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Quality of Life among Patients with Celiac Disease: Assessment and Treatment in an Understudied Population

A dissertation submitted in partial satisfaction of the
requirements for the degree Doctor of Philosophy

in

Clinical Psychology

by

Cara Dochat

Committee in charge:

University of California San Diego

Professor Niloofar Afari, Chair
Professor Kerri Boutelle
Professor Matthew Herbert

San Diego State University

Professor Vanessa Malcarne
Professor Scott Roesch

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The dissertation of Cara Dochat is approved, and it is acceptable in quality and form for publication on microfilm and electronically.

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Chair

University of California San Diego

San Diego State University

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DEDICATION

To my mentors, collaborators, community, ancestors, and participants, thank you.

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VITA

2013 Bachelor of Arts, Gettysburg College

2019 Master of Science, San Diego State University

2023 Doctor of Philosophy, San Diego State University/University of California San Diego Joint Doctoral Program in Clinical Psychology

PUBLICATIONS

Dochat, C., Afari, N., & Arigo, D. (2023). Psychometric validation of the celiac disease-specific quality of life survey (CD-QOL) in adults with celiac disease in the United States. *Quality of Life Research*. https://doi.org/10.1007/s11136-023-03380-7

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FIELDS OF STUDY

Major field: Clinical Psychology

Studies in Behavioral Medicine
Professor Niloofar Afari

ABSTRACT OF THE DISSERTATION

Quality of Life among Patients with Celiac Disease: Assessment and Treatment in an Understudied Population

by

Cara Dochat

Doctor of Philosophy in Clinical Psychology

University of California San Diego, 2023
San Diego State University, 2023

Niloofar Afari, Chair

Celiac disease is a chronic illness in which quality of life (QOL) is compromised and psychiatric illness is commonly co-occurring. The only available treatment for celiac disease is to consume a gluten-free diet indefinitely, which is burdensome and costly. Further, adults with celiac disease present with a variety of gastrointestinal and extraintestinal symptoms that can persist after diagnosis and may relate differently to gluten-free diet adherence, psychiatric wellbeing, and QOL. Despite a need for behavioral intervention to address these challenges, adults with celiac disease are understudied. This three-paper dissertation addressed gaps in the literature by (1) examining the factor structure and psychometric properties (internal reliability, convergent validity, known groups validity, incremental concurrent validity) of Celiac Disease

Quality of Life Survey (CD-QOL) scores among U.S. adults with celiac disease; (2) examining patterns of persisting physical symptoms and their respective relationships to gluten-free diet adherence, psychiatric symptoms, and QOL using latent profile analysis; and (3) systematically reviewing the design of single-session Acceptance and Commitment Therapy (ACT) interventions for chronic illness populations and meta-analyzing QOL and functioning outcomes to inform future behavioral intervention development for celiac disease. Studies 1 and 2 used U.S. adult participant data from the iCureCeliac® patient-powered research network. Study 1 (*N*=453) results supported use of the 20-item English CD-QOL as a measure of celiac disease-specific QOL with a total score and four subscale scores (limitations, dysphoria/stigma, health concerns, and inadequate treatment). Study 2 (*N*=523) identified four unique physical symptom profiles characterized by variations in gastrointestinal and extraintestinal symptoms and subjective ratings of health. Subgroups associated with these profiles also differed regarding anxiety and depression symptoms, limitations due to physical and emotional health, social functioning, and fatigue/sleep, but not gluten-free adherence or celiac-disease specific QOL. Study 3 found support for the acceptability, feasibility, and preliminary efficacy of single-session ACT for improving QOL and psychiatric symptoms among chronic illness populations. Findings suggest that healthcare providers should screen for psychiatric symptoms and QOL deficits among adult celiac disease patients regardless of symptom burden, and development of brief ACT for celiac disease is warranted. Findings must be replicated in culturally diverse samples.

Introduction

Celiac disease is one of the most common autoimmune conditions in the western world. Approximately 3 million Americans and 48 million people worldwide have been diagnosed with celiac disease (Rubio-Tapia, Ludvigsson, Brantner, Murray, & Everhart, 2012; Singh et al., 2018) and there may be as many as 21 million and 300 million undiagnosed cases in the U.S. and worldwide, respectively (Green, 2007). Celiac disease is an uncurable chronic condition in which ingestion of gluten causes damage to the structure and function of the small intestine. Celiac disease presents with aversive gastrointestinal and extraintestinal symptoms (Leonard, Sapone, Catassi, & Fasano, 2017). Celiac disease is more prevalent in women than in men worldwide (Caio et al., 2019; Singh et al., 2018) and more prevalent among non-Hispanic whites than other racial/ethnic groups in the U.S. (Choung et al., 2015). The only available treatment for celiac disease is to abstain from consuming gluten, a protein found in wheat and other grains including rye, barley, and malt. Gluten is found in many grain-based food products as well as other food and personal care products in which it is used as a thickening or binding agent. Thus, adhering to a gluten-free diet is both challenging and costly, and individuals with celiac disease report significant treatment burden (Shah et al., 2014).

A genetic predisposition is necessary but not sufficient for the development of celiac disease (i.e., HLA-DQ2/DQ8 positivity and non-HLA genes). Celiac disease is diagnosed when serological tests identify elevated celiac disease-specific antibodies (i.e., anti-tTG antibodies, anti-endomysium antibodies, and deamidated gliadin peptide antibodies) and duodenal biopsy finds evidence of small intestinal damage (i.e., atrophy of the duodenal villi and lesions of the intestinal mucosa). Markers of intestinal inflammation are also considered when making a differential diagnosis. Environmental factors such as viral infections and dysbiosis of gut

microbiota appear to contribute to development of celiac disease in susceptible individuals (Caio et al., 2019).

Accelerated research, earlier screening, and more reliable diagnostic methods have improved identification of celiac disease cases, contributing to the rise of global incidence of celiac disease, which has been estimated at 7.5% increase per year over the past four decades (Alkhayyat et al., 2021; King et al., 2020). However, rising incidence is not fully explained by improved case identification and there are yet unknown factors contributing to increased development of the condition, especially in adulthood (Catassi et al., 2010). Whereas celiac disease was once considered a disease of childhood, it is now clear that it can occur at any age and present with a variety of symptoms. Heterogeneous clinical presentations of celiac disease can delay diagnosis and contribute to ongoing physical and psychiatric challenges after diagnosis and initiation of a gluten-free diet.

Diverse Clinical Presentation and Subtypes of Celiac Disease

The earliest identified cases of celiac disease were observed in children who presented with significant weight loss, malabsorption, diarrhea, abdominal pain and distention, anemia, and growth failure. These symptoms are sometimes called “classical” celiac disease symptoms and can be observed in both children and adults (Cossu et al., 2017). As medical understanding of celiac disease has progressed, other common symptoms have been identified, including other gastrointestinal symptoms, headache, fatigue, metabolic bone disease and osteoporosis, anemia, skin manifestations, neurologic conditions, and psychiatric conditions. These are considered “non-traditional” celiac disease symptoms (Hernandez & Green, 2006). In clinical practice today, a “non-traditional” presentation is more common than a “classical” presentation, due to more awareness of the condition and improved diagnostic capacity. A prominent group of

international celiac disease physicians estimated that 52% of their patients present with "non-traditional celiac disease," 27% present with "classical celiac disease," and 21% present with no symptoms (Caio et al., 2019).

Accordingly, several phenotypes of celiac disease have been identified: *gastrointestinal, extraintestinal, subclinical, potential, seronegative, non-responsive, and refractory* (Caio et al., 2019). *Gastrointestinal* and *extraintestinal* are the primary clinical phenotypes and occur individually or in combination. Rare but severe cases of *gastrointestinal* celiac disease present with malabsorption syndrome and chronic diarrhea, weight loss, and significant physical weakness. The more common *gastrointestinal* celiac disease presentation is similar to irritable bowel syndrome (**IBS**), with constipation or alternating bowel dysfunction and/or dyspepsia-like symptoms such as nausea and vomiting prominent (Volta, Caio, Stanghellini, & De Giorgio, 2014). *Extraintestinal* celiac disease symptoms in both children and adults include anemia and changes in bone mineral density or osteoporosis. Reproductive functioning may be impacted, presenting as late menarche, amenorrhea, miscarriage, premature birth, early menopause, and changes in the number and mobility of spermatozoa. Psychiatric and neurological conditions such as depression and chronic headache are also considered *extraintestinal* manifestations of celiac disease.

Symptoms of *gastrointestinal* and *extraintestinal* manifestations of celiac disease can be alleviated for many patients with a gluten-free diet. However, fatigue, neurological manifestations, and gastrointestinal symptoms persist in a subgroup of patients. This subgroup, traditionally considered *non-responsive* and accounting for 10-26% of celiac disease cases (Galli et al., 2021; Leffler et al., 2007), experiences persistent symptoms, which may be due to ongoing active celiac disease (also called slow response or *refractory* celiac disease), ongoing gluten

exposure, and/or a comorbid associated condition. Co-morbid associated conditions include IBS, small intestinal bacterial overgrowth, microscopic colitis, lactose intolerance, fructose intolerance, diverticular disease, Crohn's disease, pancreatic insufficiency, and autoimmune and drug-induced disease enteropathy (Caio et al., 2019). A study of 113 *non-responsive* celiac disease patients found that gluten exposure was the most common cause of *non-responsive* status (36%) and co-occurring IBS was second (22%; Leffler et al., 2007).

IBS is a disorder of gut-brain interaction (formerly a "functional gastrointestinal disorder") characterized by abdominal pain, pain related to defecation, change in the frequency and/or appearance of bowel movements (e.g., constipation, diarrhea), and bloating (Lacy et al., 2021; Schmulson & Drossman, 2017). There are no specific biological markers or diagnostic tests for IBS, so the diagnosis is made based on symptomology alone using Rome IV criteria (Usai-Satta et al., 2020). Pooled prevalence of IBS in the general population is 4.4-4.8% across the U.S., Canada, and the United Kingdom, *not* including individuals diagnosed with celiac disease and IBD (Palsson, Whitehead, Törnblom, Sperber, & Simren, 2020). Comparatively, the pooled prevalence of IBS-type symptoms in patients with celiac disease is estimated at 38%, with greater odds of IBS-type symptoms in celiac disease patients compared to non-Celiac disease controls (OR = 5.60; Sainsbury, Sanders, & Ford, 2013). Like celiac disease, IBS is more prevalent in women than men (OR = 1.9).

Historically, diagnoses of celiac disease and IBS were mutually exclusive, such that patients with IBS-type symptoms positive for celiac disease were not also diagnosed with IBS. However, a recent study demonstrated that IBS-type symptoms persisted or developed in celiac disease patients with normalized histology after gluten-free diet initiation (Galli et al., 2021). The most common persisting symptoms were constipation, diarrhea, abdominal pain, and abdominal

bloating. The authors suggested that these persisting (or novel) IBS-type symptoms might be due to nutritional aspects of a gluten-free diet diet (e.g., change in fiber intake, increased intake of foods high in fermentable oligosaccharides, disaccharides, monosaccharides and polyols/FODMAPs) and/or due to co-occurring IBS.

Another long-term follow-up study of celiac disease patients in a tertiary treatment center found that 52% of patients met criteria for IBS at diagnosis, which dropped to 22% after one year on a gluten-free diet (Silvester et al., 2017). Despite the significantly reduced proportion of patients meeting IBS criteria, nearly one-fifth continued to experience aversive IBS-type symptoms even on a gluten-free diet. Long-term follow-up that includes histological assessment has been recommended to help make a differential diagnosis between ongoing active celiac disease and co-occurring IBS among celiac disease patients with persisting symptoms (Galli et al., 2021). Thus, it is increasingly understood that celiac disease and IBS may co-occur. It is particularly important to address persisting gastrointestinal symptoms as they are associated with lower quality of life and increased likelihood of depression and anxiety (Barratt, Leeds, & Sanders, 2011; Lee & Clarke, 2017).

Psychiatric Co-morbidity

A U.S. population-based study of 37 million patient records from 26 major healthcare systems found that celiac disease patients were more likely to have a history of anxiety (OR = 1.4), depression (OR = 1.9), bipolar disorder (OR = 1.3), attention deficit hyperactivity disorder (OR = 1.8), eating disorders (OR = 15.8), and autism (OR = 4.9), compared to patients without celiac disease, adjusting for age, sex, and race/ethnicity (Alkhayyat et al., 2021). A systematic review and meta-analysis of diagnosed psychiatric conditions in celiac disease patients similarly found significantly greater risk for anxiety (OR = 6.0), depression (OR = 4.9), attention deficit

hyperactivity disorder (OR = 1.4), eating disorders (OR = 1.62), and autism spectrum disorder (OR = 1.5; Clappison, Hadjivassiliou, & Zis, 2020). Depression and anxiety co-occur so frequently with celiac disease that the medical literature conceptualizes them as extraintestinal manifestations. Causes for higher psychiatric morbidity among celiac disease patients are not well understood. Proposed biological mechanisms include gut-brain interaction dysfunction (similar to IBS), cerebral hypoperfusion, hyperhomocysteinemia, vitamin deficiency, and associated autoimmune diseases. Proposed psychosocial mechanisms include chronic illness status, experience of aversive symptoms, dietary restrictions, compromised social relationships, reduced well-being, and lower quality of life (Cossu et al., 2017; Zingone et al., 2015).

Primary Celiac Disease Treatment: Gluten-free Diet

Attempts to develop effective drug therapies for celiac disease have been unsuccessful, rendering strict lifelong adherence to a gluten-free diet the only available treatment (McCarville, Caminero, & Verdu, 2015). Adopting a gluten-free diet becomes a lifestyle, wherein one must screen the ingredients of all products consumed, including food, medication and supplements, and personal care products (e.g., shampoo, face wash, lip balm). Among patients treated at a specialty celiac disease clinic, mastering self-management skills took many years (Clerx, Silvester, Leffler, DeGroote, & Fishman, 2019).

Treatment burden. Successful gluten-free diet adherence requires knowledge, skills, and behavior change. Removing gluten often requires significant changes to the patient's personal diet, as well as the diet and functioning of the family and household. The content and experience of family meals as well as traditions and holidays involving food are likely to change. Multiple meals may need to be prepared to satisfy different family members, and ingredients, tools and materials in the kitchen must be meticulously cleaned and separated to avoid cross-

contamination. Additionally, dietary counseling is often needed (though infrequently received) to ensure patients on a gluten-free diet eat a diet adequate in calories, fiber, vitamins, and minerals, and to learn to avoid cross-contamination (Rinninella et al., 2021).

Shah et al. (2014) found that celiac disease patients reported higher treatment burden than patients with IBS, inflammatory bowel disease (**IBD**), diabetes mellitus, congestive heart failure, and significantly higher burden than patients with gastroesophageal reflux disease and hypertension. The only condition with higher reported treatment burden was end stage renal disease. The authors proposed that perceived treatment burden may be an important treatment target of adjunctive interventions (Shah et al., 2014). Indeed, an estimated 40% of celiac disease patients are unsatisfied with treatment options and are interested in alternative treatments (Caio et al., 2019).

Gluten-free diet adherence rates. Given high treatment burden and the practical difficulties of gluten-free diet adherence, gluten-free diet nonadherence is common. While *complete* nonadherence appears to be relatively uncommon, ranging from 0-32% (though most studies found about below 5%), overall rates for strict adherence are estimated at 42-91%, with specific estimates depending on the assessment method and operational definition of adherence (Hall, Rubin, & Charnock, 2009; H Muhammad, Reeves, & Jeanes, 2019). Studies using self-report measures or dietary interview tend to define adherence on a continuum from strict, to partially strict, to nonadherent, whereas studies using biomarkers (e.g., serological tests, histopathology) tend to define adherence as a binary outcome (adherent/nonadherent). Nonadherence might be operationalized as ‘less than one serving of gluten per week’ or an estimate of milligrams of gluten ingested, or something less well defined. Despite reported adherence, there is evidence that unintentional gluten exposure is common because of the

widespread use of gluten in various food and personal care products. Therefore, complete gluten removal may not be achievable and even small amounts of continued gluten consumption may contribute to persisting symptoms and incomplete recovery (Silvester et al., 2020; Silvester, Weiten, Graff, Walker, & Duerksen, 2016).

Predictors of gluten-free diet adherence and nonadherence. Factors associated with gluten-free diet adherence and nonadherence have been examined and systematically reviewed. Notable limitations of the literature include the use of self-report measures of adherence (rather than objective measures), cross-sectional analyses (which fail to establish temporality and causality), and failure to distinguish between predictors of intentional versus unintentional nonadherence, which may differ. Further, the specific factors associated with adherence may differ for patients ranging in time since diagnosis and time on a gluten-free diet, even if those variables themselves are not significant predictors. Limitations notwithstanding, specific correlates of gluten-free diet adherence and nonadherence have been consistently reported and are reviewed here. These factors may represent viable treatment targets for improving gluten-free diet adherence.

Sociodemographic and cultural factors. There are mixed findings as to whether patient age and sex are related to adherence (Abu-Janb & Jaana, 2020). Higher income and higher level of education usually relate to greater adherence, and lower income relates to lower adherence. Lack of access to healthcare, and specifically to healthcare providers who can competently treat celiac disease, are related to lower adherence. Supportive family and friends promote gluten-free diet adherence, while certain cultural factors (e.g., gluten-containing foods prominent in cultural tradition) and non-supportive family and friends relate to lower adherence. Cultural factors may explain some preliminary findings that gluten-free diet adherence differs by race/ethnicity (Abu-

Janb & Jaana, 2020). Membership in a celiac disease patient support group or society consistently relates to better adherence (Muhammad et al., 2019).

Disease factors. While there are mixed findings about the relationship between length of time on a gluten-free diet and adherence, later age at diagnosis appears to relate to better adherence (Abu-Janb & Jaana, 2020). Having more severe symptoms post-diagnosis or when exposed to gluten relates to greater adherence (Abu-Janb & Jaana, 2020; Hall et al., 2009; Muhammad et al., 2019).

Gluten-free diet knowledge and gluten-free food availability. Nutrition counseling, greater gluten-free diet education, more knowledge about gluten-free foods, better understanding of gluten-free food labels, and the presence of labelling laws are related to greater adherence. Lower cost, greater availability of (appealing) gluten-free foods in grocery stores and restaurants, and receiving gluten-free foods by prescription also are related to greater adherence (Abu-Janb & Jaana, 2020; H Muhammad et al., 2019). Among "long-term" celiac disease patients (mean time on gluten-free diet = 9.9 +/- 5.4 years), perceptions of cost, effectiveness, and knowledge about the gluten-free diet related to adherence (Villafuerte-Galvez et al., 2015). Lack of celiac disease knowledge and low confidence in treatment information from the gastroenterologist and dietician may relate to lower adherence (Abu-Janb & Jaana, 2020; Hall et al., 2009). Lack of knowledge among food service staff relates to worse adherence (Abu-Janb & Jaana, 2020).

Cognitive, affective, and motivational factors. Embarrassment or social discomfort during shared meal times relates to lower adherence, as does lower quality of life and anger toward the disease (Abu-Janb & Jaana, 2020; Hall et al., 2009). A significant negative relationship between depressive symptoms and adherence is generally identified, which is likely bidirectional in nature. That is, worse adherence may causally predict greater depressive

symptoms, and greater depressive symptoms may causally predict worse adherence (Busby, Bold, Fellows, & Rostami, 2018; DiMatteo, Lepper, & Croghan, 2000; Sainsbury & Marques, 2018; Zingone et al., 2015). However, at least one study found that stricter adherence was related greater depression (Wolf et al., 2018).

Beliefs about the harmful effects of gluten or concerns about exposure relate to greater adherence, as does higher quality of life (Abu-Janb & Jaana, 2020). Intention to follow a gluten-free diet, greater celiac disease-specific self-efficacy, and greater self-regulatory efficacy relate to greater adherence whereas lower intention and motivation to adhere to a gluten-free diet relate to nonadherence (Abu-Janb & Jaana, 2020; Fueyo-Díaz, Magallón-Botaya, et al., 2020). The specific type of motivation may be important, as one large survey study found that autonomous and well-being-based motivations relate to greater adherence but control-based motivation does not. Further, greater self-compassion, habit, lower psychological distress, lower conflict, and fewer self-control lapses when busy or under stress relate to greater adherence (Dowd & Jung, 2017; Sainsbury, Halmos, Knowles, Mullan, & Tye-Din, 2018). Further, a patient's perception of their ability to maintain adherence despite changes in mood or stress level relates to better adherence (Leffler et al., 2008). These cognitive and affective processes could be targets of behavioral interventions aimed at improving gluten-free diet adherence.

Quality of Life in Celiac Disease

Quality of life is often negatively impacted among celiac disease patients. The World Health Organization defines quality of life as "an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns." The U.S. Centers for Disease Control and Prevention further defines *health-related* quality of life as "a multidimensional concept that includes self-

reported measures of physical and mental health and has replaced biochemical markers as primary outcome measure for many disease states." Thus, assessment of clinical outcomes for celiac disease patients must include quality of life in addition to symptoms and biomarkers of celiac disease pathology.

Measurement. Quality of life can be operationalized as the synthesis of functioning and well-being across various life domains. Quality of life is a construct that is relative and subjective by nature, for which self-report measurement is appropriate. Health-related quality of life instruments have been validated across patient populations, though condition-specific measures may be more psychometrically appropriate (Burger, van Middendorp, Drenth, Wahab, & Evers, 2019; Wiebe, Guyatt, Weaver, Matijevic, & Sidwell, 2003). That is, generic measures of health-related quality of life (e.g., Medical Outcome Survey Short-Form-36/SF-36) do not query celiac disease-specific domains, such as implications of the treatment on social activities, mental health, and sense of well-being. Therefore, generic measures may not reliably and validly inform clinicians about the treatment needs of celiac disease patients, nor would they be sensitive to change in response to intervention.

Four measures of celiac disease-specific quality of life have been developed in adult patients: the Celiac Disease Questionnaire (CD-Q; Häuser, Gold, Stallmach, Caspary, & Stein, 2007), the Celiac Disease-Specific QOL Survey (CD-QOL; Dorn, Hernandez, Minaya, Morris, Hu, Leserman, et al., 2010), the Coeliac Disease Quality of Life Questionnaire (CDQL; Skjerning, Hourihane, Husby, & DunnGalvin, 2017), and the Coeliac Disease Assessment Questionnaire (CDAQ; Crocker, Jenkinson, & Peters, 2018a, 2018b). The CD-Q and CD-QOL have been translated, adapted, and cross-culturally validated in numerous populations worldwide (Guennouni, Elkhoudri, Bourrhouat, & Hilali, 2020). In their systematic review of these

measures, Guennouni et al. (2020) reported adequate to good internal consistency (Cronbach's α < .7), acceptable test-retest reliability (intra-class correlation coefficient > .4), and good convergent validity for these measures (except for inadequate internal consistency in the CDQL). The CDQ assesses frequency of gastrointestinal symptoms, psychological symptoms (depression, stress, happiness), and functioning (sexual, recreational, and professional) over the past two weeks. The CD-QOL does not assess symptomology, but rather assesses specific and general health concerns, celiac disease-related stigma and dysphoria, functional impact and limitations, and perceptions of celiac disease-treatment, over the past 30 days (Dorn, Hernandez, Minaya, Morris, Hu, Leserman, et al., 2010). Given that subjective ratings of celiac disease-specific quality of life may not be strongly related to objective symptoms (Sainsbury, Mullan, & Sharpe, 2013b), it is important not to confound quality of life with symptomology in the same measure.

