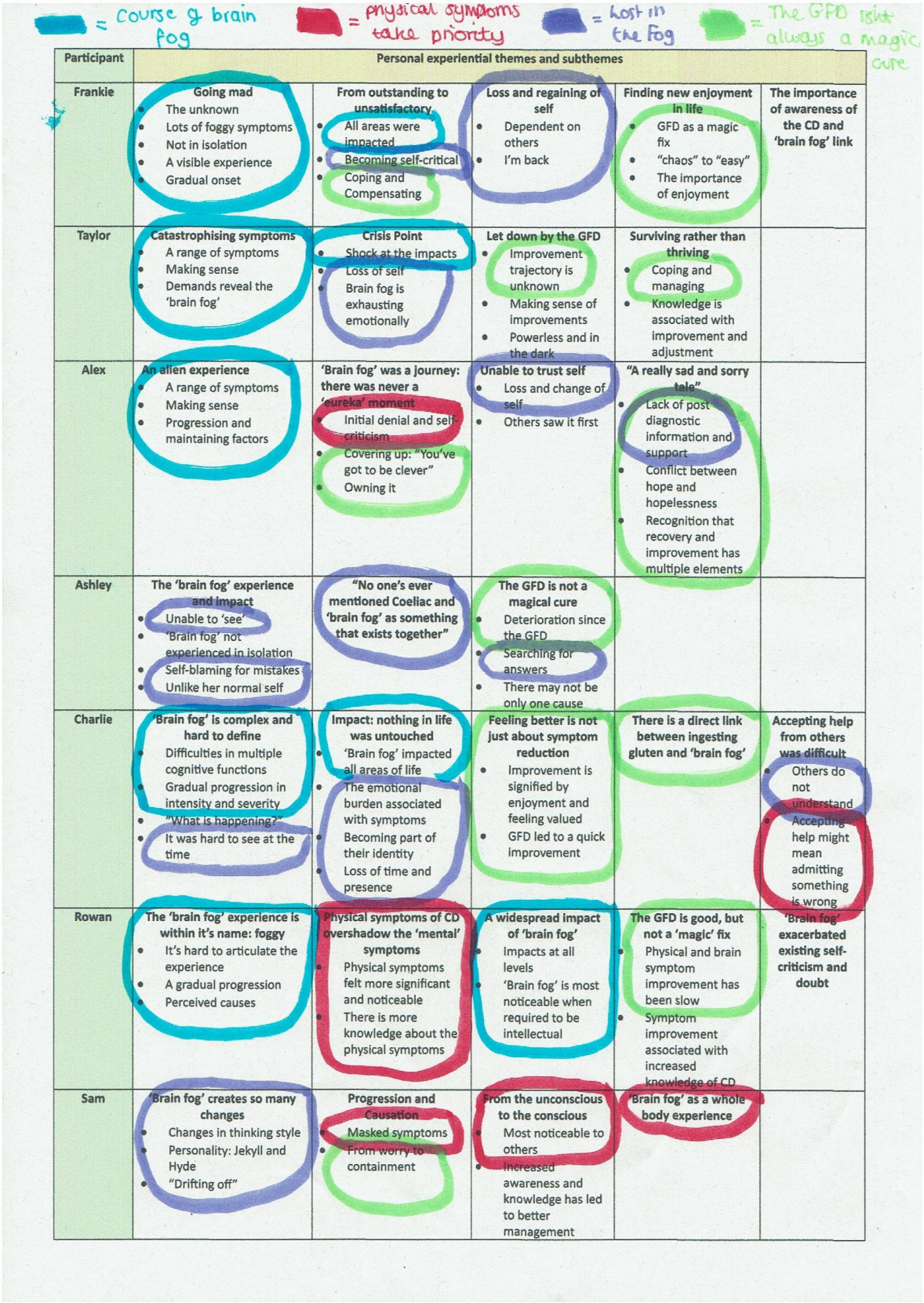
An Excerpt of an Annotated Transcript with Exploratory Noting and Experiential Statements

Descriptive
Conceptual
Linguistic

2. Experiential Statements		Transcription	1. Exploratory Notes
	1	**Interviewer (I):** Okay whenever you're ready, I guess, could	Progressive decline
	2	you just tell me about the brain fog that you have	There may have been a difference between when it was noticed and when it actually started
	3	experienced?	
	4		
	5	**Participant (P):** Yeah. Umm, my experience of it (pause). So	
'Brain fog' was experienced as a progressive, gradual decline which was variable in nature	6	about, before I was diagnosed with Coeliac Disease, I I	Fog/mist metaphor - things are unclear, confusing, hazy, unable to see a way out
	7	probably had it quite badly, but getting progressively worse	
	8	for a number of .. about 9 months or so. Or that's when I	Feeling slowed down
It is easier to identify 'brain fog' symptoms now looking back, it was hard to tell at the time	9	started noticing it. And what the brain fog meant to me was	Difficulties retrieving words
	10	sort of being really, really, sort of, I feel like the word fog is a	Not a constant experience/ variable in nature
	11	really good word. It really feels like that, it's like a mist.	
Brain fog felt like a barrier to taking information in and out – to capture in and out/bidirectional nature	12	Something about feeling slow in my brain, umm, its often	Use of humour – relationship building? Coping with difficult conversation? "Not great anyway" – self-critical? Self-deprecating? Confidence?
	13	affected my, not affecting my speech but I wasn't very good	
	14	at recalling like vocabulary, very much, so sometimes I'd be	
'Brain fog' was characterised by feeling slower to understand and process, having difficulties retrieving words and with short term memory	15	struggling for words. When talking my memory was really	
	16	bad, my short-term memory was really really bad – it's not	
	17	great anyway (laughs), but this was terrible. Things would	
	18	take me a really long time to do and like understand. It was,	
Self-critical about difficulties – like she had control over them?	19	it was, it was sort of like a mist that doesn't allow things in	Mist/Fog as an impermeable barrier
	20	or sort of doesn't really allow them out and sort of slows,	
Forgetfulness as the most significant symptom	21	like things would get lost in between. The forgetfulness was	Memory difficulties most significant
	22	like the biggest thing I'd say and also having to concentrate	
	23	in like (pause) in meetings, at work was just impossible, like	Impact at work mentioned first – due to being most noticeable there or about her priorities etc?
	24	from the moment meetings started it was like I just couldn't	
	25	get anything, uh let anything in, really struggle to share	Experiences lost
	26	anything but I would also like affect me at home if I was	Struggling to follow tv story lines
Experiences/ time/time holes lost	27	watching a film or something. And actually there is a whole	
Impacted functioning in work and home life	28	chunk of time now that I just don't, like I know I watch films	No recollection of a period of time – signifies severity of brain fog?
	29	a lot, and I don't remember them so it's sort of like, it's sort	
	30	of like completely blocked out. So then.... Yeah I sort of	
	31	noticing it about 9 months before I was diagnosed with CD	Unknown cause of brain fog
The physical symptoms of CD were more noticeable than the brain fog symptoms	32	and it was getting progressively worse. I didn't attribute... I	Feeling like the physical symptoms were the most noticeable and/or impactful symptoms
	33	didn't think it was a coeliac thing. I didn't, well, when I went	
	34	to the doctor for it, I was presenting with bloating so that	
	35	was the main thing and I'm actually, I thought I was	Feeling like it was due to depression – attributing it to work stress.
Recognition that different factors could be contributing to the brain fog	36	depressed because there was quite a lot going on for me at	
	37	work, it was quite difficult. It was covid time – there was	
	38	probably a bit of depression in there but as soon as I started	Perceived cause to be a combination of depression and coeliac
Following the GFD led to a magic quick improvement	39	the GFD, like it just cleared so quickly and it wasn't, it did	
	40	feel like depression, it did feel like depression, and it's hard	Quick improvement linked to GFD
	41	to pinpoint what was a depression and what wasn't but it	GFD as a magic healer/change agent
	42	did magically disappear once I'd gotten on the gluten free.	

Appendix K

Finding Connections Across Cases to Create Group Experiential Themes (GETs)



Participant	Personal experiential themes and subthemes				
Frankie	**Going mad** • The unknown • Lots of foggy symptoms • Not in isolation • A visible experience • Gradual onset	**From outstanding to unsatisfactory** • All areas were impacted • Becoming self-critical • Coping and Compensating	**Loss and regaining of self** • Dependent on others • I'm back	**Finding new enjoyment in life** • GFD as a magic fix • "chaos" to "easy" • The importance of enjoyment	**The importance of awareness of the CD and 'brain fog' link**
Taylor	**Catastrophising symptoms** • A range of symptoms • Making sense • Demands reveal the 'brain fog'	**Crisis Point** • Shock at the impacts • Loss of self • Brain fog is exhausting emotionally	**Let down by the GFD** • Improvement trajectory is unknown • Making sense of improvements • Powerless and in the dark	**Surviving rather than thriving** • Coping and managing • Knowledge is associated with improvement and adjustment	
Alex	**An alien experience** • A range of symptoms • Making sense • Progression and maintaining factors	**'Brain fog' was a journey: there was never a 'eureka' moment** • Initial denial and self-criticism • Covering up: "You've got to be clever" • Owning it	**Unable to trust self** • Loss and change of self • Others saw it first	**"A really sad and sorry tale"** • Lack of post diagnostic information and support • Conflict between hope and hopelessness • Recognition that recovery and improvement has multiple elements	
Ashley	**The 'brain fog' experience and impact** • Unable to 'see' • 'Brain fog' not experienced in isolation • Self-blaming for mistakes • Unlike her normal self	**"No one's ever mentioned Coeliac and 'brain fog' as something that exists together"**	**The GFD is not a magical cure** • Deterioration since the GFD • Searching for answers • There may not be only one cause		
Charlie	**'Brain fog' is complex and hard to define** • Difficulties in multiple cognitive functions • Gradual progression in intensity and severity • "What is happening?" • It was hard to see at the time	**Impact: nothing in life was untouched** • 'Brain fog' impacted all areas of life • The emotional burden associated with symptoms • Becoming part of their identity • Loss of time and presence	**Feeling better is not just about symptom reduction** • Improvement is signified by enjoyment and feeling valued • GFD led to a quick improvement	**There is a direct link between ingesting gluten and 'brain fog'**	**Accepting help from others was difficult** • Others do not understand • Accepting help might mean admitting something is wrong
Rowan	**The 'brain fog' experience is within it's name: foggy** • It's hard to articulate the experience • A gradual progression • Perceived causes	**Physical symptoms of CD overshadow the 'mental' symptoms** • Physical symptoms felt more significant and noticeable • There is more knowledge about the physical symptoms	**A widespread impact of 'brain fog'** • Impacts at all levels • 'Brain fog' is most noticeable when required to be intellectual	**The GFD is good, but not a 'magic' fix** • Physical and brain symptom improvement has been slow • Symptom improvement associated with increased knowledge of CD	**'Brain fog' exacerbated existing self-criticism and doubt**
Sam	**'Brain fog' creates so many changes** • Changes in thinking style • Personality: Jekyll and Hyde • "Drifting off"	**Progression and Causation** • Masked symptoms • From worry to containment	**From the unconscious to the conscious** • Most noticeable to others • Increased awareness and knowledge has led to better management	**'Brain fog' as a whole body experience**	

Appendix L

Master Table of Group Experiential Themes (GETs)

Table N1

Master Table of Group Experiential Themes

Group Experiential Theme	Subtheme	Quote
1. The Course of 'Brain Fog'	1.1 A gradual "creep"	Frankie (line 154-157): It was difficult to notice it because it all happened so gradually, so it wasn't just like one day where I just couldn't remember anything, it was more that it slowly and surely got worse Frankie (line 161-163): so yeah things like that, and having to write everything down more and more, so yeah, it was just like a gradual creep Frankie (line 244-246): Um, so things you know, didn't get worse, they weren't getting better but they weren't getting better if you know what I mean Taylor (line 57-59): You think with the gluten free diet your symptoms would improve, but I've kind of gone the other way (line 57-59). Alex (line 54-60: It seems like it's been kind of a gradual thing, like it started off as really little things, like going into a shop and not understanding what I was doing or swearing blind I'd spoken to my [partner] and I hadn't. Like sitting there and watching the TV and being like "what was that what am I watching, why am I watching that Ashley (line 374-373): Yeah I feel like my brain fog has started since my gluten free diet, but remember I was asymptomatic. Charlie (line 63-64):…it was so gradual it's quite hard to separate it and it was kind of all going together Charlie (line 83-85): Yeah I mean it was the same, like all the things I've mentioned but they would start off in a mild way and it would just like, like, it would just get more and more full on. Charlie (line 250-254): , I noticed it as in I couldn't remember back to 9 months but as it had come on so gradually it wasn't like oh why is this suddenly happening to me, it was like I was just getting worse and worse as it goes on Rowan (line 11-15): …cause I was always really bright in school and everything, very organised, very motivated, umm and for about a year/18 months before I was diagnosed that all just started to trail off and I became a bit more away with the fairies at times Rowan (line 23-24): I was able to look back and see the symptoms I was having that I didn't know I was having Sam (line 484-484): Looking back, there are occasions then I must have had it, and I had it before I was diagnosed, and I didn't realise it was part and parcel of what it was
	1.2 A range of "foggy" difficulties	Frankie (line 5-11): Umm, yeah, so, um, yeah it kind of feels a bit like you're going mad or that you're really drunk or something. It's like knowing the answers somewhere but you just can't reach it. So, I suppose brain fog is a very apt term because it's like everything is plugged, you can't, your thoughts in your brain can't find the right way through is the best way to describe it. Frankie (line 157-162): And I'd get quite easily confused, so things like, I was absolutely convinced it was red nose day on the Thursday but red nose day is always on a Friday (laughs), so it was like the wrong date had got stuck in my head, is the only way I could describe it, so yeah things like that, and having to write everything down more and more