Quality of life outcomes in celiac disease. There are historically mixed findings as to whether quality of life is significantly reduced in celiac disease patients compared to healthy controls (Ciacci et al., 2003; Roos, Kärner, & Hallert, 2006). This may be an artifact of using generic quality of life measures, due to changes in quality of life over time, or the subgroup of patients examined (Guennouni et al., 2020; Hall et al., 2009). A meta-analysis of 16 studies found that generic health-related quality of life was significantly lower in celiac disease patients on a gluten-free diet compared to healthy controls and was significantly lower in symptomatic compared to asymptomatic patients (Burger et al., 2017). Gluten-free diet adherence prospectively improved health-related quality of life among celiac disease patients but did not necessarily normalize it (Burger et al., 2017; Hall et al., 2009). A prospective study of quality of life in newly diagnosed adult celiac disease patients found that generic quality of life scores,

depressive symptoms, and gastrointestinal symptoms were worse among celiac disease patients compared to healthy controls at baseline (Nachman et al., 2010). At one-year follow-up, quality of life scores, depression scores, and gastrointestinal symptoms were significantly improved among patients and comparable to healthy controls. However, at four-year follow-up, quality of life scores significantly decreased from one-year follow-up in five SF-36 domains (social function, general health perception, role limitation due to physical problems, role limitations due to emotional problems, and vitality), as did depressive symptoms, despite no significant change in gastrointestinal symptoms. Therefore, quality of life is an important outcome for celiac disease patients across the illness trajectory and should a primary target of any treatments designed for celiac disease.

Predictors of quality of life. Various predictors of quality of life in celiac disease have been identified, including gluten-free diet adherence, sociodemographic characteristics, disease factors, and cognitive and affective factors.

Gluten-free diet adherence. In the longitudinal study by Nachman et al. (2010), gluten-free diet adherence was related to quality of life at four-year follow-up. Compared to partially adherent patients, strictly adherent patients had significantly better quality of life scores on SF-36 domains (physical function, social function, role limitations due to physical problems and emotional problems, mental health, and general health) as well as lower depressive symptoms and gastrointestinal symptoms (abdominal pain, indigestion, diarrhea). Italian researchers similarly found that celiac disease-specific quality of life (using CD-QOL) was higher among patients considered gluten-free diet-adherent (Marsilio et al., 2020). Spanish researchers found that gluten-free diet adherence was positively associated with celiac disease-specific quality of life (using CD-QOL) among 738 patients with an average time since diagnosis of 10 years,

where 97% reported strict adherence (Fueyo-Díaz, Montoro, et al., 2020). Conversely, a U.S. study (using CD-QOL) found significantly lower quality of life among strictly gluten-free diet adherent patients compared to less adherent patients, on the total score as well as the dysphoria and limitations subscales (Wolf et al., 2018). Strictly adherent patients in that study were characterized as "extremely vigilant" and consistently ate at celiac disease-friendly restaurants or avoided dining out altogether, eliminated cross-contamination potential in their home kitchens, etc. Thus, there may be specific aspects of following a gluten-free diet (such as impacts on social functioning and mood) that negatively impact quality of life.

Thus, greater gluten-free diet adherence seems to relate to higher quality of life. However, the direction and magnitude of this relationship may vary over time, similar to the relationship between gluten-free diet adherence and depression. That is, gluten-free diet initiation may be followed by improvements in quality of life due to symptom alleviation associated with the gluten-free diet; however, long-term gluten-free diet adherence may negatively impact quality of life due to functional limitations, impacts on career, family life, and social life, stigmatization, and increased stress, depression, and anxiety (Clifford et al., 2020; Ludvigsson et al., 2015; Zingone et al., 2015). This hypothesis is supported by findings that quality of life scores do not improve for asymptomatic patients following gluten-free diet initiation, given that they experience no benefit of symptom alleviation but do experience the burden and functional limitations associated with the treatment.

Sociodemographic and cultural factors. There may be a positive association between current age and celiac disease-specific quality of life (Fueyo-Díaz, Montoro, et al., 2020). The extent to which the gluten-free diet is challenging to follow and thus negatively impacts quality of life may depend on geographic location and culture. Gluten-free diet is better recognized as a

medical necessity (rather than a fad) in European countries compared to the U.S., and European food service employees are better trained to accommodate gluten-free diet requests (Wolf et al., 2018). This may reduce stigma and stress related with eating a gluten-free diet outside the home, which is a significant determinant of quality of life for many celiac disease patients. Further, celiac disease-specific quality of life may vary by country based on factors such as availability of gluten-free foods, affordability of gluten-free foods, access to healthcare and celiac disease specialists, social support, and recognition of celiac disease. These cultural differences may contribute to the inconsistent findings regarding the relationship between gluten-free diet adherence and quality of life reported in the literature.

Disease factors. Greater time since diagnosis may relate to higher celiac disease-specific quality of life over and above the influence of gluten-free diet adherence (Fueyo-Díaz, Montoro, et al., 2020). Higher incidence of gastrointestinal symptoms, longer duration of symptoms before diagnosis, and persisting symptoms despite gluten-free diet adherence are related to lower quality of life (Harnett & Myers, 2020; Paarlahti et al., 2013; K. Sainsbury et al., 2013b). Presence of psychiatric, neurologic, and/or gastrointestinal co-morbidities are associated with lower quality of life (Paarlahti et al., 2013). Lower energy is related to lower celiac disease-specific quality of life (Wolf et al., 2018).

Cognitive, affective, and motivational factors. Depression is strongly associated with lower quality of life in celiac disease. In one study, depression was a stronger (cross-sectional) predictor of generic quality of life than gluten-free diet adherence, gastrointestinal symptoms, and perceived difficulty of the gluten-free diet, and remained significant when controlling for these variables (Sainsbury et al., 2013b). Coping style is related to quality of life, such that coping characterized by greater catastrophizing and less perceived ability to decrease symptoms

relates to lower health-related quality of life (Dorn, Hernandez, Minaya, Morris, Hu, Lewis, et al., 2010), as does emotion-oriented coping and other maladaptive forms of coping (Sainsbury et al., 2013b). Celiac-specific (rather than general) self-efficacy and *lower* risk perception are related to better celiac disease-specific quality of life (Fueyo-Díaz, Montoro, et al., 2020). Perceived level of difficulty following a gluten-free diet is related to lower quality of life (Barratt et al., 2011; Sainsbury et al., 2013b).

Numerous researchers have suggested that greater gluten-free diet adherence negatively impacts quality of life, which in turn increases depression and anxiety (Alkhayyat et al., 2021; Clappison et al., 2020), though this relationship has not been prospectively examined. Indeed, gluten-free diet adherence and quality of life share several predictors (e.g., self-efficacy, depression) that could be targeted by behavioral interventions to jointly improve these two critical functional outcomes.

Behavioral Treatment

Celiac disease is a lifelong condition for which the only available treatment is dietary behavior change. Given ubiquitous difficulties with gluten-free diet adherence and its negative relationship with mental health and quality of life, physicians and researchers alike have noted an urgent need to develop behavioral interventions that address these challenges concurrently in celiac disease patients. The biopsychosocial model provides a framework for understanding connections between symptoms, psychiatric and behavioral variables, and social influences, and elucidates possible treatment targets (Dorn, Hernandez, Minaya, Morris, Hu, Lewis, et al., 2010). Cognitive and behavioral factors are among many modifiable correlates identified for both gluten-free diet adherence and quality of life that could be targets of behavioral interventions (see *Figure 1.0*). Further, intervention components such as mindfulness could target persistent

gastrointestinal symptoms specifically. Treatments targeting similar processes and outcomes have been developed for related conditions, including IBS and IBD.

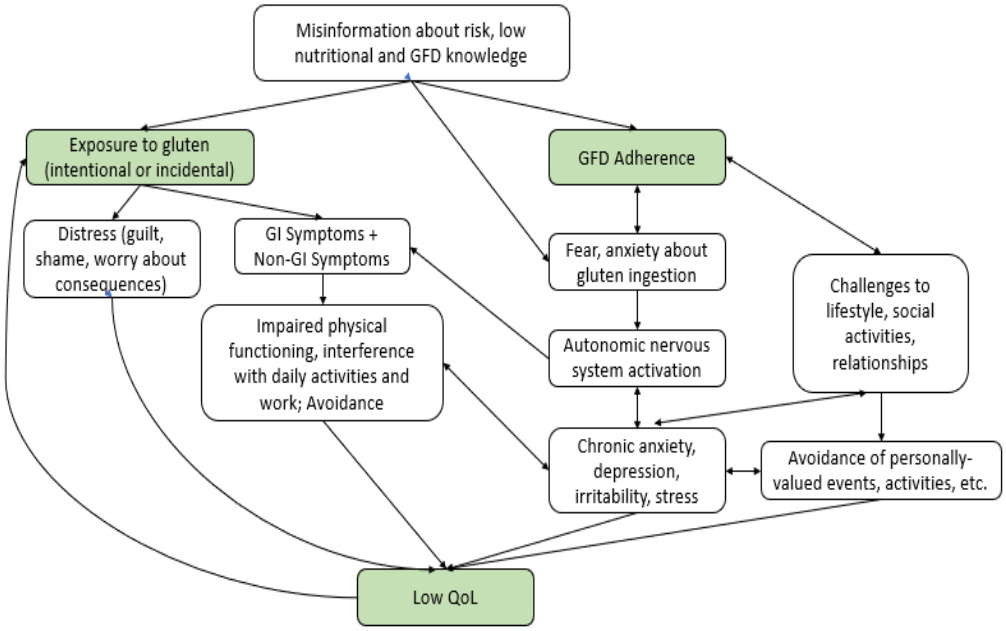

Figure 1.0. *Conceptual Model of Distress in Celiac Disease*. *Note*: Diagram shows proposed mechanisms (white boxes) and outcomes (green boxes) of interest in potential behavioral interventions. Not pictured: bidirectional relationship between chronic anxiety, depression, and gluten-free diet adherence.

Evidence-based behavioral treatment for IBS. The biopsychosocial model of IBS posits that genetic and environmental factors (e.g., early life experiences, social learning, stress, culture, infection) act upon gut physiology (e.g., gut permeability, sensation, microbiome, inflammation/immune response), central nervous system structure and function (e.g., emotional and cognitive modulation of visceral afferent signals, classical fear conditioning), and psychological factors (e.g., depression, anxiety, health anxiety, somatization, attentional biases, catastrophizing), which produces the clinical presentation (i.e., symptoms, severity, comorbidity, behavior) and outcomes of interest in IBS (quality of life, healthcare utilization; Van Oudenhove et al., 2016). Dysregulation in the bidirectional communication between the brain and gut via the autonomic nervous system and hypothalamic-pituitary-adrenal axis is also implicated in the clinical presentation. Similar processes are hypothesized to be active in celiac disease, especially

given the high rates of persistent IBS-type symptoms among celiac disease patients (Lerner & Benzvi, 2021).

Current recommendations from the American Gastroenterological Association and the American College of Gastroenterology recommend psychological treatment be incorporated into treatment for gastrointestinal conditions (Keefer, Palsson, & Pandolfino, 2018; Lacy et al., 2021). Behavioral interventions for reducing gastrointestinal symptoms and improving quality of life and mental health in IBS are well-established, with the strongest evidence base for cognitive-behavioral therapy (**CBT**), gut-directed hypnotherapy, and mindfulness-based therapies (Ballou & Keefer, 2017; Zijdenbos, de Wit, van der Heijden, Rubin, & Quartero, 2009).

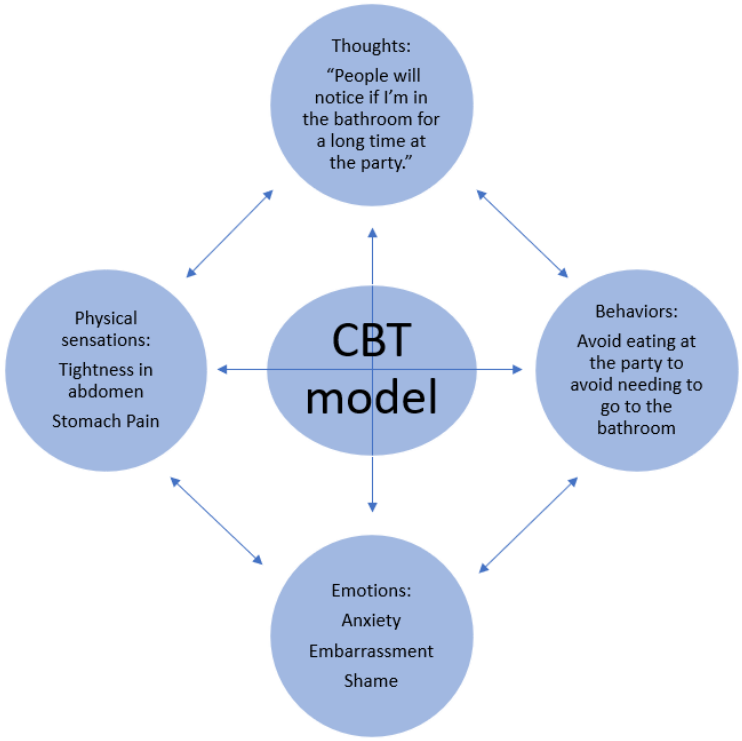

Figure 2.0. *Example of Cognitive-Behavioral Conceptualization in IBS. Note:* Adapted from Ballou & Keefer (2017).

CBT interventions target the interactions between condition-related thoughts, feelings, and behaviors (see *Figure 2.0*). CBT interventions for IBS generally include psychoeducation about the stress response and its relationship to gastrointestinal symptoms (via physiological and

psychosocial pathways), identifying cognitions and behaviors directly related to gastrointestinal symptoms or fear of symptoms, and modifying those cognitive and behavioral responses in order to decrease psychological distress and physical reactivity.

Gut-directed hypnotherapy protocols include psychoeducation, induction of deep relaxation, scripted gut-directed post-hypnotic suggestions, and transition to wakeful awareness. Mechanisms of gut-directed hypnotherapy are thought to include direct effects on gut functioning and pain processing in the brain, visceral sensitivity, and psychological factors (e.g., cognitions, anxiety, depression).

Mindfulness-based interventions use meditation and relaxation exercises to promote awareness and acceptance of the present moment. Awareness and acceptance are cultivated from a non-judgmental stance, from which the patient makes no attempts to change their present experiences. Mindfulness-based interventions for IBS include exercises such as mindful breathing, mindful eating, mindful listening, and mindful observation, which can be general or gastrointestinal -specific, practiced in the presence of acute gastrointestinal symptoms or not (Ballou & Keefer, 2017). Mindfulness-based interventions are shown to decrease hypervigilance to visceral sensations, decrease catastrophizing of symptoms, and improve overall symptoms and quality of life in IBS. Ballou and Keefer (2017) note that mindfulness-based exercises can be incorporated into CBT protocols to enhance efficacy, which has preliminary evidence (Ljótsson et al., 2010).

Third-wave CBTs offer a formal integration of traditional CBT and mindfulness-based interventions. Acceptance and Commitment Therapy (ACT) is one such third-wave CBT with preliminary evidence in IBS (Ferreira, Gillanders, Morris, & Eugenicos, 2018). ACT differs from traditional or ‘second-wave’ CBT in that it does not attempt to change the content or

frequency of thoughts, but rather focuses on the patient's position relative to their thoughts. That is, it emphasizes that the conscious self is separate from thoughts [self-as-context] and conceptualizes thoughts as occurrences of the mind rather than literal or absolute truth [defusion] with the goal of producing flexibility behavioral responses. ACT incorporates a strong behavioral component wherein patients identify and perform goal-directed behaviors [committed action] that are chosen in accordance with personally held values [values identification]. ACT uses mindfulness exercises to promote a non-judgmental and accepting stance toward all internal and external experiences (i.e., thoughts, physiological sensations, affect, situations) [acceptance]. ACT explicitly promotes experiential acceptance as a response to internal and external stimuli rather than maladaptive patterns of avoidance and other unhelpful coping styles. A pilot study for ACT for IBS found reductions in gastrointestinal symptoms, gastrointestinal anxiety, and avoidance behaviors, and increases in IBS-specific and general quality of life at three-month and six-month follow-ups (Ferreira et al., 2018). The AGA clinical practice guidelines identified ACT intervention as a promising area for future research in gastrointestinal conditions (Keefer et al., 2018).

Mechanisms and treatment targets. A systematic review of eight CBT studies and one mindfulness-based intervention study for IBS found that changes in illness-specific cognitions (i.e., catastrophizing, negative illness perceptions, symptom-focusing, symptom control beliefs) and gastrointestinal-specific anxiety (i.e., fear of gastrointestinal symptoms, their context, meaning, and responses) were mediators of treatment outcomes (symptom severity and quality of life; (Windgassen et al., 2017). Changes in illness-related behaviors (i.e., avoidance, safety behaviors) may also be important mediators but are less often examined as such. It is

unsurprising that change in illness-related cognitions was a significant mediator among (mostly) traditional CBT interventions given that cognitive restructuring is a primary intervention in CBT.

As described previously, emergent ACT interventions for IBS would be expected to operate via slightly different mechanisms, such as *acceptance* of IBS, its manifestations, and one's thoughts about it rather than attempts to control or change these experiences. This approach is predicated on behavioral theory suggesting that attempts to eliminate thoughts are counterproductive and often increase their frequency and intensity (Törneke, Luciano, & Salas, 2008). Ferreira et al. (2018) found that IBS acceptance increased from pre- to post-treatment and this change was associated with improvements in other outcomes (quality of life, gastrointestinal-specific anxiety, IBS avoidance behaviors) from pre-treatment to follow-up. A cross-sectional moderated mediation analysis found that gastrointestinal anxiety and behavioral response mediated the relationship between IBS symptom severity and quality of life, but the strength of the mediatory relationship was moderated by acceptance. Specifically, the less IBS acceptance a patient reported, the stronger the mediatory relationship, and the more IBS acceptance reported, the weaker the mediatory relationship. Thus, higher IBS acceptance may attenuate the relationship between greater symptom severity and lower quality of life, allowing for improved quality of life regardless of symptom change (Bowers, Gillanders, & Ferreira, 2020). Though longitudinal research is needed to examine causal relationships between these dynamic factors, findings suggest that IBS acceptance may be an appropriate treatment target for IBS and by extension, celiac disease. In common with CBT interventions, ACT for IBS might decrease illness avoidance behaviors, particularly via increases in committed action for values-based behaviors (e.g., engaging socially in service of being a supportive friend). ACT interventions may also decrease gastrointestinal-specific anxiety (i.e., fear of gastrointestinal

symptoms, their context, meaning, and responses) by reducing judgmental responses to these experiences via increases in mindfulness and present moment awareness.

Evidence-based behavioral treatment for IBD. IBD encompasses multiple conditions characterized by chronic inflammation of the gastrointestinal tract. These conditions are distinct from but similar in clinical presentation to celiac disease and IBS (e.g., diarrhea, fatigue, abdominal pain and cramping, unintended weight loss) and IBD patients experience similar treatment burden (Ballou & Keefer, 2017). IBD is more common among celiac disease patients than non-celiac disease controls (OR = 3.8) and is highly comorbid with IBS (estimated 30-50% of IBD patients have IBS-type symptoms; Assa, Frenkel-Nir, Tzur, Katz, & Shamir, 2017; Fukuba et al., 2014). There is a small evidence base supporting the use of traditional CBT, gut-directed hypnotherapy, and mindfulness-based therapies for IBD. These interventions often improve quality of life and psychiatric outcomes despite not improving gastrointestinal

Table 1.0 *Behavioral Intervention Studies to Promote Gluten-free Diet Adherence in Celiac Disease*

First author (year), study type, *N*	Intervention Sample	Behavioral intervention	Delivery method	Intervention duration	Clinician	Outcomes assessed (measure)	Results
Jacobsson (2012), RCT, *N* = 106	Adult women on a GFD for ≥5 years	"Educational program" addressing "anxiety and fears associated with CeD, attitudes to surroundings, psychological reactions, coping strategies, obstacles in daily life, new knowledge, and various questions associated with food and cooking"	Small group, in-person	10 sessions over 10 weeks	Tutor familiar with the problem-based learning pedagogy and acting as a moderator	**GI Symptoms** (GI Symptom Rating Scale)	Significant reduction in **GI symptoms** in intervention group (but not control)
Sainsbury (2013), RCT, *N* = 189	Adults on GFD for ≥3 years (GFD adherence rates allowed to vary)	Online intervention providing (a) education, (b) validated (health-) behavior change techniques, and (c) evidence-based strategies drawn from CBT to treat anxiety and depression and improve coping behavior	Self-guided internet modules	6 modules over 6 weeks (~30 min/ module)	N/A; automated emails and text messages	**GFD adherence** (CDAT) **GFD knowledge** **QoL** (World Health Organization QoL Assessment BREF) **Depression, Anxiety, and Stress symptoms** (Depression, Anxiety, Stress Scale) **Eating Disorder Risk** (Eating Disorders Inventory-3)	Significantly greater improvements in intervention group (versus control) for **GFD adherence and GFD knowledge**
Addolorato (2014), RCT, *N* = 66	Newly diagnosed adults "affected by anxiety and depression" (not yet on GFD)	"Psychological support" including discussion of CeD-related distress and impairment, including the emotional impact of GFD adherence, problem-solving to promote QoL and GFD adherence	1:1, in-person	12 sessions (biweekly) for 6 months	Professional staff	**GFD adherence** (self-report, family member interview, clinical symptoms, histological recovery) **Depression** (Zung self-rating depression sale) **Anxiety** (State and Trait Anxiety Inventory)	Greater **GFD adherence** rates and lower **depression** rates in intervention group (versus control) at 6-month FU
Muhammad (2020), RCT, *N* = 125	Adults reporting non-adherence	"Personalized intervention focusing on areas of knowledge or behavior that was important to the participant" including education on CeD, gluten-free foods, food labeling, logistics of GFD adherence, social aspects of GFD, coping statements, support networks, SMART goals	Individual telephone clinic plus written material	Unknown number of calls and weeks (~50 min/call); first follow-up at 3 months	Gastroenterologist and a Clinical Nutrition MSc with expertise in CeD	**GFD adherence** (CDAT) **GFD knowledge** **CeD-related QoL** (CD-QOL)	Significant improvements in intervention group (but not control) for **GFD adherence and GFD knowledge**

symptoms (Ballou & Keefer, 2017). There is also a small evidence base for use of ACT in IBD for improving psychiatric outcomes, IBD-specific quality of life, and perhaps symptoms (Hou et al., 2017; Wynne et al., 2019). Qualitative research on IBD patients' perspectives found that they generally perceived ACT as useful for treating IBD-related distress (Dober et al., 2020).

Evidence-based behavioral treatment for celiac disease. Despite the critical need for interventions to promote gluten-free diet adherence and improve quality of life among celiac disease patients, there have been few high-quality studies. A scoping review found seven trials of interventions designed to increase gluten-free diet adherence in adults with celiac disease, of which four included a behavioral or psychological component (Addolorato et al., 2004; Jacobsson, Friedrichsen, Göransson, & Hallert, 2012; Humayun Muhammad, Reeves, Ishaq, & Jeanes, 2020; Humayun Muhammad, Reeves, Ishaq, Mayberry, & Jeanes, 2020; Sainsbury, Mullan, & Sharpe, 2013a). No intervention studies explicitly designed to promote quality of life in adults with celiac disease have been published. Among the four behavioral intervention trials for promoting gluten-free diet adherence, interventions ranged in design, duration, provider, and treatment components (*Table 1.0*). Samples ranged from newly diagnosed celiac disease patients not yet following a gluten-free diet to patients on a gluten-free diet for five or more years. Common intervention components included education about celiac disease and gluten-free diet and discussion of the social and emotional impacts of gluten-free diet. However, only one study explicitly identified CBT as the underlying theory of the intervention and indicated that evidence-based CBT skills were adapted for the program (Sainsbury et al., 2013a). Across all studies, gluten-free diet adherence and gluten-free diet knowledge improvement was consistent, with greater improvements in the intervention groups compared to control groups. However, K. Sainsbury et al. (2013a) found that change in gluten-free diet knowledge did not predict change

in gluten-free diet adherence, suggesting that improvements in knowledge are not sufficient for behavior change. There were mixed findings for psychiatric outcomes (anxiety, depression). Of the two studies reporting quality of life outcomes, one found significant improvement in both the intervention and control groups using a generic quality of life measure (Sainsbury et al., 2013a), and one found no significant improvement in either group using the CD-QOL (Humayun Muhammad, Reeves, Ishaq, Mayberry, et al., 2020). Limitations of these studies include varied measures of gluten-free diet adherence, inconsistent reporting of outcomes, lack of strong theoretical grounding for intervention content, and provider credentials. Interventions were delivered by healthcare providers (physician and nutritionist), "tutors," "professional staff," or internet modules (no clinician interaction), none of whom were specified to have formal training in psychology or behavior change. Further, the highest quality study had 50% attrition, perhaps due to the online nature and lack of clinician interaction (Sainsbury et al., 2013a).

Future directions. Development of robust evidence-based behavioral interventions for celiac disease delivered by trained clinicians is an important next step. These interventions should target both gluten-free diet adherence and celiac disease-specific quality of life as outcomes. Based on theory and findings in behavioral studies for IBS and IBD, acceptance and mindfulness components (which were not included in previous studies) should be included. ACT is a promising behavioral treatment approach for improving celiac disease outcomes with preliminary evidence in other chronic health conditions (Dindo, 2015; Graham, Gouick, Krahe, & Gillanders, 2016). Ultimately, the goal of ACT is to promote *psychological flexibility*, which enables a flexible repertoire of behavior that serves to improve quality of life and functioning and reduce avoidance. Therapeutic ACT processes may uniquely impact critical mechanisms of low gluten-free diet adherence and impaired functioning and quality of life (shown in *Figure*

1.0). For example, mindfulness and present-moment awareness could address distress following gluten exposure, fear and anxiety about gluten ingestion, chronic stress system activation, and difficulty with changes to lifestyle, social activities, and relationships. Defusion, self-as-context, values identification, and committed *action* could address behavioral avoidance patterns, interference with daily activities and work, and chronic anxiety, depression, irritability, and stress. Acceptance could address psychological distress following gluten exposure and behavioral avoidance. IBD patients noted that the acceptance component of ACT would be particularly appropriate for addressing the difficulties of living with a chronic health condition and its psychiatric sequelae (Dober et al., 2020). To our knowledge, no ACT for celiac disease interventions have been developed.

Development and implementation of such interventions must be sensitive to patient needs. A qualitative study assessing IBD patients' perspectives on a proposed ACT intervention found that barriers to treatment access and participation, timing in the illness trajectory, and amount of support were important aspects to consider. In terms of barriers to access and participation, patients reported that fatigue, busy lifestyle, and balancing competing priorities (e.g., work, school, family, relationships, medical needs) may lower motivation to participate. In terms of timing, IBD patients reported that intervention within the first few months to a year after diagnosis would be most beneficial. Further, therapist support was identified as an important component for increasing motivation at the beginning of treatment. Patients noted that a blend of therapist-supported and self-guided components was a sustainable approach in terms of time and energy (Dober et al., 2020). Thus, despite the promise of behavioral interventions for celiac disease, high treatment burden combined with competing priorities may interfere with treatment uptake. One potential adaptation to improve treatment uptake is to deliver brief

interventions, which require less resource investment from both patients and providers. Brief behavioral interventions may be more feasible, acceptable, and appropriate for chronic health condition populations than standard 10-16 session psychotherapy interventions. Further, brief behavioral interventions can be delivered in traditional healthcare settings (e.g., primary care, specialty clinics) in a non-stigmatizing way (e.g., "workshop" rather than "therapy") and more easily allow for interdisciplinary collaboration. Briefer interventions delivered in-person or remotely may also improve access for patients living in remote areas who are less well-connected to support groups and specialty clinics, which are usually located in urban areas. Given widespread issues with limited access to follow-up care among celiac disease patients, behavioral interventions optimized for accessibility are needed (Leonard et al., 2017). A small narrative review ($K = 6$) of single-session ACT interventions for chronic health conditions found preliminary support for very brief (one-day) interventions (Dindo, 2015).

Summary and Gaps in the Literature

In summary, celiac disease is a specific autoimmune condition with a known trigger (gluten) and well-defined biological indicators. However, the clinical presentation of celiac disease is diverse, especially with regards to symptoms (number, type, trajectory, remission status), extraintestinal manifestations, psychiatric symptoms, and possible co-occurring conditions (e.g., IBS). The heterogenous presentation of celiac disease patients can complicate diagnosis at the outset and complicate treatment in the long-term, especially when symptoms persist. Until recently, the possibility that co-occurring conditions (specifically IBS) might explain persisting IBS-type symptoms was infrequently considered. Findings now suggest that persisting IBS-type symptoms may be due to co-occurring IBS rather than ongoing active celiac

disease and may or may not be attributable to continued gluten exposure (Galli et al., 2021; Silvester et al., 2017).

Whether there are discrete symptom profiles that suggest the presence of specific co-occurring conditions such as IBS has not been explored. Examining patient profiles based on unique combinations of IBS-type symptoms, other gastrointestinal symptoms, and extraintestinal symptoms, and whether these profiles are differentially related to gluten-free diet adherence may help elucidate treatment targets for behavioral and biomedical intervention and aid in differential diagnosis. Given that quality of life and mood are also impaired in some celiac disease patients, examining relationships between symptom profiles and these outcomes will also guide behavioral intervention development to support patients with celiac disease. For example, patients with persisting IBS-type gastrointestinal symptoms who report low dietary adherence could benefit from behavioral interventions to address dietary adherence, whereas patients with persisting gastrointestinal symptoms who report high dietary adherence might benefit from behavioral interventions that directly target gastrointestinal symptoms, additional dietary changes (e.g., low FODMAP diet), and/or biomedical interventions for IBS. Additionally, numerous disease and other factors might vary across symptom profiles (e.g., duration of symptoms prior to diagnosis, time since celiac disease diagnosis and gluten-free diet initiation) and indicate a need for modified treatment approaches.

Development of behavioral interventions to support celiac disease patients struggling with long-term gluten-free diet adherence and/or impaired quality of life requires sensitive measurement of celiac disease-specific quality of life. To this end, the CD-QOL was developed in the U.S. in 2010 and translated and adapted for international patient groups. However, its factor structure and psychometric properties have not been confirmed in a second, independent

sample of English-speaking, U.S. adults. Further, there is a scarcity of research on behavioral interventions designed to support celiac disease patients struggling with persisting symptoms, gluten-free diet nonadherence, and impaired quality of life and mood. The literature suggests that behavioral interventions incorporating education, peer and clinician support, and evidence-based behavioral components could benefit patients, but few such interventions have been developed. Interventions developed for IBS and other chronic conditions can be used as templates for celiac disease, particularly ACT-based interventions as they integrate mindfulness, acceptance, and behavior change strategies. A review of ACT interventions that are feasible, acceptable, and effective for chronic health conditions would provide a foundation for ACT intervention development for celiac disease specifically.

Current Research

The research completed for this dissertation addressed gaps in the literature regarding the measurement of celiac disease-specific quality of life, the understanding of diverse clinical presentations and the complex associations between symptomology, gluten-free diet adherence, quality of life, and psychiatric concerns in established celiac disease patients, and the development of feasible, acceptable, and accessible ACT-based interventions for improving gluten-free diet adherence and quality of life among adult celiac disease patients.

Study 1 addressed a specific gap in the literature regarding the psychometric properties of the Celiac Disease-Specific Quality of Life Survey (CD-QOL; Dorn, Hernandez, Minaya, Morris, Hu, Leserman, et al., 2010). Best practices for patient-reported outcome measure development includes two phases: (a) development and initial validation in one sample and (b) confirmation of the psychometric properties and factor structure in a second sample. The 20-item, four-factor CD-QOL was developed according to best practices for phase (a), but its

psychometric properties and four-factor structure had not been confirmed in a second sample (phase b). Given past and current use of the CD-QOL in clinical research, phase (b) analyses were warranted to ensure the utility and adequacy of the CD-QOL among adult celiac disease patients in the U.S.

Study 2 characterized the diversity of clinical presentations among a group of adult celiac disease patients and explored the relationships between symptom profiles, gluten-free diet adherence, psychiatric symptoms, and general and celiac disease-specific quality of life. The literature suggests that symptomatic and asymptomatic patients, or patients with more or fewer IBS-type symptoms, have different experiences of celiac disease, different co-morbidities, and require different types of intervention to treat symptoms, promote disease-self management, and increase well-being. At this juncture, it is critically important to understand how symptoms are clustered and in turn related to gluten-free diet adherence and quality of life, which may provide insight into existence of co-occurring conditions and appropriate treatment targets for both pharmaceutical and behavioral interventions.

Study 3 provided a systematic review and meta-analysis of the literature on single-session ACT interventions for chronic health conditions. Brief ACT interventions hold promise for improving gluten-free diet adherence and quality of life among celiac disease but have not been specifically applied to this population. This review included ACT interventions designed for celiac disease-related conditions IBS and IBD. Results of this systematic review and meta-analysis inform ACT intervention development for celiac disease.

Psychometric Validation of the Celiac Disease-Specific Quality of Life Survey (CD-QOL) in Adults with Celiac Disease in the United States

Cara Dochat[1], Niloofar Afari[2,3], Danielle Arigo[4]

[1] San Diego State University/University of California San Diego Joint Doctoral Program in Clinical Psychology, San Diego, CA, USA

[2] VA San Diego Healthcare System, San Diego, CA, USA

[3] University of California San Diego, La Jolla, CA, USA

[4] Rowan University, Glassboro, NJ, USA

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Abstract

Purpose: Celiac disease and its treatment negatively impact quality of life, indicating potential need for interdisciplinary intervention and valid measurement of disease-specific quality of life domains. The Celiac Disease Quality of Life Survey (CD-QOL) has been used in clinical research; however, its factor structure has not been confirmed and psychometric properties have not been evaluated in English-speaking adults in the U.S. Aims: (1) Confirm the four-factor structure of the 20-item English CD-QOL; (2) assess psychometric properties including internal consistency reliability, convergent validity, known-groups validity, and incremental concurrent validity.

Methods: 453 adults with self-reported celiac disease (M_{age}=40.57; 88% female; 92% white) completed the CD-QOL and validated measures of generic health-related quality of life (SF-36), gluten-free diet adherence (CDAT), anxiety and depression symptoms (PROMIS), and physical symptoms (CSI) as part of the iCureCeliac® patient-powered research network.

Results: Confirmatory factor analysis supported a second-order factor structure, with four subscales (limitations; dysphoria; health concerns; inadequate treatment) and a total score. Total and three subscale scores demonstrated acceptable internal consistency reliability. Convergent and known-groups validity were supported. The CD-QOL demonstrated some incremental concurrent validity over the SF-36.

Conclusion: The English CD-QOL can be used as a measure of celiac disease-specific quality of life among adults with celiac disease in the U.S. Compared to generic instruments, the CD-QOL appears to capture specific cognitive, affective, and behavioral aspects of living with celiac disease that negatively impact treatment adherence and mental health. Its utility as a screening and treatment outcome measurement tool in clinical settings should be examined

Psychometric Validation of the Celiac Disease-Specific Quality of Life Survey (CD-QOL) in Adults with Celiac Disease in the United States

Celiac disease is a common autoimmune condition in the western world, affecting at least 3 million people in the United States and 48-300 million worldwide (Green, 2007; Rubio-Tapia, Ludvigsson, Brantner, Murray, & Everhart, 2012; Singh et al., 2018). In celiac disease, ingestion of gluten, a protein found in wheat and some other grains, prompts an autoimmune response that causes damage to the structure and function of the small intestine. Celiac disease often presents with aversive gastrointestinal and extraintestinal symptoms (Leonard, Sapone, Catassi, & Fasano, 2017). Celiac disease is more prevalent in women than men worldwide (Caio et al., 2019; Singh et al., 2018) and is diagnosed more often in non-Hispanic whites than other racial/ethnic groups in the United States (Choung et al., 2015).

The only available treatment for celiac disease is to abstain from consuming gluten, which is found in many grain-based food products as well as other food and personal care products in which it is used as a thickening or binding agent. Consequently, adhering to a gluten-free diet is both challenging and costly, and individuals with celiac disease report high treatment burden (Shah et al., 2014). Following a strict, lifelong gluten-free diet often requires significant changes not only to the patient's diet but also to the diet and functioning of the patient's family and household. Ingredients of all consumed foods must be carefully examined, and individuals may experience considerable lifestyle changes at work, while traveling, at social events, during holidays, and more. As a result, quality of life is often negatively impacted among people with celiac disease (Hall, Rubin, & Charnock, 2009; Nachman et al., 2010). Quality of life can be defined as a person's perception of their position in life relative to their cultural context, value system, and personal goals and expectations (WHO, 1995). Clinical characteristics related to lower quality of life among individuals with celiac disease include persisting physical symptoms

despite gluten-free diet adherence (Harnett & Myers, 2020), greater depression symptoms (Sainsbury, Mullan, & Sharpe, 2013), and presence of psychiatric, neurologic, and/or gastrointestinal co-morbidities (Häuser, Stallmach, Caspary, & Stein, 2007; Paarlahti et al., 2013). Further, lower quality of life is cross-sectionally and longitudinally related to lower gluten-free diet adherence (Häuser et al., 2007; Nachman et al., 2010; Wagner et al., 2008), suggesting that increasing gluten-free diet adherence may improve quality of life, and conversely, improving quality of life may increase gluten-free diet adherence. While these findings suggest that attending to quality of life among adults with celiac disease is important for ensuring positive long-term health outcomes, most extant research has used generic health-related quality of life measures, which may not capture important nuances of living with celiac disease that impact functioning and wellbeing.

Generic health-related quality of life measures are designed for use across various patient populations, and do not query celiac disease-specific domains. Evidence shows that generic instruments may not be psychometrically invariant across conditions (Hobart, Williams, Moran, & Thompson, 2002), and may lack sensitivity and specificity for identifying treatment needs and capturing changes in response to treatment (Burger, van Middendorp, Drenth, Wahab, & Evers, 2019; Wiebe, Guyatt, Weaver, Matijevic, & Sidwell, 2003). Further, condition-specific quality of life measures may be preferred by patients (Contopoulos-Ioannidis, Karvouni, Kouri, & Ioannidis, 2009). Celiac disease-specific quality of life self-report measures have been developed, of which the Celiac Disease Quality of Life Survey (CD-QOL) was one of the earliest (Dorn et al., 2010). There is some conceptual overlap between constructs assessed by the CD-QOL and other celiac disease-specific quality of life measures including the Celiac Disease Assessment Questionnaire (Crocker, Jenkinson, & Peters, 2018a, 2018b) and the Celiac Disease

Questionnaire (Häuser, Gold, Stallmach, Caspary, & Stein, 2007), including burden of the gluten-free diet, social and emotional impacts, disease concern, and stigma. However, the CD-QOL is unique in that it does not assess physical symptoms associated with celiac disease (e.g., nausea, abdominal pain, headaches, or fatigue), which may be an advantage for measurement of quality of life in clinical settings. Prior research has found that quality of life in celiac disease is more strongly related to psychological and social functioning than symptom burden (Sainsbury et al., 2013; Zingone et al., 2015), and changes in quality of life can occur over time despite no change in gastrointestinal symptoms (Nachman et al., 2010). Further, an estimated 21% of people with celiac disease are asymptomatic, and may experience negative impacts to quality of life for reasons other than symptoms (Caio et al., 2019). Dorn et al. (2010) used a needs-based model to develop the CD-QOL, which elicited perceptions and concerns relating to the impact of celiac disease rather than assessing specific symptoms or functional limitations (e.g., "As you think about your disease, in what ways does it affect you?") (Doward, McKenna, & Meads, 2004; McKenna, Doward, Niero, & Erdman, 2004). Participants in the development samples did not report symptoms as salient concerns, and therefore, the CD-QOL does not include items regarding symptoms or the physical impact of celiac disease. Physical symptoms can be assessed using validated symptom-focused measures, such as the Celiac Symptom Index (Leffler, Dennis, George, Jamma, Cook, et al., 2009).

Accordingly, while the CD-QOL should not be used as a primary endpoint measure for pharmaceutical trials because it does not assess physical symptoms (Canestaro, Edwards, & Patrick, 2016; Clifford et al., 2020), it has been used in behavioral research and may be useful as a screening or outcomes tool in clinical settings. Best practices for self-report instrument development involve initial construction and factor structure evaluation using exploratory factor

analysis in one sample, followed by confirmation of the factor structure using confirmatory factor analysis and assessment of psychometric properties in a separate sample. The CD-QOL was developed in the United States in the English language using feedback from mostly white, female, middle-aged individuals from community-based celiac disease support groups, who reported an average of six years since celiac disease diagnosis and relatively high gluten-free diet adherence. Dorn et al. (2010) followed best practices for instrument development and initial validation. Exploratory factor analysis with orthogonal rotation found that the 20 items yielded four independent factors ("subscales"): (1) functional impact and limitations ("limitations"), (2) stigma and mood ("dysphoria"), (3) "health concerns," and (4) perceptions of inadequate celiac disease treatment ("inadequate treatment"). Additionally, Dorn et al. (2010) provided initial evidence of adequate internal consistency reliability, convergent validity, and known-groups validity. The CD-QOL has since been used in clinical research, however, its four-factor structure and psychometric properties have not been evaluated in a separate United States sample. Further, researchers have scored the CD-QOL using a total score, though a factor structure supporting a total score with four subscale scores has not yet been evaluated empirically. Therefore, research is needed to establish the CD-QOL as a reliable and valid measure of celiac disease-specific quality of life, and to determine whether it is most appropriately scored as four subscales, a total score, or both. To address these critical gaps, the present study aimed to (1) examine the factor structure of the English CD-QOL using confirmatory factor analysis, and (2) assess psychometric properties of CD-QOL scores, including internal consistency reliability, convergent validity, known-groups validity, and incremental concurrent validity.

Methods

Participants and Procedures

Participants were adults (≥ 18 years old) who self-reported being diagnosed with celiac disease through bowel biopsy, serology (blood test), and/or genetic testing, and completed questionnaires between April 2019 and May 2020 as part of the iCureCeliac® patient-powered research network hosted by the Celiac Disease Foundation. Participants were recruited through the Celiac Disease Foundation newsletter or website and completed questionnaires at one timepoint, on a voluntary basis. All participants provided informed consent electronically. There was no compensation for participation. Only individuals who reported a diagnosis of celiac disease (at any age) and their country of origin as the United States were included in the present analyses. Complete CD-QOL data were provided by $N = 453$ participants. Complete data on all other measures used for psychometric evaluation of CD-QOL scores were provided by $n = 315$. Missing data were due to (1) late addition of some questionnaires to the battery, and (2) a response tendency toward noncompletion of questionnaires later in the survey sequence. Data were obtained for the present analyses through a data use agreement between the first and second authors and the Celiac Disease Foundation and exempted from review by local Institutional Review Boards.

Measures

Sociodemographic Variables and Clinical Characteristics

Participants self-reported sociodemographic information (e.g., age, sex, race/ethnicity, household income, education level) and clinical characteristics (e.g., age at celiac disease diagnosis, years since diagnosis, method of diagnosis, reason for diagnosis).

Celiac Disease-Specific Quality of Life

As described above, the Celiac Disease Quality of Life Survey (CD-QOL; Dorn et al., 2010) is a 20-item self-report instrument with four factor-analytically derived subscales:

limitations, dysphoria, health concerns, inadequate treatment. Participants are asked to rate items for concerns over the past 30 days on a 5-point scale from 1 (*not at all*) to 5 (*a great deal*). Example items include, "I feel like I cannot live a normal life because of my disease" (limitations), "I feel frightened by having this disease" (dysphoria), "I am concerned that my long-term health will be affected" (health concerns), and "I feel there are not enough choices for treatment" (inadequate treatment). One item is reverse coded and item ratings have been summed to create a total score and subscale scores in prior studies. Higher scores indicate lower celiac disease-specific quality of life.

Generic Health-Related Quality of Life

The RAND 36-Item Health Survey version 1.0 (SF-36) is a 36-item self-report instrument assessing eight domains conceptualized to capture generic health-related quality of life (Hays, Sherbourne, & Mazel, 1993): physical functioning (10 items), social functioning (2 items), role limitations due to physical health (4 items), role limitations due to emotional problems (3 items), energy/fatigue (4 items), emotional well-being (5 items), general health (5 items), and bodily pain (2 items). Item ratings are transformed to scaled scores and averaged within each domain to provide eight scores between 0-100. Higher scores indicate better health-related quality of life. The SF-36 has demonstrated reliability and validity across multiple chronic illness populations, and has been used in celiac disease (Häuser, Gold, et al., 2007). Internal consistency reliability of SF-36 scales in the current sample was high (Cronbach's alpha [α] range = .83-.92; McDonald's omega [ω] range = .83-.93). Participants also responded to a single item indicating whether "My health has improved since [celiac disease] diagnosis" from 1 (*not at all*) to 5 (*very much*).

Gluten-Free Diet Adherence

The Celiac Dietary Adherence Test (CDAT) is a 7-item self-report measure of gluten-free diet adherence (Leffler, Dennis, George, Jamma, Magge, et al., 2009). Items assess low energy, headaches, ability to follow a gluten-free diet while dining out, carefully considering consequences of one's behavior, and perception of oneself as a failure, rated from 1 (*none of the time/strongly agree)* to 5 (*all of the time/strongly disagree)*. A sixth item assesses perception of the impact of accidental gluten exposure on health, rated from 1 (*very important*) to 5 (*not at all important*). A seventh item assesses number of intentional gluten exposures in the past four weeks, rated from 1 (*never*) to 5 (*>10*). Item ratings are summed to create a total score. Lower scores indicate greater adherence. CDAT scores were highly correlated with standardized dietician evaluation and with biomarkers of celiac disease-linked antibodies in the validation sample. Receiver operating characteristic curve analysis in the development sample showed that a CDAT score of < 13 likely indicates good adherence, scores of 13-17 likely indicate moderate adherence, and scores > 17 likely indicate poor adherence. Internal consistency reliability in the current sample was low (α = .57).

Two CDAT items were extracted and examined individually as indicators of known groups validity: (1) ability to follow gluten-free diet while dining out and (2) intentional gluten exposure. Additionally, participants were asked to report (1) the extent to which they follow a "strict gluten-free diet" from 1 (*never*) to 5 (*always*) and (2) how many times in the past 30 days they were "inadvertently exposed to gluten" (0, 1-2, 3-5, 6-10, >10).

Physical Symptoms

The Celiac Symptom Index (CSI) is a 16-item self-report instrument assessing the extent to which respondents have been concerned with physical symptoms in the past four weeks (Leffler, Dennis, George, Jamma, Cook, et al., 2009). Eleven items assess specific symptoms,

including gastrointestinal symptoms, low energy, headaches, food craving, and appetite, rated from 1 (*none of the time*) to 5 (*all of the time*). The remaining five items assess physical health more generally, including subjective rating of celiac disease-specific health and general health rated from 1 (*excellent*) to 5 (*terrible*), physical pain rated from 1 (*none*) to 5 (*very much*), and comfort and relative health rated from 1 (*strongly agree*) to 5 (*strongly disagree*). Item ratings are summed to create a total score. Higher scores indicate worse symptomology and lower perceived health. Suggested cut-off scores differentiate between clinical remission (≤ 30), varying complaints (30–45), and active disease (≥ 45). Internal consistency reliability for CSI total scores in the development sample (α = .88) and current sample (α = .85) were good. Participants also responded to a single item indicating whether "I am symptomatic even though I follow a strict gluten-free diet" (*yes, no, I don't know*).

Anxiety and Depression

The 4-item short forms of the Patient-Reported Outcomes Measurement Information System® (PROMIS) anxiety and depression scales assess symptoms of anxiety and depression, respectively (Cella et al., 2010). Respondents rate the frequency of symptoms in the past seven days on a 5-point scale from 1 (*never*) to 5 (*always*). Example items include, "I felt fearful" (anxiety) and "I felt helpless" (depression). Item responses are converted to raw scores which correspond to t-scores with a subscale-specific range. The t-score is compared to the population mean with standard errors provided. Higher t-scores indicate greater anxiety and depression symptoms, respectively. PROMIS scales have strong psychometric properties (Cella et al., 2010). Internal consistency reliability in the current sample was excellent for anxiety (α = .90; ω = .90) and depression (α = .93; ω = .93).