	Frankie (line 191-198): Yeah, so I've always worked, always worked with children with learning difficulties and behaviour difficulties and confrontational situations happened a lot at work and weren't something that bothered me. Then there was this one low level incident that happened, no one got hurt, everything was fine, but it really upset me, really bothered me and really frightened me, and I've never, and that's not happened before Frankie (line 404-409): Oh yeah, so yeah I'm so much more able to remember, and it's not just, when people talk about forgetfulness, it's not just my ability to remember like, stuff I used to enjoy like pub quizzes and tv quizzes, and that was horrible with brain fog because I couldn't remember any of the answers, but I knew I knew them Frankie (414-423):). It was working memory as well, so to like sequence and schedule, and doing things. So say if I was going to make a cake and even if I'd done it loads of times before, I'd forget to put the oven on, or I'd forget to grease the tin, or you know, I wouldn't put the beater, or whish out, like normally when you bake you get everything out nice and ready, and I wouldn't do that, so I'd like oh no, I've gotta do this, oh no. My ability to get a task done and complete it is much easier. Taylor (line 8-10): I just really struggled with being confused, not knowing what I was doing, and this made me quite agitated as well, quite stressed. Taylor (line 25-33): I'd say like memory loss as well, I don't know whether this is all part of brain fog but memory loss, is probably the thing that I suffer with the most, still. I forget words that I need to say, I'll forget mid-sentence and I don't know what I need to remember. I'll just stop and not know what to say, and it'll take me a couple of seconds for me to kind of think, what do I need to say next. Um, so yeah, that's, that's probably one of the main things that I really suffer from with the brain fog, and the confusion in the memory loss as well Taylor (line 33-37): And also, just the agitation, and I think the agitation comes from probably being so confused and forgetting words and things like that. And again, the tiredness and things like that, whether that's related to the stress of everything that's going on with like brain fog and the confusion Taylor (line 79-82): Um, I'd probably say the memory loss started first, I didn't know why I was forgetting things or why I couldn't get my words out. Then I'd say the confusion, the tiredness, the brain fog all came at once not long after. Alex (line 6-11): I just knew that I was struggling for words, to try and articulate what I wanted to say to people and to remember, like, the most, like, it's really like, you have a memory for places you've been and people you've seen but you don't have a memory for like, recent stuff and sort of current things Alex (line 79-80): your brain doesn't kind of register with your mouth. Ashley (line 11-12): . So yeah, total forgetting of stuff. I've never done that before Ashley (line 93-100): My [partner] says I say things wrong sometimes . . . So I might say Thursday instead of Tuesday, I might get the wrong date or the wrong time or yeah, not noticed it so much, you know, going to the wrong kitchen cabinet or something like that, not really noticed that but yeah Ashley (272-277): I find it hard to sit down and concentrate, I might be online shopping or responding to someone. To sit down and do something for a couple of hours, without any distraction, I can't seem to, I can't seem to do it at all, I can't seem to focus. Like I used to be able to focus Charlie (line 12 -16): Something about feeling slow in my brain, umm, its often affected my, not affecting my speech but I wasn't very good at recalling like vocabulary, very much, so sometimes I'd be struggling for words. When talking my memory was really bad, my short-term memory was really really bad

		Charlie (line 19-21): …it was sort of like a mist that doesn't allow things in or sort of doesn't really allow them out and sort of slows, like things would get lost in between Charlie (line 21-27): The forgetfulness was like the biggest thing I'd say and also having to concentrate in like (pause) in meetings, at work was just impossible, like from the moment meetings started it was like I just couldn't get anything, uh let anything in, really struggle to share anything but I would also like affect me at home if I was watching a film or something Charlie (line 106-109): Cause there, there would be little things I'd forgotten like someone would've emailed, or filling out information, or missing deadlines and it all kind of lead into to that Rowan (line 60): when I speak, the words, I mix them up, Rowan (line 184-185): …it's like my mouth and brain weren't connected Rowan (line 445-449): It's so hard to pin down, I can pin down my physical symptoms easier than I can pin down the brain fog, cause it's, the physical symptoms are the obvious, but brain fog is, when you are feeling a bit foggy, cause you are so foggy, you don't even realise, you don't think, its only afterwards you realise Rowan (line 542-549): Like when I'm meeting with students, for example I might promise things and forget. When I'm really organised, I'll have a massive big list with priorities and colour coded and stuff, and um, I'll just not write things down then the minute the meeting has ended I'll get distracted with someone else, and then that's it, it's gone out my head and I'll only, sort of, it'll come back to me and I'll be like "damn it Lucy, you shouldn't do this". I'm just more sloppy with things that I'd normally be Sam (line 5-10): is sometimes if I'm doing something, I'm really sort of, involved with it and I sort of lose my way with it, so the concentration sort of changes, so I lack a bit of concentration and sometimes my listening isn't particularly great, so I can be really sort of listening to somebody and all of a sudden I'll be drifting off to something else Sam (line 12-15): The other thing I get sometimes is, not so much, not forgetfulness as such, but like we'll be driving to get the ferry from the isle of wight or whatever, and I'll probably drive to the shops Sam (line 50-53): So you get focused on like one task, so you tend to just do what you're doing and not be able to focus on anything else. So, I might be in the car and won't talk to my [partner] for 40 minutes because I'm just concentrating on the driving Sam (line 374-378): …everything, you tend to think about other things, the road, you tend to think about things that are going on, things that are going on that day, things you gotta prioritise, you tend sort of, uh, think of everything that's going on, that's ahead of you, rather than what's going on at the moment Sam (line 415-417): . The best way to sum it up is concentration, forgetfulness and a bit of confusion about what you are doing,
	1.3"Bigger than a little fog": impact and severity	Frankie (line 82-89): Things like, if there was a change to my routine, or to my family routine, you know I couldn't be trusted, I couldn't be trusted to pick the kids up from school, so the last day of term I couldn't be trusted to pick the kids up at 1 o'clock instead of 3 o'clock and things like that. I used to have to set reminders on my phone and everyone around me had to constantly remind me, so yeah, it just, it did feel like I was, cracking up really. Frankie (line 109-110): Oh yeah, not just my life, our whole family life was impacted I would say. Frankie (line 117-122): I was literally too tired to get off the sofa and things like that, and you know like I couldn't play games with the kids and I was like ugh, making myself do it and I was snappy as well because I was so just tired all the time, and yeah, you know, yeah, so yeah it impacted on everyone really, it was a really horrible time. Frankie (line 169-177): I'm a teacher and I've always had outstanding lesson observations, I got an unsatisfactory lesson observation, like the activity the kids were doing didn't relate to the learning objective very well, and I just wasn't bringing the learning together for

	the kids, so I could plan a lesson, and I could plan an activity but if I had to get up and sort of, the kids, the kids let you know they didn't understand, I then found it really hard to like, you know, scoop them up and put them on the right track again Frankie (line 181-186): and in the end I was like I give up, I can't remember anything, family life was pretty terrible as I was just exhausted all the time, I was absolutely convinced I was going to lose my job, so yeah it was just really stressful. And I started worrying about things I'd never even worried about before so. Frankie (line 394-398): Yeah, so I'm quite a classic, mild mannered person by nature, so when I say I was kind of ratty, I wasn't, I'm not saying I was horrible, its just not like me to get ratty but I did get, when I got the brain fog, I found I got really irritated. Frankie (line 553-556): Yeah, cause you see, any simple task you see as huge, like oh my god, I've gotta, I've gotta go to a party! You just don't want to do, you just don't want to do anything, you just struggle. Taylor (line 15-20): I couldn't remember anything I'd just learnt so I kind of had to stop doing my college work because of that. And then it was my work, so I was sat there at work one day and it got to the point where my manager asked me to do something, and I sat there and was like, I literally don't know what I'm doing, I've got no idea Taylor (line 20-24): At this point I was extremely tired as well, I had to keep lying down, I was getting stressed which kept making me dizzy. Yeah, so I think those are like the main things. And by this point it was affecting my day to day activities, I was off sick from work for a couple of days Taylor (line 69-70): Um, but yeah, it really did, like, what I really noticed this time, is how ill it can make you feel I guess. Taylor (line 129-130): I literally couldn't carry on with my work. I probably had to lie down about 3 or 4 times the day I ended up going off sick Taylor (line 153-157): And that's not like me, I'm very independent but I was getting so confused and agitated with what was going on that my friend had to sort me out, so, um, I guess it doesn't affect the relationship, but it does affect the things I'm doing when I'm out with my friends. Alex (line 144-151): I don't like going out. I feel very, kind of, isolated, because although you've got the brain fog, you feel like you've got a lot of noise around in, you don't want to make a decision, like I would hate to be out without knowing the people I'm with would look after me. Like if I went out without my [partner], I couldn't guarantee that I will, like know, where I am, what I'm doing, where I'm going Alex (line 440-442): So, it completely impacts your life, completely impacts your whole life, on every level, not just about the food Ashley (line 270-277): I feel like, I'm just distracted, like distracted, for example, I should be doing x, y and z and I'm not, I'm looking at emails, I'm replying to messages instead of doing the tasks. I find it hard to sit down and concentrate, I might be online shopping or responding to someone. To sit down and do something for a couple of hours, without any distraction, I can't seem to, I can't seem to do it at all, I can't seem to focus. Like I used to be able to focus. Charlie (line 91-92): it was almost as if everything I was doing, was, you know, affected by the brain fog. Charlie (line 186-195): "… it impacted, er, my ability to parent and be present with him and that really felt like a struggle, which makes me feel quite sad, because when I look, I think at the time I kept thinking I'm just a terrible parent, what, like I just can't get on a level with him, I can't. There was bodily fatigue I was experiencing as well, but fatigue in my body and fatigue in my brain so I just can't…like all I could do was basically sit on the sofa and watch him play and any time he tried to get me involved I just like couldn't do it. Like I just felt exhausted in every way… Charlie (line 591-597): It makes a lot of sense, it's so clear, like I said, the word fog really encapsulates what it is, and you say it and you can understand it but there's something a bit colloquial about it which doesn't get the impact or the severity of it across. Because I

		think it is severe or can be severe. If it's making you think you have early onset dementia, like I feel it's bigger than a little fog, you know Rowan (line 134-135): , I think my partner was a little worried, and still a bit now Rowan (line 181-185): It was more at work I noticed it in, and it did frustrate me, as I can get myself in trouble sometimes because of the way I spoke, cause I just couldn't get the words out. I knew what I wanted to say but I just couldn't get it out, it's like my mouth and brain weren't connected, Rowan (line 191-194): But he was the one I spoke to most every day and he was the one who, like there was arguments and all sorts about it cause he would just get so frustrated that I couldn't communicate. Sam (29-33): My [partner] says to me, sort of, we're going to Tesco or whatever and I've gone somewhere else or I'm in the wrong lane of the motorway and I've missed the turning. I've done that before where I've been on the motorway and missed the turning by three stops. Sam (line 470-472): your thinking style of what you've got to do changes, it's kind of like you're focused on getting things done in a certain way.
	1.4 "It is all so alien": making sense of the symptoms	Frankie (line 65-72): Well, I knew I was anaemic so I thought maybe it was that, and it possibly was anaemia causing it, I don't know. And people were saying I was losing a lot of weight and don't seem myself and all of that. And I was saying Oh I'm anaemic but they don't know why. People were saying was it the peri. . . or um, a few people came up to me and wondered whether my thyroid was a problem as I was just losing so much weight. Frankie (line 217-220): Well, I was absolutely convinced it was my thyroid, or I'd had covid and I didn't know, you know, like long covid or something, but yeah, I was absolutely convinced it was my thyroid. I knew I was anaemic, and my protein was low Frankie (line 224-226): Everyone knew and could see the symptoms, just know one knew what was causing it so. Taylor (line 95-103): So, I did have B12 injections, and I didn't feel, like, any different after them. Umm, whether that's now delayed and that's why my brain fog has eased off a little bit now, but as I said, they said it wasn't low enough for them to really do anything about it, they just gave me the B12 injections because I kind of moaned about it and thought I might as well try it. I have spoken to my consultant about it and he basically said that it can take up to a year for the symptoms to improve. So that's the only sense I can make of it. Taylor (line 454-457): OK, so, I suppose now, you obviously you can't be sure, but are you now thinking your brain fog is related to your CD? Yeah, definitely. Alex (line 4-6): So the initial stages, I didn't know what it was, it was one of the reasons I went to the doctors for treatment, really, I just knew that I was struggling Alex (line 24-27): It's an awful condition, it kind of makes you feel like you've got dementia, that's the only way I can put it, like you're in the early stages of a dementia Alex (line 86-89): I just sort of thought I was going to mad, and I thought it was, I just didn't know, I wasn't sure if it was . . . or to do with some kind of change, like anything really, cause you just don't know Alex (line 91-94): like I say, there was never a eureka moment where I thought, my goodness, I've got this and there is still no eureka moment where I can say it helps me on a day to day basis. Alex (line 179): it is all so alien Ashley (478-479): There's probably lots of things brain fog can be attributed to…

		Ashley (line 31-33): I've kind of put that down to not really enjoying work, but it could be a combination of them both if that makes sense [as in CD related 'brain fog] Ashley (107-108): so getting older . . . It was busy a time when I first noticed things Ashley (line 125-128): Ahh probably when I saw your advert on the Facebook, I thought ahh maybe it is linked. After doing lots of googling on it and finding there's not actually that much on it. Yeah, so I've not been to the doctors or anything about it. Charlie (line 32-42): I didn't attribute… I didn't think it was a coeliac thing. I didn't, well, when I went to the doctor for it, I was presenting with bloating so that was the main thing and I'm actually, I thought I was depressed because there was quite a lot going on for me at work, it was quite difficult. It was covid time – there was probably a bit of depression in there but as soon as I started the GFD, like it just cleared so quickly and it wasn't, it did feel like depression, it did feel like depression, and it's hard to pinpoint what was a depression and what wasn't but it did magically disappear once I'd gotten on the gluten free. Charlie (line 346-348): I no longer think I have early onset dementia (laughs) and it really doesn't stop me anymore Rowan (line 16-18): I think some of that would have been pandemic stuff, cause I was like furloughed for a little while so it could have been tied in with that. Rowan (line 118-133): Before diagnosis, I didn't even have the words brain fog in my vocabulary. I think I put it down to covid, cause I was furloughed for like 3 months, I hadn't had covid at that point but I didn't really have that academic brain stuff to do. And like I'm really creative as well as you can see from all my crochet behind me, so I was just very much engaging in that more and I wasn't communicating as much with people either, I just thought, they always say if you leave education your brain isn't as quick to learn and loses things, so I think I just thought it was that. And then the word thing, I don't know, to be honest, I've never fully got that back, it's not as bad as it was, I really struggle to articulate myself and I put that down to stress or something at the time, especially as I was experiencing all these physical symptoms and I was stressed about it. I was alone as well, quite far away from my family, so yeah, that's kind of my thought process at the time. Sam (line 207-212): I suppose really when it first, some of the stuff you think like dementia, that kind of stuff, you think oh I'm nearly 60 and I'm starting to forget things but you sort of realise, well after, I'd done it a few times it was more about me, more than my head and getting myself to conditioned to notice if I'm OK for it.
2. Physical Symptoms Take Priority	2.1 Overshadowing of 'brain fog': from the unconscious to the conscious	Alex (line 353-363):…that's another way to describe it, someone who stutters or has Tourette's or has an affliction, and when they feel calmer about it, it almost becomes easier, so someone who is calm or confident around somebody, so for instance someone with Tourette's or a stutter or something, if they are not in an environment which is going to cause them stress, then they are less likely to have that. Whereas a time where they are feeling stressed about something, it makes their stutter worse, and that's exactly how brain fog feels for me Ashley (line 309-310): …I think being Coeliac is more difficult [than 'brain fog'], like going for dinner. I think that's impacting social life more so Ashley (line 375-378): So since diagnosis, I've had brain fog, I've had much more tummy aches, bloating and feeling really unwell, since diagnosis. Following the gluten free diet, I have much more tummy aches than pre-diagnosis Charlie (line 33-35): well, when I went to the doctor for it, I was presenting with bloating so that was the main thing Rowan (line 7-11): It was a proper shock diagnosis so I hadn't, like, looked it up beforehand as I hadn't linked it up with my symptoms that were more obvious like toilet troubles that come with it. Um so I just hadn't, yeah, I hadn't put two and two together. Rowan (line 72-79): , it wasn't [the brain fog], I have to say, one the things that was bothering me most about what was sort of happening to my body, like I say, before I was diagnosed I didn't put two and two together. It just sort of felt like a natural, not