Occupational Functioning

Research suggests that adults with celiac disease have significantly more days of work lost than do general population comparators (Bozorg et al., 2021). Participants reported the number of work or school days missed in the past 12 months due to illness from gluten exposure and celiac disease, respectively. Prior studies assessing the psychometric properties of celiac disease-specific quality of life instruments have similarly used single-item measures to assess limitations to daily functioning due to celiac disease and its treatment (Burger et al., 2019) and celiac disease-related quality of life (Dorn et al., 2010).

Statistical Analyses

Confirmatory factor analysis (CFA) was conducted in MPlus version 8 (Muthén & Muthén, 1998-2017) using the 'MLR' estimator, which provides maximum likelihood parameter estimates with standard errors robust to non-normality. An estimate of minimum sample size for CFA derived from simulations conducted by Wolf, Harrington, Clark, and Miller (2013) and figures provided by Dorn et al. (i.e., item-factor loadings of ~.65, 4 factors, average of ~5 indicators per factor) suggest that a sample size of $N = 250$ should produce adequate power. CFA and single-item measure analyses were conducted on the total sample ($N = 453$). Additional psychometric analyses were conducted on the subsample with complete data ($n = 315$) using IBM SPSS Statistics for Windows, version 27 (IBM Corp., Armonk, N.Y., USA), with $\alpha \leq .05$.

Preliminary Data Analysis

Distributions of CD-QOL item responses were examined for univariate and multivariate normality. The Mahalanobis distance statistic was calculated to assess for multivariate outliers. Absence of multicollinearity among CD-QOL subscales was determined by variance inflation factor (VIF) < |5| (Kline, 2005). Distributions of all other measure scores were also assessed for normality (skew, kurtosis, outliers).

Confirmatory Factor Analysis

CFA was used to examine the absolute fit of three models: (1) the four-factor structure originally reported by Dorn et al. (2010), (2) a second-order factor structure with four first-order factors and one global factor, and (3) a one-factor structure. Whereas Dorn et al. (2010) specified uncorrelated (orthogonal) factors in their exploratory factor analysis, the current analyses specified correlated factors for Model 1 because of suspected interrelations between those latent constructs. Model fit was evaluated using the following indices: (a) Chi-square goodness-of-fit (χ^2), (b) Comparative Fit Index (CFI > .90 acceptable, and > 0.95 desirable; Hu & Bentler, 1998), (c) Tucker-Lewis Index (TLI > .90 acceptable, and > 0.95 desirable; Hu & Bentler, 1998), (d) Root Mean Square Error of Approximation (RMSEA < .05 good fit; < .08 acceptable fit; < .10 poor fit; Brown, 2014; Kline, 2005) using a 90% confidence interval, and (e) Standardized Root Mean Square Residual (SRMR < .05 good fit, and < 0.08 acceptable fit; Hu & Bentler, 1999). Nested models were compared using a chi-square difference test where a statistically non-significant difference ($p > .05$) indicates better fit of the more parsimonious model. A second-order factor structure is appropriate and more parsimonious than a first-order model with correlated factors when a single latent variable is hypothesized to account for strong relations among primary factors. Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) were also used to compare models, where lower values indicate better model fit.

Reliability

Internal consistency reliability for CD-QOL total and three of four subscale scores was assessed using (a) Cronbach's alpha (α > .80 good fit, and > .70 minimally acceptable fit; Lance, Butts, & Michels, 2006) and (b) McDonald's omega, which assumes neither equivalent factor loadings nor normal distribution among scale items, and is therefore less prone to

underestimation of composite reliability (McNeish, 2018). Because the 'inadequate treatment' subscale has two items, alpha may underestimate their true relationship as its equation penalizes small scales. Therefore, a Pearson correlation coefficient was calculated to examine internal consistency reliability for the two-item inadequate treatment subscale.

Validity

Convergent validity was assessed by computing Spearman's rho correlation coefficients for CD-QOL total and subscale scores and scores on the SF-36 scales, CDAT (gluten-free diet adherence), PROMIS anxiety and depression scales, and occupational functioning items, respectively. Coefficients $|r = .00$ to $r = .39|$ were considered small, $|r = .40$ to $r = .69|$ were considered moderate, and $|r = .70$ to $r = 1.00|$ were considered large. Because CD-QOL items assess social limitations, emotional concerns, and cognitive concerns rather than physical aspects, we hypothesized moderate negative correlations between CD-QOL total and SF-36 social functioning, emotional well-being, and general health subscale scores, and small negative correlations between CD-QOL total and SF-36 physical functioning, role limitations due to physical and emotional problems, energy/fatigue, and bodily pain, such that worse celiac disease-specific quality of life would be related to worse generic quality of life.

We expected a moderate positive correlation between CD-QOL total and CDAT total, such that lower celiac disease-specific quality of life would be related to lower gluten-free diet adherence. We hypothesized moderate positive correlations between CD-QOL total and PROMIS scale scores, such that worse celiac disease-specific quality of life would be related to greater anxiety and depression symptoms. We also hypothesized moderate positive correlations between CD-QOL total and occupational functioning, such that worse celiac disease-specific quality of life would be related to more days missed (i.e., worse functioning). We also expected

CD-QOL dysphoria subscale scores to be more strongly related to measures of mental health (PROMIS anxiety and depression, SF-36 emotional well-being) than other CD-QOL subscales. Because prior research suggests that the relationship between celiac disease-specific quality of life and physical symptoms may be limited, we expected a small, positive correlation between CD-QOL and CSI scores, with worse quality of life related to greater symptom burden.

Known groups validity was assessed by grouping participants according to established cut-off scores for gluten-free diet adherence on the CDAT and examining mean group differences in CD-QOL total score using analysis of variance and planned pairwise comparisons with Bonferroni corrections. We expected significantly greater mean CD-QOL scores (i.e., worse quality of life) among those with poor gluten-free diet adherence compared to those with good gluten-free diet adherence. Known groups validity was further assessed using independent samples *t*-tests to examine group differences in mean CD-QOL total score between (a) participants reporting strict gluten-free diet adherence (*always*) and those reporting less strict adherence (*never, rarely, sometimes, often*), (b) participants reporting no *inadvertent* gluten exposure and those reporting some, (c) participants reporting no *intentional* gluten exposure and those reporting some, and (d) participants endorsing an ability to follow a gluten-free diet when dining outside the home compared to those reporting inability. In each comparison we hypothesized significantly greater CD-QOL total scores among the less adherent groups. Finally, mean CD-QOL total scores were compared between participants endorsing persisting symptoms despite gluten-free diet adherence and participants who did not endorse them, and participants reporting significantly improved health since celiac disease diagnosis (*very much, quite a bit*) compared to those who did not (*no, a little, somewhat*). We hypothesized significantly higher

CD-QOL scores among those reporting persisting symptoms despite gluten-free diet adherence and those reporting little to no improvement in health since diagnosis.

Concurrent predictive validity of the CD-QOL total score for predicting gluten-free diet adherence (CDAT scores) was examined using linear regression analysis. Incremental concurrent predictive validity of the CD-QOL for predicting concurrent GFD adherence (CDAT score) over and above a generic health-related quality of life measure (SF-36) was examined using hierarchical linear regression. Select SF-36 scales were entered in step 1 and CD-QOL subscales were entered in step 2. Three SF-36 scales were used given their conceptual overlap with domains assessed by the CD-QOL: emotional well-being, social functioning, and general health. Models with and without CD-QOL total score were compared to determine change in total variance explained (R^2).

Results

Sociodemographic and Clinical Characteristics

Sample characteristics are shown in *Table 1.1*. Of participants who completed the CD-QOL (N = 453), the majority identified as women (88%) and white (92%), and ages ranged from 18 to 83 years (M = 41, SD = 15). Age at celiac disease diagnosis ranged from two to 77 years (M = 35, SD = 15) and years since diagnosis ranged from 0 to 78 (M = 6, SD = 8). Most participants reported diagnosis of CeD via intestinal biopsy (82%), followed by serology (16%). Most participants indicated that they were symptomatic at diagnosis (76%), though others (24%) reported that they were diagnosed after screening prompted by other considerations (e.g., diagnosis of another autoimmune disorder, family history of celiac disease).

Mean CDAT score for the entire sample was on the cut-off between good and moderate gluten-free diet adherence (M = 13.31, SD = 3.59). The majority of participants (89%) reported

that they "always" follow a strict gluten-free diet, though 75% of the sample reported inadvertent gluten exposure in the past 30 days. Half of the sample (50%) reported persisting physical symptoms despite gluten-free diet adherence. Mean CSI score in the entire sample suggested moderate celiac disease symptom burden (M = 39.75, SD = 9.85). Sample mean PROMIS Anxiety and Depression *t*-scores did not indicate clinically elevated mood symptoms. There were no differences in sociodemographic or clinical characteristics between the total sample used for CFA and the subsample used for other psychometric analyses (see *Table 1.1*, *p*s > .05).

Preliminary Data Analysis

The distributions of ten CD-QOL items evidenced positive skew. Five individual cases were suspected to be multivariate outliers but were retained in analyses to maintain representativeness of the sample. Multicollinearity was not suspected. The distributions of CD-QOL dysphoria subscale scores, CDAT total scores, SF-36 physical functioning and social functioning scale scores, and the occupational functioning items also evidenced positive skew. No transformations were performed. Analyses robust to non-normal distributions were used when possible.

Confirmatory Factor Analysis

Model 1. The four-factor structure identified by Dorn et al. (2010) was tested first. Four latent variables (limitations, dysphoria, health concerns, inadequate treatment) were indicated by nine, four, five, and two items, respectively. Inter-factor correlations were specified between the four latent variables. As shown in *Table 1.2*, the model did not fit well statistically (χ^2 [164, N = 453] = 546.612, $p < .001$) and two descriptive fit indices showed borderline acceptable fit (TLI = .889; RMSEA = .072). However, the non-parsimony adjusted descriptive fit indices showed acceptable model fit (CFI = .904, SRMR = .054). Given that the chi-square goodness-of-fit test is

sensitive to sample size and is often significant for large samples, and the non-parsimony descriptive fit indices yielded desirable values, model evaluation proceeded (Schermelleh-Engel, Moosbrugger, & Müller, 2003). All standardized factor loadings were large and statistically significant ($p < .001$): limitations (range: .437-.818), dysphoria (range: .499-.876), health concerns (range: .479-.869), and inadequate treatment (range: .570-.683). Standardized inter-factor correlations were also large and statistically significant ($p < .001$), suggesting that these four latent factors are strongly related but not redundant (rs = .603-.756). Model findings were replicated in the subsample with complete data (n = 315).

Model 2. A second-order factor structure that included four first-order factors (identical to those in model 1) and a single second-order factor (representing a total score) was tested next. As shown in *Table 1.2*, Model 2 did not fit well statistically (χ^2 [166, N = 453] = 594.769, $p <$ .001) and two descriptive fit indices showed borderline acceptable fit (TLI = .890; RMSEA = .071). However, the non-parsimony adjusted descriptive fit indices showed acceptable model fit (CFI = .904, SRMR = .054); therefore, model evaluation proceeded. As shown in *Figure 1.1*, all standardized item to first-order factor loadings were large and statistically significant ($p < .001$): limitations (range: .437-.817), dysphoria (range: .501-.875), health concerns (range: .480-.869), and inadequate treatment (range: .563-.692). Standardized loadings between the first-order factors and second-order factor were also large and statistically significant (range: .737-.868). Model findings were replicated in the subsample with complete data (n = 315). A chi-square difference test revealed no statistical difference in fit between Models 1 and 2 ($\Delta\chi^2_{0.95}$ [2, N=453] = 3.310, p=.19), suggesting that the more parsimonious model (Model 2) best represents the data. Additionally, Model 2 had lower AIC and BIC values than Model 1, providing further evidence

for a better fit. Inter-subscale correlations ranged from r = .42 to .64, suggesting that the factors are related but not redundant.

Model 3. For completeness, a single-factor structure was also tested. As shown in *Table 1.2*, the *p*-value for the chi-square goodness-of-fit test was statistically significant, and values on three of four descriptive fit indices failed to meet threshold for acceptable fit (CFI = .774; TLI 0.748; RMSEA = .108). The single-factor model did not fit well either statistically or descriptively, and model evaluation did not proceed.

Internal Consistency Reliability

Internal consistency reliability of CD-QOL total (α = .92; ω = .92), limitations subscale (α = .88; ω = .88), dysphoria subscale (α = .81; ω = .83), and health concerns subscale (α = .84; ω = .85) scores was good. Correlation between the two items in the inadequate treatment subscale was moderate (r = .39, p < .001).

Convergent Validity

As shown in *Table 1.3*, correlations between CD-QOL total and SF-36 social functioning, emotional well-being, and general health and scores were moderate (rs = -.48 to -.50), as expected. Correlations between CD-QOL total and SF-36 physical functioning, role limitations, and bodily pain were small, as expected (rs = -.26 to -.36). The correlation between CD-QOL total and SF-36 energy/fatigue subscale was moderate, which is slightly larger than expected (r = -.49). The correlation between CD-QOL total and CDAT total was small, which is slightly smaller than expected (r = .38).

As expected, CD-QOL total and all subscales except ‘inadequate treatment’ were moderately correlated to PROMIS anxiety and depression scores (rs = .40 to .55). The CD-QOL subscale ‘dysphoria’ was more strongly correlated with measures of mental health (PROMIS

anxiety, PROMIS depression, SF-36 emotional well-being) than other CD-QOL subscales, as predicted. The correlation between CD-QOL total and occupational functioning was smaller than expected (*r*s = .34 and .37). Finally, CD-QOL total and CSI scores were minimally correlated (*r* = .08), as predicted.

Known Groups Validity

As shown in *Table 1.4*, there were significant differences in mean CD-QOL total score between CDAT adherence groups, $F(2, 311) = 20.24$, $p < .001$. Planned pairwise comparisons revealed significant differences between good and moderate adherence groups ($p < .001$), good and poor adherence groups ($p < .001$), and moderate and poor adherence groups ($p = .03$) in the expected directions. Similarly, individuals who reported no inadvertent gluten exposure ($p < .001$), no intentional gluten consumption ($p = .02$), and ability to adhere to a gluten-free diet when dining outside the home ($p < .001$) reported significantly lower (better) CD-QOL scores than did groups with worse adherence. There was a marginally significant difference between those who reported following a strict gluten-free diet *always* compared to those who did not ($p = .07$). Those who endorsed persisting symptoms despite gluten-free diet adherence reported higher CD-QOL scores ($p < .001$) and those who reported greater improvements to health since diagnosis reported lower CD-QOL scores ($p < .001$), as expected.

Incremental Concurrent Validity

Linear regression analysis showed that CD-QOL total scores significantly predicted CDAT total scores, $F(1, 313) = 57.44$, $p < .001$, explaining 16% of their variance. Step 1 of a hierarchical linear regression analysis that used SF-36 scales as predictors or CDAT total scores was statistically significant, $F(3, 311) = 48.31$, $p < .001$, explaining 32% of their variance. When CD-QOL total was added in step 2 of the hierarchical model, the omnibus model remained

significant, $F(4, 310) = 37.50$, $p < .001$, and there was a 1% increase in variance explained. In step 2, CD-QOL total score was a significant predictor of CDAT scores, as were SF-36 social functioning and general health.

Discussion

The aims of the current study were to confirm the factor structure and examine the psychometric properties of the English language CD-QOL among adults with celiac disease in the United States. We found support for the original four-factor structure and extended prior work by examining a second-order factor structure that incorporates a total score. We found superior fit for the second-order structure, indicating that the CD-QOL can be scored as four subscales and/or a total score. Moderate relationships among CD-QOL subscales suggest that they measure related subconstructs that offer unique information when examined individually. Three subscales and the total score demonstrated acceptable to good internal consistency reliability. The two items in the inadequate treatment subscale were moderately correlated and evidenced good factor loadings; however, additional items may be needed to better operationalize this subscale.

Convergent and known groups validity were supported. The pattern of relationships between CD-QOL and SF-36 scores suggest that the CD-QOL assesses the specific aspects of celiac disease-related quality of life that it purports to measure, and that these constructs are related to but not redundant with generic health-related quality of life constructs. The correlation between CD-QOL total and gluten-free diet adherence was slightly smaller than expected, however, participants who reported greater gluten-free diet adherence across multiple measures reported significantly better celiac disease-specific quality of life, as expected. The negligible correlation between CD-QOL and physical symptom scores was consistent with prior research demonstrating that celiac disease-specific quality of life may be more strongly relate to

challenges with gluten-free diet adherence, psychiatric symptoms, and lifestyle limitations than physical symptoms (Sainsbury et al., 2013; Zingone et al., 2015), especially as years since diagnosis increase (Nachman et al., 2010).

Incremental concurrent validity findings suggest that researchers and clinicians might choose to use either the generic SF-36 or CD-QOL to assess quality of life in adults with celiac disease. Despite limited incremental validity in explaining gluten-free diet adherence scores, the CD-QOL may nevertheless account for aspects of celiac disease-specific functioning and well-being that are not captured by generic measures and are important indicators of treatment needs. For example, the SF-36 captures information about general physical and mental health status (e.g., "My health is excellent;" "Have you felt downhearted and blue?") whereas the CD-QOL captures more specific information about celiac disease-specific health concerns (e.g., "I feel worried about the increased risk of one of my family members having celiac disease;" "I feel depressed because of my disease"). Further, the CD-QOL assesses celiac disease-specific limitations (e.g., "I feel like I am not able to have special foods;" "I have trouble socializing because of my disease"). These celiac disease-specific concerns would be appropriate targets for behavioral intervention. Thus, selecting one or both measures may depend on the purpose. Clinicians screening for celiac disease-specific concerns that impact mental health may prefer the CD-QOL, whereas researchers comparing quality of life scores between adults with celiac disease and other conditions may prefer the SF-36. For incremental concurrent validity analyses we selected the SF-36 subscales with the most conceptual overlap with CD-QOL, and other SF-36 scales may not provide equally useful information. In selecting a single instrument, the 20-item CD-QOL is shorter than the 36-item SF-36 and may therefore reduce burden on both administrators and respondents. In summary, our findings are aligned with prior research

recommending use of both specific and generic health-related quality of life measures when possible (Contopoulos-Ioannidis et al., 2009; Huang et al., 2008), or selection of a single measure depending on the specific purpose (Linde, Sørensen, Østergaard, Hørslev-Petersen, & Hetland, 2008).

Strengths and Limitations

The current study extended previous work by examining a second-order factor structure using CFA and using validated instruments to assess additional psychometric properties with related constructs not previously examined. Further, whereas Dorn et al. (2010) had administered a 24-item version of the CD-QOL and extracted the final 20 items for psychometric analyses, the current study administered the 20-item CD-QOL directly. This is important for establishing validity, given the possibility of item-order effects on reporting (Schwarz, 1999). Further, the current study did not recruit from community-based support groups as many other celiac disease studies do (Hall et al., 2009), but rather, included a broader community of individuals with celiac disease throughout the United States seeking information and support online.

Nevertheless, our findings may not generalize to all adults with celiac disease in the United States. Participants in the present study were self-selected and represent a population with access to the internet, knowledge of how to find relevant health information online, willingness to be part of a research community, and capacity to complete online questionnaires. Further, most participants identified as female and white, which accurately reflects characteristics of the diagnosed celiac disease patient population in the United States (Choung et al., 2015; Mardini, Westgate, & Grigorian, 2015; Stahl et al., 2021), but findings may not generalize to patients of other genders and races/ethnicities in this country and abroad (Krigel et al., 2016). Because the original CD-QOL items were developed and refined using feedback from mostly white, mostly

female patient groups, item wording or response options may not represent the construct adequately in other groups. To accurately capture patient experiences, researchers should seek to validate CD-QOL scores among individuals of more diverse gender identifications, socioeconomic resources, and racial and ethnic backgrounds in the United States. It is also important to note that samples in Dorn et al. (2010) and the present study had been diagnosed for an average of nine and six years, respectively, were mostly diagnosed as adults, and reported relatively high gluten-free diet adherence. The validity and utility of the measure among newly diagnosed individuals or those explicitly struggling with gluten-free diet adherence should be assessed further.

Another possible limitation of the current study is exclusive use of self-report measures, including for celiac disease diagnostic status. Individuals were invited to participate in the iCureCeliac® registry if they had a "gluten-related condition," which includes but is not limited to celiac disease. Participants were provided various diagnostic category options and were allowed to select more than one (e.g., celiac disease, gluten ataxia, dermatitis herpetiformis, wheat allergy/intolerance, other gluten-related disorder, self-diagnosed with a gluten-related disorder, not diagnosed with a gluten-related disorder). Participants were also asked to report which of many diagnostic methods were used to diagnose their gluten-related condition, including various blood tests and biopsies, genetic testing, gluten challenge, food sensitivity tests, stool test, saliva test, allergy skin test, other test, or no test. Individuals were invited to participate in the registry regardless of their answers to these questions. These procedures are expected to reduce demand characteristics (i.e., for individuals to report a diagnosis of celiac disease if no diagnosis has been made), and thereby increase the validity of the current data.

Only participants reporting a celiac disease diagnosis made by biopsy, serology (blood test), or genetic testing were included in the present analyses.

Finally, the present analyses were limited to data from instruments pre-selected for survey inclusion by the Celiac Disease Foundation and confined by the cross-sectional nature of the data. Future studies should capture longitudinal data to examine the CD-QOL's test-retest reliability and sensitivity to change, which will provide information about its utility for screening and outcomes assessment purposes, respectively.

Conclusion

The 20-item English CD-QOL is a reliable and valid measure of celiac disease-specific quality of life among adults with celiac disease in the United States. The CD-QOL assesses important cognitive, affective, and behavioral aspects of living with celiac disease that may negatively impact gluten-free diet adherence and mental health independent of symptom burden, and which represent appropriate targets for interdisciplinary intervention to improve long-term outcomes. Additional research is needed to evaluate the test-retest reliability, sensitivity to change, and cross-cultural equivalence of CD-QOL scores, as well as the clinical utility of the CD-QOL as a screening tool and outcomes measure in health services research and routine clinical care.

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Table 1.1

*Sociodemographic Variables, Clinical Characteristics, and Mean Questionnaire Scores for Total Sample used in CFA (*N *= 453) and Subsample with Complete Data (*n *= 315)*

Measure	Total (N = 453)	Subsample (n = 315)
Sociodemographic and Clinical Characteristics		
Age, *M* (*SD*)	40.57 (14.84)	40.94 (15.15)
Female	87.6%	87.6%
Race/Ethnicity		
White	92.3%	91.7%
Hispanic/Latino	3.5%	3.5%
American Indian/Alaskan Native	2.2%	2.5%
Black	0.7%	1.0%
Asian	0.2%	0.3%
Native Hawaiian/Pacific Islander	0.2%	0.0%
Other	0.4%	0.6%
Household Income		
Less than $50,000	23.7%	23.3%
$50,000-$100,000	36.8%	37.0%
$100,000-$200,000	29.8%	30.0%
$200,000 or more	9.6%	9.7%
Education		
High School Diploma	5.7%	5.1%
Vocational, Trade, or Associate's	13.9%	14.1%
Bachelor's or some college	54.0%	54.4%
Professional, Master's, or Doctorate	26.5%	26.5%
Age at diagnosis, *M* (*SD*)	34.65 (15.00)	34.94 (15.05)
Years since diagnosis, *M* (*SD*)	5.94 (7.81)	5.93 (7.49)
Diagnostic method		
Biopsy (small bowel/intestine)	82.3%	83.8%
Serology/blood test	15.9%	14.6%
Other	1.8%	1.6%
Diagnostic reason		
Symptomatic	76.2%	76.8%
Other	23.8%	23.2%
Missed school or work days, *M* (*SD*)		
Due to illness from gluten exposure	12.25 (42.83)	13.00 (46.32)
Due to Celiac Disease	13.74 (46.00)	13.13 (45.02)
Symptomatic despite gluten-free diet adherence		
Yes	51.1%	50.7%
No	31.4%	32.6%
I do not know	17.4%	16.8%

Table 1.1, continued

Measures	*M* (*SD*)	*M* (*SD*)
CD-QOL Total	63.07 (16.17)	62.40 (16.17)
CD-QOL Limitations	29.77 (8.27)	29.74 (8.29)
CD-QOL Dysphoria	9.45 (4.09)	9.25 (4.04)
CD-QOL Health Concerns	17.10 (4.82)	16.76 (4.87)
CD-QOL Inadequate Treatment	6.75 (2.11)	6.66 (2.06)
SF-36 Physical Functioning		81.37 (22.55)
SF-36 Role Limitations – Physical health		55.63 (42.86)
SF-36 Role Limitations – Emotional problems		56.19 (42.56)
SF-36 Energy/Fatigue		39.83 (24.06)
SF-36 Emotional Wellbeing		63.86 (19.84)
SF-36 Social Functioning		70.79 (26.07)
SF-36 Bodily Pain		61.24 (24.99)
SF-36 General Health		51.14 (23.88)
CDAT total		13.33 (3.59)
CSI total		39.85 (9.90)
PROMIS Anxiety		54.40 (9.68)
PROMIS Depression		51.97 (9.54)

Note. M = mean; *SD* = standard deviation; CD-QOL = Celiac Disease Quality of Life Survey; CDAT = Celiac Dietary Adherence Test; CSI = Celiac Symptom Index; PROMIS = Patient-Reported Outcomes Measurement Information System®. All values are raw scores except for PROMIS measures which are *t*-scores. Blank spaces indicate incomplete data for *N* = 453.