		progression, but degression, if that's the word? I dunno, my brain, I didn't consciously, it was just after I got better after I was diagnosed, that I was like oh my god, that explains a lot. Rowan (line 138-140): So I probably just didn't pay attention to it [the brain fog] as much as I probably could have done to it, um, yeah that was it, and that's what all I really thought about. Rowan (line 445-449): It's so hard to pin down, I can pin down my physical symptoms easier than I can pin down the brain fog, cause it's, the physical symptoms are the obvious, but brain fog is, when you are feeling a bit foggy, cause you are so foggy, you don't even realise, you don't think, its only afterwards you realise. Rowan (line 496-497): , it was only afterwards that I linked it, cause it wasn't straight away Rowan (line 499-502): But something like brain fog, is like a hidden symptom, it's not the obvious one, so when you've got like violent diarrhoea happening, you don't always think about other symptoms" Rowan (line 610-614): "…whereas now it's more if I'm feeling ill [physically], I will worry about it and stress about it and get quite anxious about it, so that's where my brain is focused than on the tasks I'm meant to be doing, so that's where the fog comes in, so it might be linked in that way Sam (line 58-59): you tend to sort of, erm, sort of do something unconsciously Sam (line 193-198): And when I don't have something then its more noticeable by other people than it is with me. I'm quite happy, and I'd probably not talk to anyone, and they probably think I'm being miserable but it's when I haven't got the right nutrients, that's when I go in that sort of, not daze, sort of become, within myself Sam (line 537-538): the thing is you don't know until someone tells you
3.2	"I guess I was in denial about them": the (possible) stigma around "mental" symptoms	Frankie (line 103): And you're like, come on, get it together Frankie (line 24-25): couldn't remember like really obvious details, that you should know Taylor (line 162-168): Um, I know that I'm getting stressy, and I know I'm getting agitated so I feel a little bit embarrassed about it sometimes. And obviously, I don't, some people might not understand so I don't want them to think I'm being a cow about it I suppose, or I'm being an idiot, so it makes me worry about what other people think about me. More than anything it feels embarrassing as I just can't control it. Alex (line 34-36): …I guess I was in denial about them, but 18 months I guess [time she had her 'brain fog' symptoms for], so I was just noticing things in the initial stages Alex (line 52): I thought I was going a bit mad really Alex (line 112-118): Embarrassed, really embarrassed. I still get very embarrassed by it now. You end up trying to cover it up as well, you almost, sort of, sort of overcompensate for stuff, or you know you try to find a different excuse or different reason for something happening, because you don't want to feel you are inadequate but that's how it makes you feel Alex (line 135-137): just trying to blag that you're not sort of mad, or you're not, you're not the person that you're kind of being portrayed to be. Alex (line 168-172): He thinks I've got my own language, I'll say something and he'll say "do you mean such and such?" and I'll say yeah, and he'll be like oh you're talking Rachel-ese again. Again, it's like, it makes you feel embarrassed again Charlie (line 155-156): Like I was actually just losing my mind. Charlie (line 230-234): I think it's like, um, and this is probably common in lots of people but it was like your brain, feelings and emotions can be sort of like put off, it will resolve, whereas if it's a bodily or physical pain it's like, Oh I need that treated

		Charlie (line 442-447): but you know, there were just like, they'd have meetings and be like, what is going on? Do you need support here or support there? And that would bruise my ego a bit so I would never accept any support, and as it was a job I'd been doing for a long time. Charlie (line 472-480): : Mmm, yeah, I think I just felt, I looked at myself in a not very favourable light, it was like a real feeling of being like useless and not having any skills at all, having nothing at all in any area of life and feeling sort of like a hindrance and that I made, with the mistakes I was making, it wasn't just feeling useless like I wasn't able to help, it was as if I was making things worse for other people. So, yeah, I wasn't thinking positively about myself, at all. I just sort of reinforced this idea that I had nothing to offer. Rowan (line 135-138): I think I come from a family background that doesn't openly talk about mental stuff or doesn't go get checked out about something that's mental. So, I probably just didn't pay attention to it as much as I probably could have done to it Rowan (line 185-188): I just couldn't speak it out. I'd say the wrong thing or would just look really stupid, trying to fumble around with my words and trying to express myself. Rowan (line 359-360): Yeah, it really really gets me. And I beat myself up actually, about feeling so awful about it.
3. Lost in the Fog	3.1 "A shell of myself": loss of their 'normal' self	Frankie (line 81-85): I just couldn't trust myself or rely on myself. Things like, if there was a change to my routine, or to my family routine, you know I couldn't be trusted, I couldn't be trusted to pick the kids up from school Frankie (line 128 – 130): My . . . [partner] said he was sort of, like he had an extra child, because he was having to remember everything for me Frankie (line 352): woaaaah I'm back Taylor (line 153-154): . And that's not like me, I'm very independent but I was getting so confused and agitated Taylor (line 163-169): Um, I know that I'm getting stressy, and I know I'm getting agitated, so I feel a little bit embarrassed about it sometimes. And obviously, I don't, some people might not understand so I don't want them to think I'm being a cow about it I suppose, or I'm being an idiot, so it makes me worry about what other people think about me. More than anything it feels embarrassing as I just can't control it Taylor (line 196): I just had no hope, I had nothing, I was empty Taylor (line 204-207): I just felt like I'd really lost myself, like a shell of myself basically because I couldn't do anything, I had no energy to do anything, I had nothing in my brain to do anything, so yeah I guess that's just how I felt with that Alex (line 15-17): And it's sometimes like, you run day to day, like today, now, I run day to day and I'm present, I'm here and I'm living but then there's (pause) something empty. Alex (line 36-37): you're not the person that you're kind of being portrayed to be [by the brain fog] Alex (line 121-122): it makes you feel really inadequate and really awful Alex (line 178-183): You know, it is all so alien, all these feelings, I'm quite a outgoing person, I'm quite chatty, and you know, quite, I think quite happy, quite good at going into new situations where I don't know people and I can hold my own. It kind of feels like, I can't do all that as much as I did. Alex (192-195): I'm just not the person I was, I'm not the happy go lucky person, who feels confident and ease at herself. I don't like myself that much, because I don't like the person I am towards other people Alex (line 416-419): I just don't know, know how long, I hate to say it but I just don't know when I'll be well. So you kind of think to yourself, is this the best I'm going to be? Will I be 'me'? Ashley (line 60-62): And now I feel like it's more absent mindedness, and it's not like me. I've got quite good attention, I'm quite well organised

		Charlie (line 109-110): And also in terms of meetings, I may as well have not been there, I Charlie (150-161): Yeah, so when I was experiencing the brain fog. Like it was, yeah it was horrible. It was really horrid! And really difficult, like you know, the fact I was like worried for myself and I best keep an eye on how my brain is working cause like uhh, I just feel like this isn't normal and like really thinking it was something serious. Like I was actually just losing my mind. But yeah, it was, it was not, it was really depressing not being able to function, feeling really useless and cause like, I wasn't able to pick up on things or I was forgetting things, it meant that people were always chasing me up or being like "why haven't you done this? so like to suddenly, a real loss in confidence and my abilities and skills Charlie (158-161): I wasn't able to pick up on things or I was forgetting things, it meant that people were always chasing me up or being like "why haven't you done this? so like to suddenly, a real loss in confidence and my abilities and skills Charlie (line 411-414): Um, but there is, I feel like I'm still a little bit burned by the lack of confidence I had when I still had brain fog, so I'm still a little bit of that mindset like "Oh I can't do this" and so on Charlie (line 472-480): Mmm, yeah, I think I just felt, I looked at myself in a not very favourable light, it was like a real feeling of being like useless and not having any skills at all, having nothing at all in any area of life and feeling sort of like a hindrance and that I made, with the mistakes I was making, it wasn't just feeling useless like I wasn't able to help, it was as if I was making things worse for other people. So, yeah, I wasn't thinking positively about myself, at all. I just sort of reinforced this idea that I had nothing to offer Charlie (line 543-545): But I don't have much, I really don't have much else. It's like existing with it. Rowan (line 211-212): …made me quite self-conscious about that. I still am quite self-conscious about it Sam (line 198-199): That's what its like, the foggy bit is all of that, you kind of go within yourself, Sam (line 319-329): Er, yeah, I suppose really its kind of like, when you make mistakes you don't want to make them then you realise you've just made them. And if someone tells you you've just done this, and then you realise, you get a bit frustrated and annoyed with it. Err, and that's the bit where I get frustrated, as I've made error or I've done something, and I know I've done it and I cant defend it because I've just done it. Sam (line 460-461): I think when you've had the brainy foggy bit, your thinking style changes a little bit Sam (line 502-505): Even little things, someone will say something and you'll get a bit more annoyed and upset with it, minor things, minor things and you just get annoyed with it. It's just getting yourself balanced again, that's the key with it all really Sam (line 595-598): I've found more now if I don't eat, you know, you get the brain fog, you get, not aggressive but you're thinking style changes. You tend to become a bit Jekyll and Hyde-y, you tend to become a bit of a different person
3.2"You're there, you're awake but you're not 'there'": loss of presence and time		Alex (line 60): just getting kind of vacant is the only way I can describe it. Ashley (line 60-61): I feel like it's more absent mindedness Ashley (line 76-79): …so yeah frustration and annoyance, like I've just wasted half an hour or I've just asked the same question twice and like I'm like ugh oh god Alex (line 99-102): you know like you're watching something, you kind of go a bit vacant into it and you kind of go in the room and back in the room, so the concentration is, its like you're having mini sleeps Alex (line 103-104): you're there, you're awake but you're not 'there' Ashley (line 60-61): And now I feel like it's more absent mindedness, and it's not like me. Ashley (line 76-79): Umm, yeah so yeah frustration and annoyance, like I've just wasted half an hour or I've just asked the same question twice and like I'm like ugh oh god

		Charlie (line 27-30): And actually, there is a whole chunk of time now that I just don't, like I know I watch films a lot, and I don't remember them so it's sort of like, it's sort of like completely blocked out Charlie (line 183-188): I tell you where it really impacted. I think it impacted my home life in not being able to do much. It impacted er, I've got an almost 4-year-old so he was almost 3 at the time or coming up to 3 and it impacted er, my ability to parent and be present with him and that really felt like a struggle, which makes me feel quite sad Charlie (line 199-201): . I couldn't finish any books, I really couldn't contribute, like I was just lost in the discussions. Rowan (line 29-34): I just couldn't, it was like I just wasn't in, in my head, like I'd been in meetings that I'd normally be really enthusiastic about and really engaged with and I'd be sitting there and listening and just be like ..(makes a blank face gesture). So, I had to sort of snap myself back (laughs) Rowan (line 241-242): …because brain fog becomes like you're distanced from what's going on Sam (line 8-12): so I can be really sort of listening to somebody and all of a sudden I'll be drifting off to something else and I'll probably start a conversation about something totally different to what we were talking about. Sam (line 18-20): So I tend to kind of wander sometimes, and wander off what I'm supposed to be doing, and erm, I guess that's a bit about the concentration thing. Sam (line 45-46): Yeah you're not fully aware all the time that you're actually doing it Sam (line 464-472): So like I could be cutting the grass and half way through the lawn I'd be thinking about emptying the shed out and all that sort of thing, and you're thinking well I'm cutting the grass. And you cut the grass and all you want to do is do the shed, and you get to the shed and then you think about, cleaning the mower and it's all, sort of, you tend to, your thinking style of what you've got to do changes, it's kind of like you're focused on getting things done in a certain way
3.3 "No one's ever mentioned coeliac disease and 'brain fog' as something that exists together": feeling lost and alone in the 'brain fog' journey		Taylor (line 403-408): I don't know really, as I don't know how to improve it. The only thing I can do really is speak to the doctors, and I have done that, I told them all my symptoms the other day. He kind of just brushed it off with that it will improve over time with the gluten free diet, so I guess the only thing I can do is just wait it out and see what happens. Taylor (line 422-427): Yeah, there's quite a lot of support on the groups I'm in and it helps me to feel that I'm not alone. As I didn't know this was down to Coeliac in the beginning, and at the start, it's seeing people comment on the groups and on the facebook I'm in and I was like oh my god I have the same symptoms. And you talk to people about it and it helps you feel that you're not the only one Taylor (line 436-441): I thought that, I thought that I had some sort of illness, it sounds stupid. I thought there was something wrong in my brain basically, and that caused me to panic, and yeah, I started googling about what it could be, I did notice that coeliac was on there, but I still didn't connect the two, no one told me that, I wasn't really given much information when I was diagnosed Taylor (line 484-489): And again, the other groups everyone sharing their symptoms, how they feel, how they know they've been glutened, which helped me understand my symptoms and now I feel I can help other newly diagnosed people who are commenting on this group and aren't sure. So yeah, it does make you feel a lot better about everything really. Alex (line 232-238): But there the only kind of things, like I'm say I'm fairly new into it, I kind of had to figure it out, I haven't had a lot of support from any service really, they sort of say to you just stop eating gluten and everything will be better, but I've done that now and I'm nearly six months and its, I just don't know when it's going to change. Alex (line 259-267): But they don't, it's not explained to you really, essentially it's a complete lifestyle change but they don't…. I wasn't given anything, like it was almost like here's a leaflet and this is what's going to happen, but nobody really says, too much about it. And when you go out, people don't know, or don t understand, and they assume that people who have been diagnosed have been given information about it but you don't know unless you're told.