Table 1.2

Goodness-of-fit Statistics for Comparative Confirmatory Factor Analytic Models (N = 453)

Models	**Chi-square**	**Df**	**CFI**	**TLI**	**RMSEA [90% CI]**	**SRMR**	**AIC**	**BIC**
1. 4 factors	546.612	164	.904	.889	.072 [.065, .078]	.054	26072.605	26344.254
2. 2nd order	594.769	166	.904	.890	.071 [.065, .078]	.054	26072.330	26335.747
3. 1 factor	1074.474	170	.774	.748	.108 [.102, .115]	.068	26642.816	26889.769

Note. Df = degrees of freedom; CFI = Comparative Fit Index; TLI = Tucker-Lewis Index; RMSEA = Root Mean Square Error of Approximation; CI = Confidence Interval; SRMR = Standardized Root Mean-Square Residual; AIC = Akaike Information Criterion; BIC = Bayesian Information Criteria. All models tested using maximum likelihood estimation with robust standard errors. All chi-square tests were statistically significant, $p < .001$.

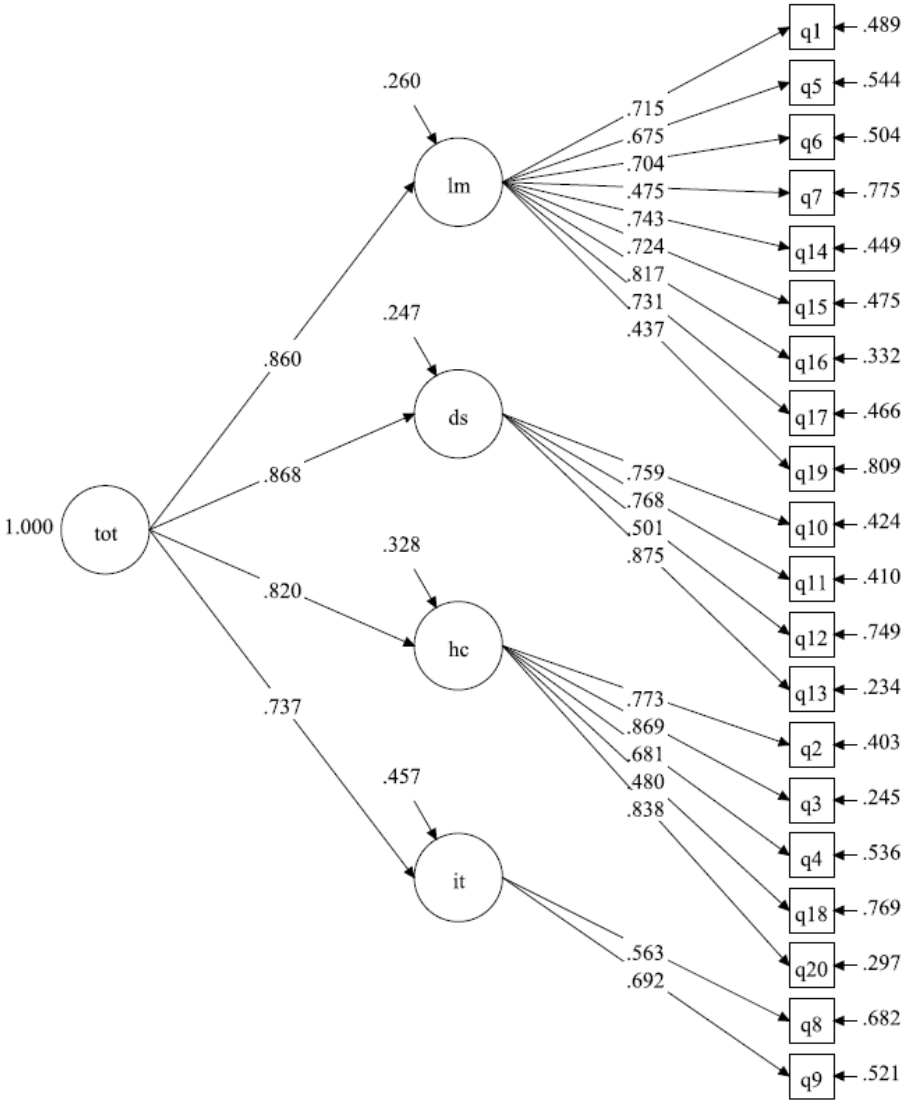

Figure 1.1. *Second-order Factor Structure Model Confirmatory Factor Analysis Results*

Note. Standardized path coefficients are shown. All paths are statistically significant ($p < .001$). lm = limitations; ds = dysphoria; hc = health concerns; it = inadequate treatment; tot = total celiac disease-specific quality of life.

Table 1.3

*Correlations Between CD-QOL Total, Subscale Scores, and Related Construct Scores (*n = *315)*

Construct Measure	CD-QOL Total	CD-QOL Limitations	CD-QOL Dysphoria	CD-QOL Health Concerns	CD-QOL Inadequate Treatment
Generic health-related QoL					
SF-36 PF	-.26**	-.20**	-.27**	-.22**	-.21**
SF-36 RP	-.35**	-.28**	-.32**	-.31**	-.29**
SF-36 RE	-.34**	-.29**	-.41**	-.23**	-.18**
SF-36 EF	-.43**	-.36**	-.38**	-.38**	-.29**
SF-36 EW	-.49**	-.43**	-.54**	-.36**	-.24**
SF-36 SF	-.48**	-.43**	-.49**	-.37**	-.24**
SF-36 BP	-.36**	-.27**	-.34**	-.31**	-.32**
SF-36 GH	-.50**	-.39**	-.46**	-.45**	-.35**
Gluten-free diet adherence					
CDAT total	.38**	.31**	.45**	.29**	.28**
Anxiety					
PROMIS Anxiety	.50**	.41**	.55**	.44**	.19**
Depression					
PROMIS Depression	.49**	.40**	.54**	.40**	.25**
Occupational functioning					
Missed school/work days due to illness from gluten exposure	.34**	.26**	.31**	.30**	.18**
Missed school/work days due to Celiac Disease	.37**	.29**	.36**	.31**	.20**
Celiac disease-related symptoms					
CSI total	.08	.08	.05	.07	-.02

Note. Values shown are Spearman's rho coefficients. Moderate to large coefficients are bolded. CD-QOL = Celiac Disease Quality of Life Survey; PF = Physical functioning; RP = Role limitations due to physical health; RE = Role limitations due to emotional problems; EF = Energy/fatigue; EW = Emotional well-being; SF = Social functioning; BP = Bodily pain; GH = General health; CDAT = Celiac Dietary Adherence Test; PROMIS = Patient-Reported Outcomes Measurement Information System®; CSI = Celiac Symptom Index. For occupational functioning items, $n = 344$.

**$p < .001$.

Table 1.4

Known Groups Validity and Incremental Validity Results for CD-QOL Total Score

Known Groups Validity	***N***	***M* (*SD*)**	***F*/*t***	***p***
CDAT total			20.24	< .001
Poor adherence	39	72.28 (15.93)		
Moderate adherence	142	65.26 (15.16)		
Good adherence	133	56.63 (15.10)		
Inadvertent gluten exposure (past 30 days)			-4.76	< .001
None	89	56.67 (16.85)		
Any	251	65.64 (14.70)		
Intentional gluten consumption (past 4 weeks)			-2.44	.02
Never	388	62.35 (16.04)		
Any	62	67.70 (15.91)		
Able to follow GFD outside home			-7.00	<.001
Agree	350	60.11 (15.46)		
Disagree	78	73.47 (14.21)		
Symptomatic despite GFD adherence			7.61	<.001
No	137	55.85 (16.17)		
Yes	223	68.45 (14.66)		
Health has improved since diagnosis			-4.99	<.001
Very much/Quite a bit	243	59.75 (15.60)		
No/A little/Somewhat	201	67.24 (15.89)		

Incremental Validity	**B (*SE*)**	***F*/*t* (*p*)**	**R^2**	**ΔR^2**
Outcome: CDAT total				
Step 1		48.31 (<.001)	.318	
Constant	19.21 (0.58)	33.4 (<.001)		
SF-36 Emotional wellbeing	-0.02 (0.01)	-1.46 (.15)		
SF-36 Social functioning	-0.03 (0.01)	-3.18 (.002)		
SF-36 General health	-0.05 (0.01)	-5.16 (<.001)		
Step 2		25.29 (<.001)	.366	.048
Constant	16.71 (1.27)	13.20 (<.001)		
SF-36 Emotional wellbeing	-0.003 (0.01)	-1.07 (.29)		
SF-36 Social functioning	-0.03 (0.01)	-2.95 (.003)		
SF-36 General health	-0.04 (0.01)	-4.52 (<.001)		
CD-QOL Limitations	-0.3 (.03)	-1.17 (.24)		
CD-QOL Dysphoria	0.24 (.06)	4.30 (<.001)		
CD-QOL Health concerns	-0.08 (.05)	-1.57 (.12)		
CD-QOL Inadequate treatment	0.15 (.09)	1.64 (.10)		

Note. M = mean; *SD* = standard deviation; B = unstandardized regression coefficient; SE = standard error; CDAT = Celiac Dietary Adherence Test; CD-QOL = Celiac Disease Quality of Life Survey.

Celiac Disease Symptom Profiles and their Relationship to Gluten-free Diet Adherence, Anxiety and Depression, and Quality of Life

Cara Dochat[1], Niloofar Afari[2,3], Rose-Marie Satherly[4], Shayna Coburn[5,6], Julia F. McBeth[7]

[1] San Diego State University/University of California San Diego Joint Doctoral Program in Clinical Psychology, San Diego, CA, USA

[2] VA San Diego Healthcare System, San Diego, CA, USA

[3] University of California San Diego, La Jolla, CA, USA

[4] University of Surrey, Surrey, United Kingdom

[5] Children's National Health System, Washington, DC, USA

[6] George Washington University School of Medicine & Health Sciences, Washington, DC, USA

[7] Celiac Disease Foundation, Woodland Hills, CA, USA

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Abstract

Background: Aversive symptoms persist in a subgroup of adults with celiac disease, the cause for which is unclear, and the management of which may require different approaches.

Aims: Elucidate patterns of persisting symptoms and their relationships to gluten-free diet adherence, psychiatric symptoms, and quality of life (QOL)

Methods: U.S. adults with biopsy-confirmed celiac disease (*N*=523; 93% white; 88% female) completed questionnaires: (a) Celiac Symptoms Index (CSI) for physical symptoms and subjective health; (b) Celiac Dietary Adherence Test for gluten-free diet adherence; and (c) PROMIS-29, SF-36, and Celiac Disease Quality of Life Survey (CD-QOL) for psychiatric symptoms and QOL.

Results: Latent profile analysis of CSI items determined a four-profile solution fit best. Profiles were characterized by: (1) little to no symptoms and excellent subjective health (37%); (2) infrequent symptoms and good subjective health (33%); (3) occasional symptoms and fair to poor subjective health (24%); (4) frequent to constant symptoms and fair to poor subjective health (6%). Profiles differed on anxiety and depression symptoms, limitations due to physical and emotional health, social functioning, and sleep, but not clinical characteristics, gluten-free diet adherence, CD-QOL, or pain interference.

Conclusions: Adults with celiac disease vary in specific persisting symptoms, symptom severity, and subjective health. Lack of profile differences in gluten-free diet adherence suggests other causes for persisting symptoms that may require additional dietary, medical, or pharmacological intervention. Lower symptom burden did not necessarily translate to better mental health and QOL, suggesting adjunctive behavioral intervention may be helpful even for those with lower celiac symptom burden.

Celiac Disease Symptom Profiles and their Relationship to Gluten-free Diet Adherence, Anxiety and Depression, and Quality of Life

Celiac disease is an autoimmune condition affecting 48-300 million people worldwide (Rubio-Tapia et al., 2012; Singh et al., 2018). For individuals with celiac disease, ingestion of gluten, a protein found in wheat, rye, and barley, prompts an autoimmune response that causes damage to the structure and function of the small intestine. Celiac disease is diagnosed in those with genetic predisposition when serology identifies elevated anti-tTG, anti-endomysium, and deamidated gliadin peptide antibodies, and/or histology finds evidence of duodenal villous atrophy, intraepithelial lymphocytosis, and crypt hyperplasia. The symptoms of celiac disease are diverse and can include both gastrointestinal and extraintestinal symptoms, including headache, fatigue, skin manifestations, and neurologic symptoms (Caio et al., 2019; Durazzo et al., 2022; Leonard et al., 2017). There is no pharmacological treatment for celiac disease, but the condition is managed by consuming a strict gluten-free diet. Strict adherence to a gluten-free diet supports intestinal recovery and symptom remission for the majority (Laurikka et al., 2016).

However, even with optimal gluten-free diet adherence, gastrointestinal and extraintestinal symptoms persist for 20-40% of adult patients, and the cause is not always clear (Barratt et al., 2011; Caio et al., 2019; Galli et al., 2021; Häuser et al., 2006; Häuser, Musial, et al., 2007; Leffler et al., 2007; Silvester et al., 2017; Stasi et al., 2016; van Megen et al., 2021). In a cross-sectional study of 99 U.S. adults with persisting symptoms on a gluten-free diet, the most common causes included ongoing gluten exposure (36%), co-occurring irritable bowel syndrome (IBS; 22%), and refractory celiac disease (13%; Leffler et al., 2007) a finding replicated in 140 adult patients in Italy (Volta et al., 2014). Complete gluten removal from one's diet may not be achievable, and even small amounts of gluten exposure can contribute to persisting symptoms and incomplete histological recovery (Silvester et al., 2020; Silvester et al., 2016). In addition to

gluten exposure, persisting symptoms may indicate presence of non-gluten food sensitivities (e.g., short-chain carbohydrates known as FODMAPs), or other medical conditions such as IBS, a disorder of gut-brain interaction characterized by specific gastrointestinal symptoms (abdominal pain and bloating, painful bowel movements, and diarrhea and/or constipation; Lacy et al., 2021; Schmulson & Drossman, 2017). Persisting gastrointestinal symptoms in celiac disease may be more common in women (Häuser, Stallmach, et al., 2007) and those with fewer years since celiac diagnosis (van Megen et al., 2021).

Research has broadly shown that persisting symptoms in celiac disease relate to worse physical functioning, lower quality of life, and greater likelihood of anxiety and depression (Barratt et al., 2011; Harnett & Myers, 2020; Häuser et al., 2006; Häuser, Musial, et al., 2007; Parker et al., 2021; van Megen et al., 2021). Severity of persisting gastrointestinal reflux and IBS symptoms specifically may be associated with reduced quality of life across specific domains (e.g., social functioning), as well as greater anxiety and depression symptoms (Barratt et al., 2011). However, the relationship between persisting symptoms and wellbeing may be nuanced, depending on the type of symptoms, their severity, and the domain of psychiatric symptoms or quality of life assessed. Some research has found that quality of life in celiac disease is more strongly related to psychological and social functioning than symptom burden (Sainsbury et al., 2013; Zingone et al., 2015), and changes in quality of life can occur over time despite no change in gastrointestinal symptoms (Nachman et al., 2010). Further, an estimated 21% of people with celiac disease are asymptomatic, but may nevertheless experience reduced quality of life due to managing a chronic condition and its treatment (Caio et al., 2019). Adults with celiac disease have a significantly greater risk for depression and anxiety than those without celiac disease, due

to a variety of proposed biological and psychosocial mechanisms that may or may not related to symptoms (Clappison et al., 2020; Therrien et al., 2020; Zingone et al., 2015).

In summary, physical symptoms persist in some adults with celiac disease despite adequate gluten-free diet adherence, and negatively impact mental health, functioning, and quality of life. The extent to which persisting symptoms are due to ongoing gluten exposure, co-occurring conditions, or other variables is often difficult to ascertain, and this uncertainty creates challenges in celiac disease management. Further, the causes of persisting symptoms are varied, and there may be unique clinical presentations based on those unique causes. Examining patterns of persisting symptoms and their associations with relevant clinical variables including disease factors, gluten-free diet adherence, psychiatric symptoms, and various quality of life domains may provide insight into differential diagnosis and need for a modified treatment approach. To date, no study has examined patterns of persisting gastrointestinal and extraintestinal symptoms and their relation to these variables. Accordingly, the aims of this manuscript were to use data from the iCureCeliac® research network to: (1) identify patterns of persisting symptoms and subjective rating of health among adults with celiac disease; (2) characterize these patterns according to symptom type, severity, and subjective rating of health; (3) estimate the prevalence of each pattern or "profile" type; and (4) examine whether those in various profiles report differences in gluten-free diet adherence, psychiatric symptoms, functioning, and quality of life.

Methods

Design and Participants

This cross-sectional survey was administered between April 2019 and May 2020 as part of the iCureCeliac® research network registry hosted by the Celiac Disease Foundation. Participants are invited to participate in the registry on a rolling basis through the Celiac Disease

Foundation's website and email list. All participants provided informed consent before beginning the survey. De-identified data from registry participants were included from adults (≥18 years old) with a self-reported celiac disease diagnosis made via intestinal biopsy, serology (blood test), or genetic testing, who reported their country of origin as the United States. The validated celiac symptom measure used in the present analyses was completed by *N*=523. Complete data on all other measures were provided by *n*=317.

Measures

Sociodemographic Variables, Disease Factors, and Co-occurring Conditions

Participants self-reported sociodemographic, health, and disease factor information, including current age, gender, race/ethnicity, household income, educational attainment, age at celiac disease diagnosis, diagnostic method, diagnostic reason, and co-occurring physical and mental health conditions.

Gastrointestinal Symptoms

The Patient-Reported Outcomes Measurement Information System® (PROMIS) Gastrointestinal Symptoms Scales (Khanna et al., 2017; Spiegel et al., 2014) were used to characterize the sample's gastrointestinal symptomology compared to the general U.S. population. Symptoms are rated for frequency over the past seven days. Symptom-level data are aggregated into scales representing belly pain (5 items), bowel incontinence (4 items), constipation (9 items), diarrhea (6 items), disrupted swallowing (7 items), gas and bloating (13 items), nausea and vomiting (4 items), and gastrointestinal reflux (13 items). Raw scores are converted to *t*-scores for all scales except bowel incontinence. Higher *t*-scores indicate greater symptomology. *T*-scores below 40 and above 60 are considered significantly lower and greater than the U.S. population norm, respectively.

Celiac Symptoms and Subjective Health

Specific celiac symptoms were assessed using the Celiac Symptom Index (CSI; Leffler, Dennis, George, Jamma, Cook, et al., 2009) a 16-item self-report instrument assessing the extent to which respondents have been “concerned with" physical symptoms and subjective health in the past four weeks. Twelve items assess specific symptoms rated from 1 (*none of the time*) to 5 (*all of the time*). The remaining four items assess subjective aspects of physical health, including subjective rating of celiac disease-specific health and general health rated from 1 (*excellent*) to 5 (*terrible*), and subjective rating of comfort and one’s health compared to the health of others rated from 1 (*strongly agree*) to 5 (*strongly disagree*). Item ratings are summed to create a total score. Higher scores indicate greater symptom burden and lower perceived health. Internal consistency reliability for CSI total scores were good in the development sample (α=.88) and current sample (α=.85).

Gluten-free Diet Adherence

The Celiac Dietary Adherence Test (CDAT; Leffler, Dennis, George, Jamma, Magge, et al., 2009) is a 7-item self-report measure of gluten-free diet adherence. Items assess low energy, headaches, ability to follow a gluten-free diet while dining out, carefully considering consequences of one’s behavior, and perception of oneself as a failure, rated from 1 (*none of the time/strongly agree)* to 5 (*all of the time/strongly disagree)*. A sixth item assesses perceived impact of accidental gluten exposure on health, rated from 1 (*very important*) to 5 (*not at all important*) and the seventh item assesses number of intentional gluten exposures in the past four weeks, rated from 1 (*never*) to 5 (*>10*). Item ratings are summed to create a total score. Lower scores indicate greater gluten-free adherence. CDAT scores are highly correlated with standardized dietician evaluation and biomarkers of celiac disease-linked antibodies,

demonstrating the validity of this measure. Receiver operating characteristic curve analysis in the development sample showed that CDAT scores < 13 likely indicate good adherence, scores of 13-17 likely indicate moderate adherence, and scores > 17 likely indicate poor adherence (Leffler, Dennis, George, Jamma, Magge, et al., 2009). Internal consistency reliability in the current sample was low (α=.57).

Anxiety and Depression

The 4-item short forms of the PROMIS anxiety and depression scales assess symptoms of anxiety and depression, respectively (Cella et al., 2010). Respondents rate the frequency of symptoms in the past seven days from 1 (*never*) to 5 (*always*). Raw scores are converted to *t*-scores for both scales. Higher *t*-scores indicate greater anxiety and depression symptoms. *T*-scores below 40 and above 60 are considered significantly lower and greater than the U.S. population norm, respectively. PROMIS scales have strong psychometric properties (Cella et al., 2010). Internal consistency reliability in the current sample was excellent for both anxiety (α=.90; ω=.90) and depression (α=.93; ω=.93).

General Health-Related Quality of Life and Functioning

The PROMIS-29 is a 29-item self-report instrument assessing seven domains of general health-related quality of life: depression (4 items), anxiety (4 items), physical function (4 items), fatigue (4 items), sleep disturbance (4 items), and ability to participate in social roles and activities (4 items). A final item assessing pain intensity was not included in the present analyses. Raw scores are converted to *t*-scores for all scales. Higher *t*-scores indicate more of the domain being assessed (e.g., higher physical functioning or greater fatigue). *T*-scores below 40 and above 60 are considered significantly lower and greater than the U.S. population norm, respectively. PROMIS scales have strong psychometric properties (Cella et al., 2010).

The RAND 36-Item Health Survey version 1.0 (SF-36; Hays et al., 1993) is a 36-item self-report instrument assessing eight domains of general health-related quality of life: physical functioning (10 items), social functioning (2 items), role limitations due to physical functioning (4 items), role limitations due to emotional problems (3 items), energy/fatigue (4 items), emotional well-being (5 items), general health (5 items), and pain (2 items). Item ratings are transformed to scaled scores and averaged within each domain to provide eight scores between 0-100. Higher scores on each scale indicate better health-related quality of life. The SF-36 has demonstrated reliability and validity across multiple chronic illness populations, and has been used in celiac disease (Häuser, Gold, et al., 2007). Internal consistency reliability of SF-36 scales in the current sample was high (α range=.83-.92; ω range=.83-.93).