		Ashley (line 118-120): no one's ever mentioned Coeliac Disease and brain fog as something that exists together Ashley (line 179-181): So yeah, it's hard, it's also hard when I don't know it's working, the doctors won't give me another blood test, to tell me what my TCG is Ashley (line 363-367): Yeah, I could talk to the GP about it but I don't know whether he'd be any help. Um, I don't think there's a magical pill I can take to stop the brain fog. Ashley (406-408): So I'm just frustrated and annoyed. I'm not under any specialist or anything for this, so it's all, I feel very unsupported by my GP, if I'm honest Ashley (line 419): Yeah, and I've taken it on my own back, unsupported Charlie (line 552-559): I suppose when I went to the GP about my bloating, not even he, he was just like why don't we put coeliac on the blood test, why not, that sort of thing. Almost like if I'd been asked questions at the time, I was asked loads of physical questions like how often I went to the toilet, that sort of thing but I was never asked about my brain function, you know? About how that was going Rowan (394-397): …but what Coeliac UK aren't very good at it is going into the mental health side of things, the mental things, the mood symptoms, so I got a lot of that from Instagram
4. The GFD isn't Always the Magic Cure	4.1 "Will I be me?": improvement is not just about symptom reduction	Frankie (line 198-200): . And luckily since I've gone gluten free it hasn't happened since, it really got to me, it really bothered me. Frankie (line 246-249): And then just after Christmas I got my coeliac diagnosis, and within 2 years, 2 weeks I mean, I felt 20 years younger. Really quick. Frankie (line 345-348): Oh well it started getting better after a week, after two weeks it was, ahh like a million times better, really was, it was just like, it was like a light was back on, I felt 20 years younger Frankie (line 360-371): Oh brilliant, like confidence back, I'm so much motivated to do things, like before, I suppose because of the brain fog, say for example, um, I wanted to take the kids out somewhere, I had to remember all the kids stuff for a start, then my stuff, and you know, remembering everything else, and I'd got a toddler, and you know, a toddler isn't easy but when you've got brain fog, it's just sooo (emphasised) hard cause you're sort of trying to know, keep all those plates spinning, and stop a meltdown and deal with it all, you know. So just like a day out with the kids stopping being like arrrgghh and it was like yay come on guys get in the car we're going out. Yeah, it was so much nicer. Frankie (line 369-371): So just like a day out with the kids stopping being like arrrgghh and it was like yay come on guys get in the car we're going out Frankie (line 376 -378): Oh massively, I can't even, it's the best it's ever been, and not just on my life, my kids, my family, you know it's just so much nicer, so much easier. Frankie (line 422-423): My ability to get a task done and complete it is much easier. Frankie (line 465-467): Oh just, it's just, everything's just easier, happier, everything's more fun, yeah, it's just everything has been impacted all round. Frankie (line 472-474): Yeah I mean don't get me wrong, some things are stressful aren't they, there's always curveballs and stuff isn't there but my ability to adapt is much better Taylor (line 57-61): You think with the gluten free diet your symptoms would improve, but I've kind of gone the other way, um, and they've probably got worse for a little bit and now they're easing off but they're still there and you would expect it not to be with the gluten free… Taylor (line 196-198): So yeah I probably would say it was a good 8, and I'd probably say it is like a 3 or a 4 now, so yeah.

	Taylor (line 220-223): But other than that I've not really done anything to make myself feel better, I just feel its like cleared up a lot. Whether that's because my body is healing as well, I did have a consultation the other day and they said my blood levels are pretty much normal now. Alex (line 405-408): Yeah, like I say it's clearing, the brain fog is clearing, better but not fully. That's the main thing, the only thing that I would say has got worse is that I've put on a stone in weight and that's something I didn't want to do. Alex (line 416-419): I just don't know, know how long, I hate to say it but I just don't know when I'll be well. So you kind of think to yourself, is this the best I'm going to be? Will I be 'me'? Alex (line 445-455): Well, it's all very new to me so. I'd like to be hopeful and optimistic that this time next year it will feel easier and feel more in control. That I'll feel more prepared and be able to research a bit more. Like you start doing something and you think, ah shit I'm not doing that I can't be bothered, ah shit, I can't to that. To, I'd like to think in a years time, I'd like to think, people say that your stomach can take 12 to 24 months to recover, so I'd like to think that will be the same for everything, but its so far away from that at the moment so..I just don't trust it, I just don't trust that I'll ever feel fully better again. Ashley (line 38-43): Ok, yeah, and we'll talk about those specific symptoms a little bit more in a minute. But first let's go back to when you first noticed these symptoms, when was that? P: More recently, probably the last… really the last month or so actually it's got a lot worse Ashley (line 360-367): I am kind of monitoring it but is there anything that can be done for it, that's the question. Probably not. You know, I'm sticking to a gluten free diet, is it just going to get progressively worse, or is this just now the new me? I dunno, I don't know whether there's a lot I can do or change about it. Yeah, I could talk to the GP about it but I don't know whether he'd be any help. Um, I don't think there's a magical pill I can take to stop the brain fog. Charlie (line 39-42): …but as soon as I started the GFD, like it just cleared so quickly and it wasn't, it did feel like depression, it did feel like depression, and it's hard to pinpoint what was a depression and what wasn't but it did magically disappear once I'd gotten on the gluten free Charlie (line 308-310): My brain was just working in a very different way than it had been before and I just suddenly felt a lot more…. Conscious. Charlie (line 329-34): Um, first thing I noticed was, it was almost the speed I was able to do things or yeah that or think about things and it just like, it almost felt like my brain was in slow motion before and someone had just pressed the play button now and it just was going along and I had also really noticed my son – I was like oh suddenly I'm able to play with you and do things with you, its not a huge effort to leave the house and go to the shops, like before, or whatever it was we were doing. I can just do it now, its fine. So yeah, it was like I'd been held back, the feeling of being in treacle that kind of thing, then being set free. So yeah, something about momentum and speed that I felt. Charlie (line 349-351): I just have access to that part of the brain but it did all happen quite suddenly, like getting everything back and very very quickly Charlie (line 407-408) Yeah, well I'm more active, proactive, I could join in and actually enjoy things more as well which makes difference Charlie (line 414-417): I'm able to do a lot more with my day, be more productive, even on a not very productive day I seem to do things faster and err not making little mistakes all the time like I was before and things so…

	Charlie (line 421-427): I can interact in book club now, I can finish the book, I can have a proper conversation about it. I can watch films again, I enjoy them and I can remember what happens in them. Like going to the theatre again, like all these things, I feel I have the capacity to absorb and enjoy. I think enjoy is an important word as I feel I didn't have the capacity to enjoy anything and now I do Charlie (line 437-438): Like suddenly I was a lot more active and can just do a lot more. Charlie (line 482-489): (I) Yeah, and what are your thoughts about yourself now? **P**: That I have more to offer. I don't think I make people's lives difficult, I think I have a lot more confidence in terms of what I can offer people or in various different umm situations. I don't kind of worry about a meeting or friends that I would forget or whatever. So, I feel like I contribute now like I didn't feel that before. Rowan (line 22-24): I can understand why they call it a brain fog, it was like a fog lifting and I was able to look back and see the symptoms I was having that I didn't know I was having. Rowan (line 402-403): my symptoms getting better wasn't an overnight thing Rowan (line 434-438): Like I've never got back to before, like what I remember when I was younger, like I've never fully got back to that. Umm, and because it was gradual and there was no one day where I was like "wow I'm better" so it's really hard to say, but I would say it was between 3 to 6 months Rowan (line 470-471):…as my symptoms come back all in a rush Sam (line 86-2): I'll tell you when I do get it more, when I don't eat properly and I miss meals, if I don't get any nutrients, I tend to end up being a bit like that. I also get really tired and I yawn a lot, and again, I know when I'm not right, what I'd call it a bit like diabetes where you get unbalanced and you don't have enough nutrients in your body, and I tend to eat something and erm, to kind of, to make me feel a little bit better Sam (line 434-443): Uh, it all depends on my diet I think. That's probably he key to it. So, if we go out or if we miss a meal, that tends to trigger it for me. Or if we have to do something, like I've got to be somewhere for a certain time, my concentration will be on like getting there rather than anything around me, or what we got to do next. I don't know really, it doesn't happen often, it happens you know, how many times you miss your breakfast, you might miss your breakfast once a month or twice a month possibly, but you know, I'm not sure I can, I can't make it happen if you know what I mean, it happens on its own
4.2 "Owning it": navigating the 'brain fog' symptoms	Frankie (line 233-244): , I got a new job, which I wasn't, I wasn't classroom teaching, I was kind of behind the scenes, so I didn't need to rely on my working memory as much, and actually everything was in a diary for me, so that actually helped, did mask things a bit, but I was still struggling more and more, still struggling with the you know, with remembering things but I got so good at writing everything down, my routine was that first thing in the morning I would write everything down and I would just look at my phone, and I got really good at looking at my phone throughout the day to see what I'd written down, so I sort of got a coping strategy, if you will. Taylor (line 216-221): And I've just tried to push myself to do things, so I just, I haven't gone back to the gym a lot but I've tried to go back at least once a week, as I know that can help with things like mental health and stuff, so I've tried doing that. But other than that I've not really done anything to make myself feel better, I just feel its like cleared up a lot. Taylor (line 408-413): In the meantime, I guess I just need to push myself to get back to normal life, which probably will never happen, be back to normal again, but just to get back to more physical stuff again and manage the symptoms when I have them I guess. Trying to find the best way to manage them, when I get them. Taylor (line 421-425): As I didn't know this was down to Coeliac in the beginning, and at the start, it's seeing people comment on the groups and on the Facebook I'm in and I was like oh my god I have the same symptoms. And you talk to people about it and it helps you feel that you're not the only one

	Taylor (line 484-489): . And again, the other groups everyone sharing their symptoms, how they feel, how they know they've been glutened, which helped me understand my symptoms and now I feel I can help other newly diagnosed people who are commenting on this group and aren't sure. So yeah, it does make you feel a lot better about everything really. Alex (line 112-124): Embarrassed, really embarrassed. I still get very embarrassed by it now. You end up trying to cover it up as well, you almost, sort of, sort of overcompensate for stuff, or you know you try to find a different excuse or different reason for something happening, because you don't want to feel you are inadequate but that's how it makes you feel. Like I started a new job in August, and it's something completely different to what I've ever done, and I tried my hardest to learn this new job and I write notes down and like I say, it's still very apparent, it makes you feel really inadequate and really awful. I just try to brush it off and hide it, try to reason – put a reason to it, or try and find a excuse for it. Alex (line 129-135): You have to try and be really clever, like you write lots of notes down to try and remember, and if you don't know or remember, you try and brush it off like "oh it's my age" or whatever or "I've got loads of things on". Like I've got two children and I'll be like "oh I've got loads of things on my mind at the same time" and it is literally just trying to blag it really Alex (line 225-234): : Umm, repetition makes things better. Like for instance, saying things over and over again in your head helps you remember. Like for example, in gym we do things over and over again, repetition is there so you kind of know exactly what you're doing and it becomes normal, like repetitive in nature. So, the repetition makes it easier to deal with. Like I say, making notes helps you understand or to remember things better. But there the only kind of things, like I'm say I'm fairly new into it, I kind of had to figure it out Alex (line 325-332): And also, like, my awareness of it, I will tell people now, I'm not as embarrassed as I was, like I've said to my boss, "I'm really sorry, I'm just not getting it, can you go through it again, my brain is not understanding it". So, it's almost like I'm just owning it now, which makes it easier as its kind of life, more of a reality of what you've got, like you can't just, you're not accepting it, but there's an acceptance… [unrelated speech] … like if I don't own it, and I'm not, don't tell people, you're almost allowing people to have an assumption about what you're going through anyway. Whereas actually, sometimes it feels like an excuse, and I don't want it to be excuse, I want it to be a reason. And that's the only way it's got easier really, through just owning it Alex (line 365-371): Yeah, so a good day, because I'm calmer, I can kind of see things clearly, because I'm not so stressed with it, and doesn't make me so stressed, which means its easier to manage, it's easier to understand and pause and take a few breaths, taking a little bit of time out, going for a walk, getting a cup of tea, moving away from my desk or what I'm doing, changing that feeling makes it feel better. Ashley (line 419-424): Yeah, and I've taken it on my own back, unsupported, to cut out milk for two weeks and see how I feel. We are only on day five now, and that's hard, like biscuits, chocolate, they all have milk in. Muesli bars have milk in, even healthy snacks have milk in. There's lots of things that have milk in. So now I have to look at vegan gluten free food. Charlie (line 121-125): Like just nothing could get in and umm, and it, if I had to like almost, the only I could concentrate was if I took notes of absolutely everything single thing so I had to really really really concentrate or else there was no way anything else was going in. Charlie (line 538-545): I think, well now, it's just telling people, so like my manager and be like I was glutened and it means the next week I'm not going to be myself and I'll be really slow so apologies if you need to repeat things 100 times or call my attention 100 times. So, I don't know if that's a strategy but just letting people know is quite important for me. But I don't have much, I really don't have much else. It's like existing with it.

	Rowan (line 243-441): Umm, and because it was gradual and there was no one day where I was like “wow I’m better” so it’s really hard to say, but I would say it was between 3 to 6 months where like I didn’t have to worry about the toilet as much. It was probably about then that I knew all I could know about Coeliac Disease without going to study it academically Rowan (line 384-400): Um, I can’t remember. I just remember doing loads of research. I read pretty much every page on the coeliac UK website, and joined them, joined all the Facebook groups, followed gluten free influencers, um, that sort of thing. And there’s a few of them, there’s a few dieticians on, that I follow on Instagram, who talk a little bit more about the mental effects of coeliac disease, apparently there’s more, there’s like 200 symptoms or something associated with coeliac disease and um, Coeliac UK, whilst it does say, you know, most common symptoms are diarrhoea, constipation, weight loss, it does touch on other things but it doesn’t, but what Coeliac UK aren’t very good at it is going into the mental health side of things, the mental things, the mood symptoms, so I got a lot of that from Instagram, so it a took a while, but there’s one guy, um, Christian Costas? Is he called, dietician and Coeliac specialist, he’s brilliant (emphasised) on Instagram and he always answers your messages if you ask them. Rowan (line 592-593): And I feel like sometimes, feeling down can encourage the brain fog to come on. Sam (line 141-143): So what I tend to do now is that everything goes in its place, so I put things in the same place, the wallet, the keys Sam (line 213-218): , like if you don’t eat, and don’t treat, keep yourself fit, then your body, somewhere along the line, whether its chemically, your brain sort of changes and you end up in a position where you have this brainy foggy thing where you tend to lose concentration, everything’s not clear, you tend to concentrate on one thing Sam (line 497-500): my head tells me to get annoyed but then I realise, and know its me, it’s because I haven’t eaten for a while so I just say “oh that’s ok, let me look at the menu”, I try and cool it down if you know what I mean. Sam (line 513-522): I suppose when you’ve got close friends, and they see that, sort of, change, and you talk to them about it and they say its really noticeable, we know when you haven’t eaten, we know when you’re not right. My best mate, said like, “when you’re like that, how do you want us to treat you, what do you want us to say – do you want us to say are you okay, or do you want to just get on with it yourself or do you want me to tell you”. So one thing now, when I get a bit like it they say, “time for a fruit bar I reckon”, which I tend to eat which helps, so make a bit of fun of it but make you realise you’re not your proper self Sam (line 541-542): but I tend to know now when I’m not in a good place, so I tend to control it.