Celiac Disease-Specific Quality of Life

The Celiac Disease Quality of Life Survey (CD-QOL; Dorn et al., 2010) is a 20-item self-report instrument assessing overall celiac disease-specific quality of life and four domains: limitations (9 items), dysphoria (4 items), health concerns (5 items), and inadequate treatment (2 items). Participants are asked to rate concerns over the past 30 days from 1 (*not at all*) to 5 (*a great deal*). Example items include, "I feel like I cannot live a normal life because of my disease" (limitations), "I feel frightened by having this disease" (dysphoria), "I am concerned that my long-term health will be affected" (health concerns), and "I feel there are not enough choices for treatment" (inadequate treatment). One item is reverse coded and item ratings are summed to create total and subscale scores. Higher scores indicate lower celiac disease-specific quality of life. Internal consistency reliability of CD-QOL total score was excellent (α = .92; ω = .92) and subscale scores were acceptable (α range=.83-.88; ω range=.83-.88) in the current sample.

Statistical Analyses

Latent profile analysis was used to identify celiac disease health profiles using CSI items as indicators. CSI items 1-11 and 14 assess specific symptom severity in the past four weeks and items 12, 13-16 assess subjective ratings of health with no timeframe specified. Latent profile analysis was conducted on both the total sample (N=523) and subsample with complete data on all measures (n=317) in MPlus version 8 (Muthén & Muthén, 2011). Successive latent profile models were fit, increasing the number of potential profiles by one until model fit was not significantly improved. Comparative model fit was evaluated using the bootstrapped likelihood ratio test (BLRT; McLachlan et al., 2019) and Lo-Mendell-Rubin adjusted likelihood ratio test (LMRT; Lo et al., 2001) where a p-value of $< .05$ indicates better fit than a hypothetical model with one fewer profile (Nylund et al., 2007). Comparative model fit was also evaluated using Akaike Information Criterion (AIC; Akaike, 1974) Bayesian Information Criterion (BIC; Schwarz, 1978) and sample size-adjusted BIC (s-BIC; Yang, 2006) where lower values indicate better model fit. Probabilities of group classification (posterior classification probabilities) were examined for all competing models, with average probabilities ≥ 0.70 indicating an appropriate profile solution (Nylund-Gibson & Choi, 2018). Entropy, a metric of classification accuracy, was also examined. Higher entropy (preferably $> .80$) demonstrates greater classification accuracy (Tein et al., 2013). Latent profiles were qualitatively interpreted using conditional response means and latent profile probabilities.

Based on posterior classification probabilities, individuals were assigned to profile groups. Profile group differences were examined with regards to sociodemographic characteristics, disease factors, and observed outcomes (questionnaire scores) using the BCH method (AUXILIARY function) in MPlus (Asparouhov & Muthén, 2014; Bakk & Vermunt,

2016; Bolck et al., 2004; Ferguson et al., 2020). This method accounts for uncertainty in individual profile membership and provides a chi-squared test of profile differences as well as pairwise comparisons. Chi-squared tests and pairwise comparisons were considered statistically significant at $p < .05$. Because the CSI and CDAT have two overlapping items ("Have you been bothered by low energy level during the past 4 weeks?" and "Have you been bothered by headaches during the past 4 weeks?"), auxiliary analyses were conducted for both CDAT total score (7 items) and CDAT total score minus overlapping items (5 items).

Results

Sample Characteristics

Sample characteristics are shown in *Table 2.1*. The majority of participants identified as women (88%) and white (92%), and ages ranged from 18 to 83 years (M=41, SD=15). Age at celiac disease diagnosis ranged from 2 to 82 years (M=35, SD=15). Years since diagnosis ranged from 0 to 78 (M=6, SD=8), with 8% of the sample within 1 year of diagnosis, 25% within 2 years of diagnosis, and 50% within 3 years of diagnosis. Most participants reported diagnosis via intestinal biopsy (83%), followed by serology (14%). Most participants were symptomatic at celiac disease diagnosis (75%). Mean sample CDAT score suggests good to moderate gluten-free diet adherence, where 45% reported good adherence, 43% reported moderate adherence, and 12% reported poor adherence. Sample mean anxiety and depression symptom t-scores within normal range of the U.S. population. However, approximately half of the sample reported lifetime diagnosis of a mental health condition and a quarter reported significantly elevated ($t \geq 60$) anxiety and depression symptoms at present, respectively.

In the entire sample, 96.5% reported at least one comorbid physical health condition. The most common co-occurring conditions were pain-related, including bone or joint pain (52%),

fibromyalgia or muscle pain (31%), peripheral neuropathy (31%), and arthritis (23% with non-specific arthritis; 7% with Rheumatoid arthritis). In terms of gastrointestinal conditions, 23% reported an IBS diagnosis prior to celiac disease diagnosis and 8% reported an IBS diagnosis made since celiac disease diagnosis. Smaller proportions reported a co-occurring inflammatory bowel disease, including ulcerative colitis (3%) and Crohn's disease (1%). Current lactose intolerance was reported by 28% of participants. Mean gastrointestinal symptom *t*-scores were within normal range of the general U.S. population. However, proportions of the sample reported elevated gastrointestinal symptomology: gas/bloating (35%), belly pain (33%), diarrhea (22%), nausea (17%), constipation (15%), reflux (11%), and disrupted swallowing (7%).

Sample mean PROMIS-29 *t*-scores also indicated quality of life within normal range of the general U.S. population. However, half the sample reported significantly elevated fatigue, and a smaller proportion (15-20%) reported significant deficits in pain interference, physical function, ability to participate in social roles/activities, and sleep disturbance. Because there are no established cut-offs for the CD-QOL, it is unclear whether this sample presented with deficits in celiac disease-specific quality of life. There were no differences in sociodemographic, disease factors, or questionnaire scores between the total sample (N = 523) and subsample with complete data on all measures (n = 317; ps > .05; see *Table 2.1*).

Latent Profile Analysis

Model Fit

Table 2.2 displays goodness-of-fit statistics for models with one to six profiles in the subsample (n = 317). A four-profile solution evidenced best fit and had adequate entropy and high posterior classification probabilities in both the total sample and subsample. The class proportions and conditional response means for the four-profile solution were nearly identical

across the two samples. Thus, the four-profile solution was selected for interpretation and further analyses.

Profile Characteristics

Graphical representation of conditional response means is shown in *Figure 2.1*. **Profile 1 (37%; "Well-Managed")** was characterized by little to no symptoms and excellent subjective health. Despite low overall symptomology, Profile 1 showed relative elevations on low energy and headaches, which occurred "some of the time." **Profile 2 (33%; "Mildly Symptomatic")** was characterized by more frequent symptoms than Profile 1. Profile 2 showed a relative elevation on low energy and headaches, and smaller elevations on bloating, food cravings, and physical pain. Participants in Profile 2 reported good subjective health, and they neither agreed nor disagreed with statements about feeling comfortable or relative health compared to others. **Profile 3 (24%; "Moderately Symptomatic")** was characterized by more frequent symptoms than Profile 2, except for low energy, headaches, and food cravings, which were higher in Profile 2. Profile 3 showed elevations on physical pain and most gastrointestinal symptoms (i.e., abdominal pain, stomach rumbling, bloating, diarrhea, partial bowel movement). Those in Profile 3 reported fair subjective health but low comfort and poor health compared to others. **Profile 4 (6%; "Severely Symptomatic")** was characterized by frequent to nearly constant symptoms, with notable elevations on all gastrointestinal symptoms, food cravings, low energy, headaches, and physical pain. Headaches and food cravings were relatively less frequent than other symptoms in the same profile, but nevertheless more frequent than in other profiles. Participants in Profile 4 reported fair subjective health but low comfort and poor health compared to others.

Overall, Profile 4 reported the most frequent gastrointestinal and extraintestinal symptoms, with two exceptions. Despite lower overall symptom burden in Profile 3 compared to

Profile 4, frequency of diarrhea and physical pain were comparable. Profiles 2 and 3 reported moderately frequent symptoms, but Profile 3 reported relatively greater gastrointestinal symptom frequency and Profile 2 reported relatively greater extraintestinal symptom frequency. Profile 1 reported lowest overall symptom burden for both gastrointestinal and extraintestinal symptoms, but nevertheless reported persisting low energy, headaches, and food cravings at frequency comparable to or greater than Profiles 2 and 3. That is, despite symptoms appearing to be well-managed in Profile 1, these participants nevertheless reported persisting low energy, headaches, and food cravings. In terms of gastrointestinal symptom frequency, Profiles 2 and 3 were both characterized by relative elevations on abdominal pain, bloating, and partial bowel movement, but only diarrhea was elevated in Profile 3. Nausea was prominent only in Profile 4. Subjective ratings of health seemed to align with overall symptom burden, except for Profile 3, wherein participants reported subjective health comparable to or slightly worse than the highest symptom burden group, Profile 4.

Auxiliary Analyses

Sociodemographic Variables

Results of auxiliary analyses are shown in *Table 2.3*. No profile differences were found with regards to current age, sex, or race/ethnicity. Among those who reported education level (*n*=279), participants in Profile 4 were more likely to have associates or trade school degrees and less likely to have master's and doctoral degrees than Profiles 1 and 2. Among those reporting household income (*n*=228), participants in Profiles 1 and 2 were more likely to report incomes of $100K+ and those in Profile 4 were more likely to incomes less than $50K. Given that no profile differences were detected for sociodemographic variables reported by the full subsample (*n*=317), further auxiliary analyses were conducted without covariates.

Disease Factors

No profile differences were found regarding age at diagnosis, years since diagnosis, or reason for diagnosis (i.e., symptomatic versus other reason).

Gluten-free diet Adherence

Significant profile differences were found for gluten-free diet adherence when using the *CDAT total score*, χ^2 (3,317) = 17.04, p = .001. Pairwise comparisons showed that adherence for Profile 3 was significantly greater than for Profiles 1, 2, and 4. However, when overlapping symptom items were removed, there were no significant profile differences in *CDAT score*, χ^2 (3,317) = 0.07, p = .99.

Anxiety and Depression

Significant profile differences were found for *depression symptoms* (χ^2 (3,317) = 10.83, p = .001) and marginally significant differences were found for *anxiety symptoms* (χ^2 (3,317) = 6.72, p = .08). For both depression and anxiety symptoms, Profile 4 reported the most severe symptoms and Profile 3 reported the least severe symptoms. Pairwise comparisons showed that anxiety and depression symptoms were significantly more severe for Profile 4 compared to Profiles 2 and 3, but not Profile 1.

General Health-Related Quality of Life and Functioning

Significant profile differences were found for SF-36 *role limitations due to physical health* (χ^2 (3,317) = 9.00, p = .03) and SF-36 *role limitations due to emotional health* (χ^2 (3,317) = 13.47, p = .004). For both scales, Profile 4 reported the greatest limitation and Profile 3 reported the least limitation. Pairwise comparisons showed that Profiles 1, 2, and 4 reported significantly greater role *limitations due to physical health* than Profile 3. Profile 4 reported significant greater role *limitations due to emotional health* than Profiles 1, 2, and 3. Significant

profile differences were found for SF-36 *emotional wellbeing*, χ^2 (3,317) = 18.71, $p < .001$. Pairwise comparisons showed that Profile 4 reported significantly worse *emotional wellbeing* than Profiles 1, 2, and 3. Additionally, Profile 3 reported significantly greater emotional wellbeing than Profile 1.

Significant profile differences were found for SF-36 *social functioning* (χ^2 (3,317) = 8.27, $p = .04$) and PROMIS-29 *ability to participate in social roles/activities* (χ^2 (3,317) = 14.40, $p = .002$). For both outcomes, Profile 3 reported the highest social functioning and Profile 4 reported the lowest. Pairwise comparisons for both outcomes showed that Profile 3 reported significantly greater social functioning than Profiles 1 and 4. For PROMIS-29 *ability to participate in social roles/activities*, Profiles 1 and 2 were also greater than Profile 4.

Significant profile differences were found for SF-36 *energy/fatigue* (χ^2 (3,317) = 18.24, $p < .001$) and PROMIS-29 *fatigue* (χ^2 (3,317) = 12.11, $p = .007$). For both outcomes, Profile 4 reported the lowest energy and highest fatigue. Profile 3 reported the highest energy and lowest fatigue. Pairwise comparisons for both outcomes showed that Profile 4 reported significantly *lower energy/higher fatigue* than Profiles 1, 2, and 3. For PROMIS-29 *fatigue*, Profiles 1 and 2 reported significantly *higher fatigue* than Profile 3, a pattern that was marginally significant on SF-36 *energy/fatigue* (*p*s = .06 and .07). Perhaps relatedly, significant profile differences were found for PROMIS-29 *sleep disturbance*, χ^2 (3,317) = 17.70, $p = .001$. Profile 4 reported the greatest sleep disturbance and Profile 3 reported the least sleep disturbance. Pairwise comparisons showed that Profile 4 reported significantly greater *sleep disturbance* than Profiles 1, 2 , and 3. Profiles 1 and 2 reported significantly greater *sleep disturbance* than Profile 3.

Significant profile differences were found for SF-36 *general health*, χ^2 (3,317) = 8.59, $p = .04$). Profile 3 reported the greatest general health and Profile 4 reported the lowest general

health. Pairwise comparisons showed that Profile 3 reported significantly greater *general health* than Profiles 1, 2, and 4.

Omnibus tests for profile differences were not significant for SF-36 physical functioning (p = .16), PROMIS-29 physical function (p = .06), SF-36 bodily pain (p = .18), and PROMIS-29 pain interference (p = .77).

Celiac Disease-Specific Quality of Life

No profile differences were found for CD-QOL total or subscale scores (ps = .50 to .64).

Discussion

This study examined patterns of persisting symptoms and their relationships to disease management and wellbeing variables among U.S. adults with celiac disease. Four unique celiac symptom profiles were identified. The profile comprising the largest proportion of the sample (37%) was characterized by overall low symptomology and excellent subjective health, but with persisting low energy, headaches, and food cravings. The second (33%) and third (24%) largest profiles reported moderate overall symptomology, though the second profile reported relatively more frequent extraintestinal symptoms and the third profile reported relatively more frequent gastrointestinal symptoms. The smallest profile (6%) was defined by the most severe symptomology across both extraintestinal and gastrointestinal symptoms, and was especially elevated in abdominal pain, nausea, stomach rumbling, bloating, partial bowel movement, and hunger pain. While Profile 3's gastrointestinal symptoms were considerably less frequent than Profile 4's, Profile 3 reported slightly more frequent diarrhea and comparable levels of non-specific physical pain. High frequency abdominal pain, nausea, and hunger pain in Profile 4 may indicated refractory celiac disease.

Subjective ratings of health within each profile seemed to align with symptom severity, except in Profile 3. Profile 3 was characterized by moderate overall symptomology but worse

subjective health than Profile 4. Profile 3 was characterized by prominent physical pain and the most frequent diarrhea, which may contribute to lower perception of health and comfort, either directly or through presence of a co-occurring condition. Despite Profile 3's particularly low subjective health and comfort as reported on the CSI, Profile 3 reported the lowest psychiatric symptoms and overall best quality of life compared to other profiles. That is, despite relatively greater symptom burden than Profiles 1-2, and worse subjective health than Profile 4, Profile 3 reported significantly better general health and fewer role limitations due to physical health, less fatigue, and less sleep disturbance than the other profiles. Additionally, Profile 3 reported greater emotional wellbeing, social functioning, and ability to participate in social activities than Profiles 1 and 4. This finding is unexpected and suggests that overall symptom burden may not relate directly to worse wellbeing, but rather, patterns of specific symptoms are important to assess. For example, despite higher frequency of gastrointestinal symptoms in Profile 3, Profiles 1 and 2 were characterized by heightened frequency of low energy and headaches, which may differentially relate to quality of life domains such as sleep quality, fatigue, and role limitations due to physical health. Therefore, adult celiac disease patients with relatively low gastrointestinal symptom burden may nevertheless benefit from adjunctive medical, pharmacological, and behavioral treatment to address persisting symptoms such as fatigue and sleep disturbance.

Profile 4 was consistently lowest in psychiatric wellbeing and quality of life, as expected based on literature showing that higher persisting gastrointestinal symptom burden is related to lower physical functioning, lower quality of life, and greater likelihood of anxiety and depression (Parker et al., 2021; Roos et al., 2019; van Megen et al., 2021.) Most research to date has examined gastrointestinal symptom burden and its relation to quality of life (Parker et al., 2021; van Megen et al., 2021), whereas the present findings suggest that extraintestinal symptoms are

also burdensome and important to assess clinically. Low energy, headaches, food cravings, and physical pain were present across all profiles, independent of gastrointestinal symptom severity. Research has shown that fatigue is common in adults with celiac disease and can persist despite gluten-free diet adherence (Sansotta et al., 2018; Skjellerudsveen et al., 2019), which was associated with psychiatric symptoms and worse social functioning in this study. Profiles differences in sleep disturbance followed a similar pattern to fatigue, suggesting that improving sleep quality through any number of intervention approaches (e.g., pharmacological, cognitive-behavioral therapy for insomnia) may lead to reductions in fatigue and improvements in energy among adults with celiac disease. Similarly, research has shown that headaches and migraines are common in adults with celiac disease and can persist despite gluten-free diet adherence (Sansotta et al., 2018; Zis et al., 2018). Current findings link persisting headaches with role limitations due to physical functioning. Interdisciplinary intervention approaches to treating persisting headache may improve functioning for adults with celiac disease.

Food cravings assessed by the CSI are non-specific and may represent craving for gluten-containing foods caused by psychological deprivation (Meule, 2020) or perhaps nutritional deficiency. More research is needed to understand the experience of food cravings in adults with celiac disease and their relationship to gluten-free diet adherence and other outcomes. Notably, there were no differences in gluten-free diet adherence between profiles.

The type of pain endorsed across profiles was defined as ‘physical pain’ separate from ‘abdominal pain.’ Bone and joint pain is recognized as an extraintestinal manifestation of celiac disease (Holtmeier & Caspary, 2006), and 52% of the present sample reported bone or joint pain as co-occurring condition. Additionally, 31% of the sample reported current fibromyalgia or muscle pain, 31% reported current peripheral neuropathy, and 23% reported current arthritis.

Though objective severity of physical pain varied between profiles, there were no profile differences on SF-36 bodily pain or PROMIS-29 pain interference. Pain may be common experience among adults with celiac disease. Pain interference *t*-scores were positively skewed in this sample, with 15% reporting significantly elevated pain interference compared to the U.S. population. Given the known relationship between chronic pain, depression and anxiety, and lower quality of life (Lerman et al., 2015), these findings suggest a subgroup of patients may benefit from adjunctive psychosocial intervention for managing pain (Gómez Penedo et al., 2020).

Unexpectedly, there were no profile differences in gluten-free diet adherence, suggesting that differences in specific symptomology and subjective health were explained by factors other than diet adherence in this sample. Causes of variation in relative symptom severity observed in the present study may include IBS, refractory celiac disease, or other food sensitivities, as reported in other studies (Leffler et al., 2007; Volta et al., 2014). Though not examined in the present study, pre-existing co-occurring conditions may also explain differences in symptom profiles in the present sample, such as presence of other autoimmune conditions, which is common in celiac disease (Fasano, 2006).

Also unexpectedly, there were no profile differences on celiac disease-specific quality of life as measured by the CD-QOL. Prior research in the same sample demonstrated no correlation between CSI total scores and CD-QOL total and subscale scores (*r*s = -.02 to .08; Dochat, Afari, & Arigo, unpublished). The absence of association between symptom burden and celiac disease-specific quality of life may be due to the nature of the domains assessed by the CD-QOL. That is, overall symptom severity and patterns of specific persisting symptoms may not be associated with celiac disease-specific impacts on mood, social and lifestyle limitations, concerns about

health implications, and perception of inadequate available treatment. For example, CD-QOL items regarding mood include, “I feel depressed because of my disease” and “I feel frightened by having this disease,” which differ from general mood symptom items such as, “I feel depressed” and “I feel fearful.” Limitations assessed by the CD-QOL include, “I feel socially stigmatized for having this disease,” “I feel like I’m limited in eating meals with coworkers,” “I feel like I am not able to have special foods like birthday cake and pizza,” and “I find it difficult to travel or take long trips because of my disease.” These nuanced limitations may not be relevant for all adults with celiac disease (e.g., those who do not work), or may be less relevant for those with greater diagnostic latency who have ostensibly adapted to flexibly maintaining a gluten-free diet. Research suggests that the relationship between symptoms and quality of life may change over time, such that the relationship is stronger at diagnosis and weaker as years since diagnosis increase (Nachman et al., 2010). The present sample had a mean diagnostic latency of 6 years, with 8% within 1 year post-diagnosis, 25% within 2 years post-diagnosis, and 50% within 3 years post-diagnosis. Thus, the strength of relationship between symptom severity and celiac disease-specific quality of life may be lower in the present sample than in samples of newly diagnosed individuals. Nevertheless, there were significant profile differences with regards to role limitations due to physical health (“Accomplished less than [I] like”) and social functioning (“I have trouble doing all of the family activities that I want to do”), which may represent non-celiac limitations related to age, life circumstances, or other health conditions.

Finally, there were no profile differences in current age, sex, race, age at celiac disease diagnosis, or years since celiac disease diagnosis, consistent with some prior research (Galli et al., 2021). However, Profile 4 reported lower education level and lower household income than Profiles 1 and 2. Differences in education level and income may influence symptomology and

subjective health through mechanisms such as accessibility of gluten-free nutrient-dense food, access to healthcare, social support for gluten-free diet adherence, and concomitant risk for gluten exposure (Abu-Janb & Jaana, 2020).

Strengths and Limitations

Strengths of the current study include examination of patterns of both gastrointestinal and extraintestinal symptoms in relation to celiac disease management and wellbeing. This sample represents U.S. adults with celiac disease with an average of six years since diagnosis, at which stage persisting symptoms may be particularly burdensome and indicate a co-occurring condition and need for additional intervention. A limitation of the present study is that the CSI does not include all symptoms of possible interest. Items assessing gastrointestinal reflux, vomiting, and constipation were removed during CSI development, though these symptoms may be important for ruling out various functional gastrointestinal conditions, including IBS, as causes of persisting symptoms. The present study also used a self-report measure to assess gluten-free diet adherence rather than a standardized dietetic assessment or objective measure of gluten intake (e.g., stool sampling). The CDAT, which measures self-efficacy, risk behavior, estimated number of recent gluten exposures, and perceived ability to adhere to a gluten-free diet, was correlated with standardized dietetic assessment in the development study, but may not capture inadvertent gluten exposure and true nonadherence risk. The finding that symptom profiles did not differ on CDAT scores in the present study was unexpected, as gluten intake is often cited as an explanation for persisting symptoms. However, we scored the CDAT without two items that overlap with the CSI to reduce confounding, which is a novel scoring method for the CDAT. Future research should use self-reported adherence as well as standardized and objective

measures that are less subject to reporting biases to further explore the relationship between specific persisting symptom patterns and gluten-free diet adherence.

Participants in the present study were self-selected and represent a population with access to the internet, willingness to participate in research, and capacity to complete online questionnaires. Findings may not generalize to individuals with lower socioeconomic resources or those in otherwise marginalized groups. Indeed, we found that those in the profile with most severe symptomology reported lower household income and education level than other symptom profiles. While this finding is preliminary and based only on a subgroup that reported data, further research is needed to explore the relationships between persisting symptoms and sociodemographic variables, especially given evidence for disparities in celiac disease diagnostic testing based on black race, coverage by public insurance (Anyane-Yeboa et al., 2021), male sex, and older age (Lebwohl et al., 2012), and the relationship between food insecurity and heightened risk for gluten exposure (Ma et al., 2021). Further, most participants in the current study identified as female and non-Hispanic white, which reflects characteristics of the diagnosed U.S. patient population (Caio et al., 2019; Choung et al., 2015; Mardini et al., 2015; Singh et al., 2018; Stahl et al., 2021) but may not generalize to other sociodemographic groups in the U.S. (Krigel et al., 2016) and abroad.

Clinical Implications

Lower symptom burden did not necessarily translate to better mental health and quality of life in the present sample. Even profiles with lower gastrointestinal symptom burden demonstrated elevations in fatigue, headaches, and non-specific physical pain. Fatigue and pain are nonspecific extraintestinal symptoms common across various chronic illnesses, and are known to negatively impact mental health, functioning, and quality of life (Creed et al., 2013;

Jaime-Lara et al., 2020; Matura et al., 2018; Swain, 2000; Zautra et al., 2007). Given the frequency of persisting fatigue and pain and the high prevalence of co-occurring health conditions in adults with celiac disease (96.5% in this sample), this population would likely benefit from adjunctive intervention to improve sleep, coping with pain and chronic illness management, and anxiety and depression symptoms. Behavioral intervention especially could also address challenges with gluten-free diet adherence if relevant for any given patient. A novel finding from the present study is that there may be a subgroup of patients with moderate gastrointestinal symptoms but relatively lower extraintestinal symptoms and good quality of life who might benefit from intervention for gastrointestinal symptoms but demonstrate lesser need for intervention to improve mental health and quality of life.

Conclusions

Prevalence and severity of persisting gastrointestinal and extraintestinal symptoms differed among subgroups of adults with celiac disease. These subgroups also differed significantly in psychiatric health and various aspects of quality of life. Results suggest that lower overall symptom burden does not necessarily relate to better quality of life, but that the relationship between persisting symptoms and wellbeing may be nuanced and depend on the specific symptoms and domain of quality of life assessed. Future research should similarly examine patterns of persisting symptoms, including a wider range of gastrointestinal symptoms, and use histological assessment and an objective measure of gluten intake to explore these relationships more robustly. Long-term medical follow-up including histological assessment has been recommended to improve disease management and differential diagnosis in patients with persisting symptoms (Galli et al., 2021). Treatment for patients with celiac disease presenting with other food intolerances or co-occurring conditions might require additional dietary

intervention (e.g., elimination of FODMAPs), medical or pharmacological intervention, psychiatric intervention, or behavioral intervention. This research must also be replicated in samples with greater cultural diversity.

Paper 2, in part, has been submitted for publication of the material. Dochat, Cara; Afari, Niloofar; Satherly, Rose-Marie; Coburn, Shayna; McBeth, Julia F. The dissertation author was the primary investigator and author of this paper.

Table 2.1

*Sociodemographic Variables, Disease Factors, and Mean Questionnaire Scores for Total Sample (*N *= 523) and Subsample with Complete Data (*n *= 317)*

Measure	Total (N = 523)	Subsample (n = 317)
Sociodemographic Variables and Disease Factors		
Age, *M* (*SD*)	40.26 (14.94)	40.99 (15.13)
Female	88.0%	87.7%
Race/Ethnicity		
White	93.5%	92.1%
Hispanic/Latinx	3.1%	3.5%
American Indian/Alaskan Native	1.9%	2.5%
Black	0.6%	1.0%
Asian	0.4%	0.3%
Native Hawaiian/Pacific Islander	0.2%	0.0%
Other	0.4%	0.6%
Household Income[†]		
Less than $50,000	--	17.0%
$50,000-$100,000	--	26.5%
$100,000-$200,000	--	21.5%
$200,000 or more	--	6.7%
Missing data		28.1%
Education[‡]		
High School Diploma	--	3.8%
Vocational, Trade, or Associate's degree	--	12.3%
Bachelor's degree or some college	--	47.7%
Professional, Master's, or Doctorate degree	--	23.0%
Missing data	--	12.3%
Age at diagnosis, *M* (*SD*)	34.19 (15.19)	35.02 (15.06)
Years since diagnosis, *M* (*SD*)	6.00 (8.01)	5.91 (7.47)
Diagnostic method		
Biopsy (small bowel/intestine)	81.0%	83.0%
Serology/blood test	17.3%	14.2%
Other	1.7%	1.5%
Diagnostic reason		
Symptomatic	75.0%	76.7%
Other	25.0%	23.3%
Co-occurring Conditions		
Lifetime diagnosis of any mental health condition	53.2%	52.5%
Lifetime diagnosis of depressive disorder	35.4%	35.0%
Lifetime diagnosis of anxiety disorder	40.2%	40.4%
Bone or joint pain (current)	--	52.1%
Weight gain or loss (current)	--	42.0%
Fibromyalgia or muscle pain (current)	--	31.2%
Peripheral neuropathy (current)	--	30.9%

Table 2.1, continued

Measure	Total (N = 523)	Subsample (n = 317)
Co-occurring Conditions		
Irritable bowel syndrome (diagnosed at any time)	--	29.7%
Irritable bowel syndrome diagnosed prior to CeD		23.3%
Irritable bowel syndrome diagnosed after CeD		8.2%
Alopecia/Hair loss (current)	--	28.4%
Lactose intolerance (current)	--	27.8%
Thyroid disease (diagnosed at any time)	--	24.9%
Dermatitis herpetiformis (current)	--	24.0%
Arthritis (excluding Rheumatoid arthritis) (current)	--	23.0%
Menstrual irregularities (women only) (current)	--	21.9%
Eczema (current)	--	21.1%
Osteopenia or osteoporosis (current)	--	14.2%
Psoriasis (diagnosed at any time)	--	8.8%
Rheumatoid arthritis (diagnosed at any time)	--	7.3%
Ulcerative Colitis (diagnosed at any time)	--	2.8%
Type 1 diabetes mellitus (diagnosed at any time)	--	1.6%
Crohn's disease (diagnosed at any time)	--	0.9%
Measures	*M* (*SD*)	*M* (*SD*)
PROMIS GI Belly Pain	--	53.22 (13.04)[§]
PROMIS GI Constipation	--	51.34 (8.36)[§]
PROMIS GI Diarrhea	--	52.54 (9.81)[§]
PROMIS GI Disrupted Swallowing	--	47.33 (7.91)[§]
PROMIS GI Gas/Bloating	--	55.91 (8.88)[§]
PROMIS GI Nausea	--	50.46 (8.78)[§]
PROMIS GI Reflux	--	48.32 (9.16)[§]
CSI total	39.66 (9.89)	39.79 (9.89)
CDAT total	13.34 (3.69)	13.32 (3.58)
PROMIS-29 Anxiety	--	51.97 (9.51)
PROMIS-29 Depression	--	54.42 (9.66)
PROMIS-29 Pain Interference	--	52.51 (9.33)
PROMIS-29 Physical Function	--	49.20 (8.23)
PROMIS-29 Social Roles/Activities	--	49.77 (9.56)
PROMIS-29 Fatigue	--	57.79 (11.39)
PROMIS-29 Sleep Disturbance	--	52.91 (8.28)
SF-36 Physical Functioning	--	81.37 (22.48)
SF-36 Role Limitations – Physical health	--	55.54 (42.83)
SF-36 Role Limitations – Emotional problems	--	56.15 (42.61)
SF-36 Energy/Fatigue	--	38.79 (23.99)
SF-36 Emotional Wellbeing	--	63.92 (19.80)
SF-36 Social Functioning	--	70.82 (26.01)
SF-36 Bodily Pain	--	61.14 (24.95)
SF-36 General Health	--	51.07 (23.82)

Table 2.1, continued

Measure	Total (N = 523)	Subsample (n = 317)
Measures	*M* (*SD*)	*M* (*SD*)
CD-QOL Total	63.07 (16.17)[¶]	62.39 (16.15)
CD-QOL Limitations	29.77 (8.27)[¶]	29.71 (8.27)
CD-QOL Dysphoria	9.45 (4.09)[¶]	9.25 (4.03)
CD-QOL Health Concerns	17.10 (4.82)[¶]	16.77 (4.87)
CD-QOL Inadequate Treatment	6.75 (2.11)[¶]	6.66 (2.05)

Note. M = mean; *SD* = standard deviation; CSI = Celiac Symptom Index; CDAT = Celiac Dietary Adherence Test; PROMIS = Patient-Reported Outcomes Measurement Information System®; CD-QOL = Celiac Disease Quality of Life Survey. All values are raw scores except for PROMIS measures, which are *t*-scores. Missing values indicate that data were not available for the full sample. Conditions with sample prevalence < 1% are not reported.

[†] n = 228; values shown are percent out of n = 317 including missing data; valid percentages are: 23.7%, 36.8%, 29.8%, 9.6%.

[‡] n = 279; values shown are percent out of n = 317 including missing data; valid percentages are: 1.1%, 4.3%, 14.0%, 15.5%, 38.8%, 2.9%, 18.3%, 5.0%.

[§] n = 308

[¶] n = 453.

Table 2.2

Goodness-of-fit Statistics for Latent Profile Analysis Model Solutions (*N* = 317)

Profiles	Log Likelihood	AIC	BIC	s-BIC	Entropy	Smallest class %	LMRT *p*-value	LMRT meaning	BLRT *p*-value	BLRT meaning
1	-7735.392	15534.783	15655.068	15553.572	--	--	--	--	--	--
2	-7169.051	14436.102	14620.288	14464.871	0.899	44%	< .001	2 > 1	< .001	2 > 1
3	-7057.281	14246.562	14494.649	14285.313	0.850	21%	.57	2 > 3	.57	2 > 3
4	-6959.550	14085.101	14397.090	14133.833	0.882	6%	.02	4 > 3	.02	4 > 3
5	-6911.041	14022.082	14397.972	14080.796	0.876	5%	.50	4 > 5	.50	4 > 5
6	-6868.440	13970.880	14410.672	14039.575	0.892	2%	.60	5 > 6	.60	5 > 6

Note. AIC = Akaike information criterion; BIC = Bayesian information criterion; s-BIC = sample size-adjusted Bayesian information criterion; LMRT = Lo-Mendell-Rubin adjusted likelihood ratio test; BLRT = bootstrapped likelihood ratio test. All models tested using maximum likelihood estimation.

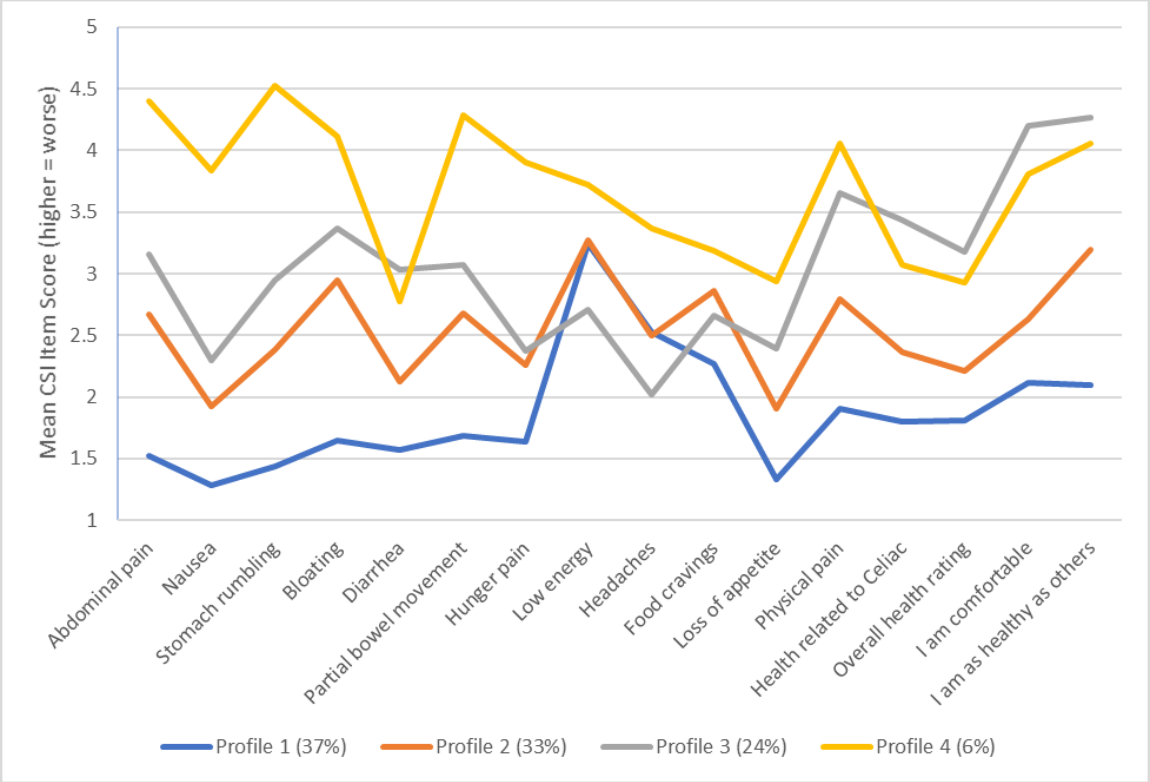

Figure 2.1. *Conditional Response Means on CSI Items for the Four-profile Solution (*N = *317)*
Note. CSI = Celiac Symptoms Index. Items are rated 1-5. Higher scores indicate worse greater symptomology and lower health ratings. Profile 1 = "Well-Managed." Profile 2 = Mildly Symptomatic." Profile 3 = "Moderately Symptomatic." Profile 4 = "Severely Symptomatic."

Table 2.3

Results of Three-step Auxiliary Analyses (*N=317 unless otherwise specified*)

Domain Measure	Profile 1 (*n* = 117) *M* (*SD*)	Profile 2 (*n* = 106) *M* (*SD*)	Profile 3 (*n* = 75) *M* (*SD*)	Profile 4 (*n* = 19) *M* (*SD*)	Test statistic	Significant post-hoc differences, $p < .05$
Sociodemographic Variables						
Age	42.26 (1.43)	40.02 (1.42)	41.28 (1.78)	37.95 (3.15)	χ^2 (3,317) = 2.22, $p = .53$	--
Sex	Probabilities Male = 0.14 Female = 0.85 Other = 0.01	Probabilities Male = 0.08 Female = 0.91 Other = 0.02	Probabilities Male = 0.14 Female = 0.86 Other = 0.00	Probabilities Male = 0.09 Female = 0.91 Other = 0.00	χ^2 (6,317) = 5.35, $p = .50$	--
Race (White, Other)	Probabilities White = .87 Other = .13	Probabilities White = .95 Other = .05	Probabilities White = .95 Other = .05	Probabilities White = .95 Other = .05	χ^2 (3,317) = 4.14, $p = .25$	--
Education level (n = 278)	Probabilities No school = .01 Some primary school = .05 HS diploma = .15 Vocational, Associates Degree, Trade School = .10 Some college = .42 Bachelors = . 04 Masters = .19 Doctorate = .05	Probabilities No school = .01 Some primary school = .03 HS diploma = .15 Vocational, Associates Degree, Trade School = .12 Some college = .40 Bachelors = .03 Masters = .20 Doctorate = .07	Probabilities No school = .02 Some primary school = .04 HS diploma = .13 Vocational, Associates Degree, Trade School = .25 Some college = .32 Bachelors = .02 Masters = .19 Doctorate = .04	Probabilities No school = .00 Some primary school = .07 HS diploma = .12 Vocational, Associates Degree, Trade School = .34 Some college = .42 Bachelors = .00 Masters = .07 Doctorate = .00	**χ^2 (21,277) = 45.05, $p = .002$**	1 v. 4 2 v. 4

Table 2.3, continued

Domain Measure	Profile 1 (*n* = 117) *M* (*SD*)	Profile 2 (*n* = 106) *M* (*SD*)	Profile 3 (*n* = 75) *M* (*SD*)	Profile 4 (*n* = 19) *M* (*SD*)	Test statistic	Significant post-hoc differences, $p < .05$
Sociodemographic Variables						
Age at diagnosis	35.77 (1.41)	34.30 (1.43)	35.78 (1.78)	31.94 (3.22)	χ^2 (3,317) = 1.64, p = .65	--
Years since diagnosis	6.31 (0.77)	5.71 (0.67)	5.50 (0.78)	6.13 (1.74)	χ^2 (3,317) = 0.64, p = .89	--
Reason for diagnostic testing	Probabilities Symptomatic = .74 Other = .26	Probabilities Symptomatic = .77 Other = .23	Probabilities Symptomatic = .80 Other = .21	Probabilities Symptomatic = .79 Other = .21	χ^2 (3,317) = 0.74, p = .86	--
Gluten-Free Diet Adherence						
CDAT total score	13.41 (0.33)	13.67 (0.24)	12.05 (0.37)	15.18 (0.89)	**χ^2 (3,317) = 17.04, p = .001**	1,2,4 > 3
CDAT score without symptom items	7.68 (0.23)	7.74 (0.24)	7.68 (0.29)	7.81 (0.57)	χ^2 (3,317) = 0.07, p = .99	--
Anxiety and Depression						
PROMIS-29 Anxiety	55.22 (0.89)	53.85 (0.91)	52.87 (1.12)	58.35 (2.07)	χ^2 (3,317) = 6.72, p = .08	4 > 2,3
PROMIS-29 Depression	52.89 (0.89)	51.28 (0.89)	50.04 (1.07)	56.96 (2.04)	**χ^2 (3,317) = 10.83, p = .001**	4 > 2,3
General Health-Related Quality of Life and Functioning						
SF-36 Physical Functioning	80.37 (2.14)	81.80 (2.10)	85.08 (2.28)	71.88 (6.11)	χ^2 (3,317) = 5.14, p = .16	3 > 4
SF-36 Role Limitations due to Physical Health	53.72 (4.01)	52.71 (4.10)	66.97 (4.74)	40.97 (9.20)	**χ^2 (3,317) = 9.00, p = .03**	3 > 1,2,4

Table 2.3, continued

Domain Measure	Profile 1 (*n* = 117) *M* (*SD*)	Profile 2 (*n* = 106) *M* (*SD*)	Profile 3 (*n* = 75) *M* (*SD*)	Profile 4 (*n* = 19) *M* (*SD*)	Test statistic	Significant post-hoc differences, $p < .05$
General Health-Related Quality of Life and Functioning						
SF-36 Role Limitations due to Emotional Health	51.36 (3.98)	61.50 (3.98)	61.82 (4.88)	31.63 (8.49)	**χ^2 (3,317) = 13.47, p = .004**	1,2,3 > 4
SF-36 Emotional Wellbeing	61.20 (1.85)	65.63 (1.81)	69.65 (2.13)	50.73 (4.50)	**χ^2 (3,317) = 18.71, p < .001**	1,2,3 > 4 3 > 1
SF-36 Energy/Fatigue	38.37 (2.20)	38.17 (2.25)	45.02 (2.87)	23.69 (4.16)	**χ^2 (3,317) = 18.24, p < .001**	1,2,3 > 4
SF-36 Social Functioning	68.14 (2.47)	72.08 (2.43)	76.33 (2.81)	60.26 (6.03)	**χ^2 (3,317) = 8.27, p = .04**	3 > 1,4
SF-36 Bodily Pain	61.88 (2.29)	59.32 (2.40)	65.15 (2.82)	52.68 (5.73)	χ^2 (3,317) = 4.87, p = .18	3 > 4
SF-36 General Health	49.72 (2.20)	49.93 (2.27)	57.36 (2.71)	42.84 (5.14)	**χ^2 (3,317) = 8.59, p = .04**	3 > 1,2,4
PROMIS-29 Pain Interference	52.69 (0.87)	52.80 (0.90)	51.55 (1.07)	53.37 (2.10)	χ^2 (3,317) = 1.13, p = .77	--
PROMIS-29 Physical Function	49.11 (0.77)	48.83 (0.79)	50.94 (0.90)	45.60 (1.88)	χ^2 (3,317) = 7.60, p = .06	3 > 4
PROMIS-29 Ability to Participate in Social Roles/Activities	48.79 (0.87)	50.51 (0.90)	51.88 (1.11)	44.04 (1.93)	**χ^2 (3,317) = 14.40, p = .002**	1,2,3 > 4 3 > 1

Table 2.3, continued

Domain Measure	Profile 1 (*n* = 117) *M* (*SD*)	Profile 2 (*n* = 106) *M* (*SD*)	Profile 3 (*n* = 75) *M* (*SD*)	Profile 4 (*n* = 19) *M* (*SD*)	Test statistic	Significant post-hoc differences, $p < .05$
General Health-Related Quality of Life and Functioning						
PROMIS-29 Fatigue	58.09 (1.04)	58.43 (1.07)	54.61 (1.36)	63.28 (2.2)	**χ^2 (3,317) = 12.11, p = .007**	4 > 1,2 > 3
PROMIS-29 Sleep Disturbance	53.76 (0.75)	52.91 (0.77)	50.20 (0.95)	57.99 (1.76)	**χ^2 (3,317) = 17.70, p = .001**	4 > 1,2 > 3
Celiac Disease-Specific Quality of Life						
CD-QOL Total	62.72 (1.51)	62.62 (1.54)	60.59 (1.89)	65.80 (3.56)	χ^2 (3,317) = 1.90, p = .59	--
CD-QOL Limitations	29.72 (0.77)	29.84 (0.79)	28.94 (0.97)	31.76 (1.79)	χ^2 (3,317) = 1.97, p = .58	--
CD-QOL Dysphoria	9.50 (0.38)	9.08 (0.38)	8.87 (0.45)	10.22 (0.96)	χ^2 (3,317) = 2.39, p = .50	--
CD-QOL Health concerns	16.66 (0.46)	17.13 (0.46)	16.24 (0.58)	17.38 (1.05)	χ^2 (3,317) = 1.84, p = .61	--
CD-QOL Inadequate treatment	6.85 (0.19)	6.58 (0.20)	6.55 (0.24)	6.40 (0.46)	χ^2 (3,317) = 1.68, p = .64	--

Note. *M* = mean; *SD* = standard deviation; CSI = Celiac Symptom Index; CDAT = Celiac Dietary Adherence Test; PROMIS = Patient-Reported Outcomes Measurement Information System®; SF-36 = Short-Form 36; CD-QOL = Celiac Disease Quality of Life Survey. All values are raw scores except for PROMIS measures**,** which are *t*-scores. Significant omnibus statistical tests are **bolded** ($p < .05$)

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Single-Session Acceptance and Commitment Therapy (ACT) Interventions for Patients with Chronic Health Conditions: A Systematic Review and Meta-Analysis

Cara Dochat[1,2], Jennalee S. Wooldridge[2,3,4], Matthew S. Herbert[2,3,4], Michael W. Lee[2], Niloofar Afari[2,3,4]

[1] San Diego State University/University of California, San Diego Joint Doctoral Program in Clinical Psychology, San Diego, CA, USA

[2] VA San Diego Healthcare System, San Diego, CA, USA

[3] Department of Psychiatry, University of California, San Diego, San Diego, CA, USA

[4] VA Center of Excellence for Stress and Mental Health

Abstract

Rationale: Chronic health conditions (CHCs) are costly and difficult to manage. Patients often struggle with behavioral adherence to complex treatment regimens and experience psychiatric distress. Acceptance and Commitment Therapy (ACT) is a transdiagnostic behavioral approach that aims to improve functioning and quality of life (QoL), which are important treatment outcomes for this population. Preliminary efficacy of multi-session ACT in patients with CHCs has been demonstrated, and single-session ACT interventions have since been developed to increase feasibility, acceptability, and accessibility. The purpose of this systematic review and meta-analysis was to describe the literature on single-session ACT intervention studies in CHC populations with regards to (1) study design and methodology, (2) patient characteristics and conditions targeted, and (3) efficacy for outcomes across various domains, using narrative and quantitative methods.

Methods: PsycINFO, PubMed, and Web of Science were systematically searched in August 2020. Studies of single-session ACT interventions in adult patients with CHCs that reported quantitative outcomes in any of the following domains were included: (a) functioning and related domains (e.g., disability, QoL, well-being); (b) mental health; (c) physical health; (d) ACT processes. Both controlled and uncontrolled studies were included. Study quality was assessed using the Psychotherapy Outcome Study Methodology Rating Scale (POMRF). Between-group random effects meta-analysis was conducted on general functioning outcomes.

Results: Fourteen manuscripts reporting outcomes from 13 studies (N = 793) met inclusion criteria. Ten studies were identified by their authors as pilot or feasibility trials. Eight studies used comparison or control groups. Twelve studies delivered the ACT content in workshop format. Studies recruited for a variety of conditions. Narrative review found that between- and within-group effect sizes showed generally positive results favoring single-session ACT overall

(69%), especially for measures of functioning and related domains (88%), mental health (67%), and ACT processes (73%). Meta-analysis found that ACT did not significantly outperform comparison groups on measures of general functioning (Hedges' *g*: -0.51, 95% confidence interval: [-1.19, 0.16]; I^2 = 86%; *K* = 5) despite a medium-sized pooled effect.

Discussion: Use of single-session ACT interventions in CHC populations is an emergent field. There is preliminary evidence for the acceptability, feasibility, and efficacy of these interventions, which provides support for further testing in fully-powered RCTs. Additional RCTs will enable larger meta-analyses and stronger conclusions about efficacy. Recommendations for future trials are provided.

Single-Session Acceptance and Commitment Therapy (ACT) Interventions for Patients with Chronic Health Conditions: A Systematic Review and Meta-Analysis

Physical illness is part of the human experience. While some illnesses are transient and curable, many become chronic and present ongoing challenges to the individual, their families and communities, and the healthcare system. An estimated 60% of Americans have at least one chronic health condition (CHC; Hartzler, Castle, Lewis, & Zakaria, 2020). These conditions account for approximately 75% of healthcare expenditures and can lead to hospitalization, long-term disability, reduced quality of life (QoL), and death (Raghupathi & Raghupathi, 2018). Treatment for CHC often requires a shift from trying to get rid of the condition to managing it and preventing complications. CHC management often requires health behavior change (e.g., diet, exercise, medication adherence) and ongoing engagement with the healthcare system (e.g., in-office treatments, routine checkups, specialist visits).

Many individuals living with CHCs also experience psychiatric symptoms. Psychiatric distress might be pre-existing and become exacerbated by the condition, appear following diagnosis or CHC-related impairment, or occur as a response to difficulties managing the condition (e.g., diabetes distress; Skinner, Joensen, & Parkin, 2019). For example, the prevalence of comorbid depression ranges from 30-60% in chronic pain (Bair, Robinson, Katon, & Kroenke, 2003), 20-40% in cardiovascular disease (Davidson et al., 2006), 11-30% in diabetes (Anderson, Freedland, Clouse, & Lustman, 2001), and 16-30% in irritable bowel syndrome (Mykletun et al., 2010; Van Oudenhove et al., 2016). Co-occurring depression is associated with more severe medical pathology, poorer prognosis, and higher healthcare utilization compared to having a CHC only (Arnow et al., 2006; Celano & Huffman, 2011; Jeong et al., 2017; Löwe et al., 2008; Merikangas et al., 2007). There is a bidirectional relationship between physical and psychiatric symptoms (Evans et al., 2005). Comorbid psychiatric symptoms and disruptions to daily living

contribute to poor QoL in people with CHCs (Megari, 2013). Interventions that maximize self-management behaviors and behavioral activation in the face of complex treatment regimens and accompanying mental health challenges hold promise for maximizing patients' QoL while decreasing healthcare burden.

Acceptance and Commitment Therapy (ACT), a third-wave cognitive-behavioral therapy, is a promising adjunctive treatment for people with CHCs (Dindo, Van Liew, & Arch, 2017). ACT's primary treatment target is not amelioration of symptoms, but rather improved functional outcomes specifically aligned with an individual's values. Though symptom reduction often does occur following ACT treatment (A-Tjak et al., 2015), ACT is particularly well-suited for patients with CHCs, for whom symptom remission may not be a reasonable treatment outcome. ACT is hypothesized to improve functioning and QoL via increases in psychological flexibility. Psychological flexibility is the synthesis of six interrelated processes, which include: (1) acceptance (rather than avoidance) of any and all valanced internal and external experiences; (2) cognitive defusion (rather than fusion with or attachment to one's thoughts as absolute truth); (3) present-moment awareness (rather than maladaptive past- or future-focus); (4) self-as-context (rather than personal identification with one's thoughts or attachment to one's imagined self); (5) defining personally-relevant valued life directions (rather than lack of values clarity); and (6) committed action consistent with those values (rather than inaction or values-incongruent action) (Luoma, Hayes, & Walser, 2007).

ACT is said to be transdiagnostic, as processes can be applied flexibly to address multiple overlapping issues. For example, patients with CHCs may attempt to avoid the disappointment and discomfort associated with having their condition by not taking medication, avoiding activities where modifications must be made or that are related to symptom increase (e.g.,

physical activity in chronic pain), and engaging in unhealthy coping behaviors (e.g., substance use, overeating). While these behaviors may serve short-term goals (e.g., decreased stress, enjoyment of unhealthy foods, etc.), in the long-term these behaviors paradoxically increase distress and illness severity, and often lower QoL. Personal identification with and attachment to thoughts and feelings about one's condition can be targeted with ACT (e.g., using cognitive defusion and self-as-context exercises) to disrupt these behavioral repertoires. Ruminating thoughts about life before the condition, worries about future complications, or concerns about symptom flair-ups can be addressed using acceptance and present moment awareness exercises. Values identification and committed action exercises can then be used to help patients identify and commit to behaviors that would make their lives personally meaningful given the unique context of their diagnosis and prognosis.

A prior systematic review of general ACT interventions for patients with CHCs found preliminary evidence for efficacy (Graham, Gouick, Krahe, & Gillanders, 2016). Across the 18 studies reviewed, the mean number of treatment sessions was 6.5. For patients with CHCs, low-intensity or truncated interventions may be more feasible, acceptable, and appropriate, as they can be delivered in traditional healthcare settings and require less resource investment from patients and providers. Many patients live in remote areas, making it logistically and financially challenging to attend multiple sessions. Additionally, the modal number of treatment sessions attended in psychotherapy interventions is one (Gibbons et al., 2011). Thus, using single-session protocols specifically may increase adherence and potentially effectiveness because they ensure every participant receives all intervention components.

A small narrative review of single-session ACT intervention studies for patients with CHC found preliminary support (Dindo, 2015); however, this review was not systematic nor did

it include meta-analysis, and included only six studies published prior to 2015. In response to growing interest in this area, the current paper aims to provide a systematic review and meta-analysis of single-session ACT interventions in populations with CHCs to describe the state of the literature with regards to (1) study design and methodology, (2) patient characteristics and conditions targeted, and (3) efficacy for outcomes across various domains, using narrative and quantitative summary methods.

Methods

This systematic review with meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher, Liberati, Tetzlaff, Altman, & Prisma Group, 2009).

Eligibility Criteria

We used the five PICOS components (participants, interventions, comparators, outcomes, and study design) to design our research question and eligibility criteria (Moher et al., 2009). Studies were required to meet the following inclusion criteria: (P) sample was adults, 18 years and older, with physical illness(es); (I) delivered a single-session intervention based on the ACT model; (C) due to the nascent stage of the literature, both controlled and uncontrolled studies were included; (O) assessed any of the following outcomes quantitatively: functioning and related domains (e.g., impairment, disability, symptom interference, well-being, QoL, health behaviors), mental health (e.g., symptom severity, diagnoses changes), physical health (e.g., symptom severity, biomarkers), or ACT processes (e.g., experiential avoidance, psychological flexibility); and (S) used a prospective design. We only included manuscripts published in English. Studies were excluded if: (P) the condition, population, or sole outcome of interest was a health behavior outside the context of a CHC (e.g., physical activity or eating behavior in

adults without a discrete physical illness) or the intervention was designed to treat caregivers of individuals with a CHC exclusively; (I) a self-help or web-based design was used with no substantive therapist interaction; (O) only qualitative outcomes were reported; or (C/S) study design was cross-sectional, case study, or case series.

Information Sources and Search Strategy

The online databases of PsycINFO, PubMed, and Web of Science were systematically searched in August 2020. No search limitations or filters were imposed. We reviewed both peer-reviewed manuscripts and grey literature (i.e., theses and dissertations) for inclusion. No lower limit to year of publication was imposed. Manuscripts were identified using a pre-defined search strategy developed with the assistance of a research librarian. The following search terms were entered, joined by the operator "AND":

1. "acceptance and commitment therapy" OR "acceptance"

2.. "brief" OR "single-session" OR "One-day" OR "focused" OR "workshop" OR "FACT" OR "adjunct*" OR "single-session" OR "Pilot" OR "short"

3. "chronic" OR "disease*" OR "health" OR "physical" OR "medical" OR "illness*" OR "condition*" OR "diabetes" OR "cancer" OR "pain" OR "migraine*" OR "HIV"

Reference lists of included manuscripts, as well as Dindo (2015) and Dindo et al. (2017), were hand searched. We also searched the Association for Contextual Behavioral Science (http://contextualscience.org) website and contacted the email listserv of that professional organization for peer review of the final inclusion list.

Study Selection

Study selection proceeded in three stages. In stage 1 (screening), all manuscripts returned from database searches were imported into reference management software (EndNote X8). These manuscripts received title/abstract review. Studies that clearly failed to meet inclusion criteria or met exclusion criteria were removed and categorized according to exclusion reason (see *Figure*

3.1). In stage 2 (selection), remaining studies received a full-text review to determine inclusion status. Again, ineligible studies were removed and categorized according to exclusion reason. In stage 3 (hand-searching), the reference section of studies selected for inclusion were reviewed to identify additional potential manuscripts not previously identified through database searches. The titles, abstracts, and full texts of these manuscripts were examined as necessary. Ineligible studies were removed and categorized according to exclusion reason. Step 3 was also conducted with reference lists from Dindo (2015) and Dindo et al. (2017). Two independent reviewers (C.D. and M.S.H.) conducted stages 1-3. Disagreements about final study inclusion (k = 2; 2%) were discussed in a consensus meeting with other co-authors.

Data Extraction and Management

EndNote X8 was used to store results from database and hand searches, and to categorize manuscripts according to inclusion and exclusion criteria. Duplicates were removed using the EndNote X8 “remove duplicates” feature and by hand. Study coding and data extraction occurred in Excel. Data extraction was performed by the primary author (C.D.) and verified by co-authors (J.S.W. and M.W.L.). Authors of included studies were contacted directly to clarify study procedures as needed.

The following outcome variables were extracted: functioning and related outcomes (e.g., impairment, disability, symptom interference, well-being, QoL, health behaviors), mental health outcomes (e.g., symptom severity, diagnoses changes), physical health outcomes (e.g., symptom severity, biomarkers), and ACT process outcomes (e.g., experiential avoidance, psychological flexibility). In addition, we extracted demographic characteristics (employment, gender, race/ethnicity, education), study population/condition, study design (e.g., pilot, randomized controlled trial), setting, intervention duration, assessment schedule, and intervention and

comparator conditions. Results from intention-to-treat (ITT) analyses and analyses controlling for relevant covariates were reported when available. Where two measures were used to examine the same construct (e.g., both Hamilton Rating Scale for Depression and Inventory of Depression and Anxiety Symptoms), results from the measure identified by the study authors as primary were reported. Where outcomes were assessed at multiple follow-up intervals, results from three-month (12-week) follow-up were reported, as this was the most common interval across studies (k=10; 77%). Otherwise, the follow-up interval closest to three months was selected. Effect size information was extracted when reported and calculated by the primary author (C.D.) and confirmed by a co-author (J.S.W.) when not reported. A Cohen's *d* or Hedges' *g* value of .2 is considered small, .5 is considered medium, and .8 is considered large. A phi value of .1 is considered small, .3 is considered medium, and .5 is considered large.

Meta-analysis

Quantitative analysis of treatment efficacy on functional outcomes for controlled trials was conducted using random effects meta-analysis. Functional outcomes were chosen as they are central transdiagnostic treatment targets of ACT. To avoid dependence among multiple effect sizes from the same study, one outcome per controlled study was selected. Where controlled studies reported more than one relevant outcome, the general (rather than condition-specific) measure was selected to reduce heterogeneity.

Statistical heterogeneity was assessed using I^2, Cochran's Q-statistic, and τ^2 (using DerSimonian-Laird estimator) (Higgins, Thompson, Deeks, & Altman, 2003). I^2 is the percentage of variability in effect sizes due to heterogeneity rather than sampling error. The Q-statistic is the weighted sum of squared differences between individual study effects and the pooled effect, from which I^2 is derived. The Q-statistic chi-squared significance test is known to

be low-powered for analyses with few studies and should be interpreted with caution (Higgins et al., 2003). τ^2 is another metric of between-study variance in effect sizes (Deeks, Higgins, & Altman, 2019). A prediction interval, which accounts for between-study variance and is less sensitive to number of studies than standard heterogeneity estimates, was also calculated (Harrer, Cuijpers, Furukawa, & Ebert, 2019). Prediction intervals provide a range in which future study effects are predicted to fall based on present evidence in the meta-analysis.

Analysis was conducted in R version 3.6.1 (R Core Team, 2013) using the metafor and dmetar packages (Harrer et al., 2019), using the inverse variance method and Hedges' *g* as the standardized mean difference. Random effects modeling was used due to considerable statistical heterogeneity among the analyzed effects (i.e., $I^2 > 75\%$, per Cochrane guidelines). All measures included in the meta-analysis were scored such that higher scores indicated poorer results, except for one (the World Health Organization Quality of Life-BREF psychological subscale reported in Dindo et al., 2015), which was reverse scored for consistency of interpretation. Authors of four studies were contacted to request additional information. Given concerns about inflation in pre-post effect size estimates (Cuijpers, Weitz, Cristea, & Twisk, 2017), within-group effect sizes are depicted graphically but not meta-analyzed.

Individual Study Quality Assessment

Study quality was assessed using the Psychotherapy Outcome Study Methodology Rating Form (POMRF; Öst, 2008). The POMRF is a 22-item measure that assesses methodology and reporting for psychotherapy trials specifically. Each item is rated on a 3-point scale where 0 = *poor*, 1 = *fair*, 2 = *good*. Given that this review includes studies focused on CHC populations rather than strictly psychiatric populations, POMRF items #2 (severity/chronicity of the disorder), #4 (reliability of the diagnosis in question), and #21 (clinical significance) were

deemed not directly applicable and were not assessed. For pilot/feasibility studies, item #11 (power analysis) was not assessed. For uncontrolled studies, items #10 (design) and #22 (equality of therapy) were not assessed. Because some items were not assessed and because it is unclear if the total score is a reliable and valid measure of study quality (Liberati et al., 2009), we do not report total POMRF scores. Two reviewers (C.D. and J.S.W.) independently assessed quality of each study and met to reach consensus. Risk of bias was not formally assessed but was approximated at the study level based on whether or not the trial was pre-registered.

Results

Figure 3.1 shows the number of manuscripts identified throughout the screening, hand-searching, and selection phases. Fourteen manuscripts reporting results from 13 unique studies met inclusion criteria. Half of the manuscripts excluded during the selection phase were ACT interventions in CHC populations that delivered more than one session (k = 37). One of the nine studies identified by hand-searching met final inclusion criteria (Ferreira, Gillanders, Morris, & Eugenicos, 2018). One grey literature manuscript met inclusion criteria (Welch, 2014). Two included manuscripts (Dindo, Recober, Marchman, O'Hara, & Turvey, 2014; Dindo, Recober, Marchman, Turvey, & O'Hara, 2012) reported separate outcomes from a single study. Five of the 14 included manuscripts (36%; Gregg, Callaghan, Hayes, & Glenn-Lawson, 2007; Sheppard, Forsyth, Hickling, & Bianchi, 2010; Dindo et al., 2012; Dindo et al., 2014; Dindo, Marchman, Gindes, & Fiedorowicz, 2015) were included in prior reviews by Dindo (2015) and Graham et al. (2016). Of the nine newly reported studies, two were RCTs, one was a dissertation, and the remaining were pilot/feasibility trials.

Quality Assessment

POMRF item scores for each manuscript are presented in *Table 3.1*. Overall, studies ensured inclusion of representative samples, used valid and reliable outcome measures specific to the condition and treatment targets, delivered the intervention by clinical psychologists with advanced training, and used appropriate analytic methods with thorough reporting. Most manuscripts presented ITT analysis. Three studies reported both ITT and dropout analysis (Dindo et al., 2018; Gregg et al., 2007; Pedersen et al., 2019). All studies reported attrition rates, which ranged from 0% to 30%. The highest attrition rates were in patients with irritable bowel syndrome (30% at six-month follow-up), patients with migraines and current depressive episode (29% at three-month follow-up), and patients with multiple sclerosis (27% at three-month follow-up), which the authors noted was typical for this population (Sheppard, Forsyth, Hickling, & Bianchi, 2010). Attrition from enrollment to two-week follow-up was 35% in Welch (2014), but 100% of those who attended treatment completed follow-up.

The content of the respective ACT interventions was described in good detail for 12 of 13 studies (92%). Three studies (23%) made the treatment manual available with the manuscript (Ferreira et al., 2018; Gregg et al., 2007), one (8%) reported that the manual was modified from an existing publicly available manual (Dindo et al., 2020a), and one (8%) reported the manual was available upon request (Dindo et al., 2020b). Likely due to the short duration of the intervention, only one study (8%; Welch, 2014) assessed outcomes at 'post-treatment' (i.e., directly after the single-session intervention).

Seven out of eight controlled studies used random assignment to treatment, of which one also randomly assigned to therapist within condition. Two studies reported power analyses (Gregg et al., 2007; Pedersen et al., 2019). Equality of therapy hours in studies with treatment as usual (TAU) control conditions was difficult to assess. Many studies did not provide descriptions

of assessor training and blinding, checks for treatment adherence or therapist supervision, or attempts to control for concomitant treatment (particularly other psychotherapy interventions). Many studies used two or more therapists, but none controlled for therapist effects in statistical analyses. One study was pre-registered (Dindo et al., 2020b).

Study Design and Methodology

The design and methodology of each study is described in detail in *Table 3.2*. Sample sizes ranged from 15-136 participants (*M* = 61, *SD* = 36). Across the 13 studies, the range of female participant inclusion was 0-100% of the sample (*M* = 61%, *SD* = 32%); the range of participants identifying as white was 24-92% of the sample (*M* = 61%, *SD* = 24%). Mean sample ages ranged from 33-63 years (median: 46.5; *M* = 46, *SD* 8.5). Employment rates ranged from 19-89% and unemployment or disability rates ranged from 11-62%.

Study design. Eight of the 13 studies (62%) included a control or comparison condition (Dindo et al., 2015; Dindo et al., 2014; Dindo et al., 2012; Dindo et al., 2018; Dindo et al., 2020a; Dindo et al., 2020b; Gregg et al., 2007; Hadlandsmyth et al., 2019; Pedersen et al., 2019), all of which used random assignment except one that assigned participants based on availability (Dindo et al., 2014; Dindo et al., 2012). Four controlled studies used medical TAU (Dindo et al., 2015; Dindo et al., 2018; Dindo et al., 2020a; Hadlandsmyth et al., 2019), one used waitlist/medical TAU (Dindo et al., 2014; Dindo et al., 2012), and three provided an active control (disease management education in Gregg et al., 2007; enhanced care in Pedersen et al., 2019; support and migraine education in Dindo 2020b). The specific content of intervention and control conditions is shown in *Table 3.3*. Ten studies (77%) were identified by their authors as pilot or feasibility studies (Dindo et al., 2015; Dindo et al., 2012; Dindo et al., 2018; Dindo et al., 2020a; Ferreira et al., 2018; Hadlandsmyth et al., 2019; Hou et al., 2017; Huddleston, Martin,

Woods, & Dindo, 2018; Sheppard et al., 2010; Welch, 2014), suggesting that assessing feasibility and acceptability were primary aims for those trials. Five out of 10 (50%) pilot/feasibility studies reported qualitative feedback regarding feasibility, acceptability, or treatment satisfaction, with generally positive feedback (Dindo et al., 2015; Hadlandsmyth et al., 2019; Hou et al., 2017; Huddleston, Martin, Woods, & Dindo, 2018; Welch, 2014). Among those studies, common reasons for eligible individuals declining participation included practical constraints such as time and distance (47% in Hou et al., 2017; 18% in Hadlandsmyth et al., 2019) and a general sense of overwhelm (33% in Hadlandsmyth et al., 2019).

Study methodology. Twelve studies (92%) delivered the ACT intervention in workshop format and one delivered it in an individualized session (Hadlandsmyth et al., 2019). Two studies provided individualized follow-up calls after the workshop as part of the intervention (Dindo et al., 2018; Ferreira et al., 2018), and one included a self-guided bibliotherapy component (Ferreira et al., 2018). Across all studies, average single-session ACT intervention length was 5.5 hours, with a range of two to eight hours. Median and modal length was five hours. The modal follow-up period for assessment of post-treatment outcomes was three months (k = 10, 77%). Four studies (31%) assessed outcomes beyond three months: six months in Dindo et al. (2015), Ferreira et al. (2018), and Dindo et al. (2020b), and six, 14 and 20 months in Pedersen et al. (2019). Seven manuscripts (54%) explicitly indicated where the intervention was delivered, and personal communication with authors clarified the setting for the remaining six studies. All interventions were delivered in-person. All interventions but two (Sheppard et al., 2010; Welch, 2014) were delivered in medical settings, including a community clinic (Gregg et al., 2007), Veterans Affairs hospitals or clinics (Dindo et al., 2018; Dindo et al., 2020a; Hou et al., 2017; Huddleston et al., 2018), a comprehensive cancer treatment center (Hadlandsmyth et al., 2019), a

gastroenterology outpatient clinic (Ferreira et al., 2018) and university hospitals or clinics (Dindo et al., 2015; Dindo et al., 2014; Dindo et al., 2012; Dindo et al., 2020b; Hou et al., 2017; Pedersen et al., 2019).

Patient Characteristics and Conditions

The primary patient population and CHC of interest varied widely. Across 13 studies, three (23%) targeted migraine (Dindo et al., 2014; Dindo et al., 2012; Dindo et al., 2020a; Huddleston et al., 2018), two (15%) diabetes mellitus type 2 (Gregg et al., 2007; Welch, 2014), two (15%) primary gastrointestinal conditions (inflammatory bowel diseases in Hou et al., 2017; irritable bowel syndrome in Ferreira et al., 2018), one (8%) multiple sclerosis (Sheppard et al., 2010), one (8%) multiple functional somatic syndromes including irritable bowel syndrome, chronic fatigue syndrome, fibromyalgia, tension headaches, and non-cardiac chest pain (Pedersen et al., 2019), one (8%) recruited male military veterans with chronic pain and mild traumatic brain injury, and one (8%) recruited patients characterized as "at risk" for vascular disease, where risk was defined as having a diagnosis of hypertension, diabetes mellitus, impaired fasting glucose, dyslipidemia, or obesity (Dindo et al., 2015). Two studies (15%) targeted patients undergoing surgery who were identified *a priori* as being at risk for post-surgical pain and/or chronic opioid use. One recruited female breast cancer patients undergoing breast surgery (Hadlandsmyth et al., 2019), where risk was defined as being under the age of 50, having a pre-existing chronic pain condition, or reporting elevated anxiety, depression, or pain catastrophizing. The final study targeted Veteran patients (93% male) undergoing orthopedic surgery, where risk was defined as having high levels of preoperative pain and clinically significant anxiety or depression (Dindo et al., 2018).

Eight studies (62%) required participants to meet a minimum threshold of psychiatric distress for inclusion. Of those, three required participants to meet DSM-IV criteria for a current major depressive episode (Dindo et al., 2014; Dindo et al., 2012; Dindo et al., 2020b; Huddleston et al., 2018). Three required participants to meet established cut-offs for clinically significant depression or anxiety symptomatology (Dindo et al., 2015; Dindo et al., 2018; Hou et al., 2017). One required participants to meet DSM-IV criteria for either current major depressive disorder, generalized anxiety disorder, or DSM-5 criteria for posttraumatic stress disorder (PTSD; Dindo et al., 2020a). One required significant condition-related distress (Welch, 2014). In samples from studies not requiring psychiatric distress for inclusion, rates of clinically significant depression and anxiety ranged from 17-53% and 16-30%, respectively (Hadlandsmyth et al., 2019; Pedersen et al., 2019; Sheppard et al., 2010). One study did not report mental health comorbidities (Gregg et al., 2007).

Narrative Review: Outcomes Assessed and Intervention Efficacy

For the purpose of this review, treatment outcomes were categorized into four domains: (a) functioning and related domains (k = 13, 93% manuscripts reporting); (b) mental health (k = 11, 79% manuscripts reporting); (c) physical health (k = 10, 71% manuscripts reporting); and (d) ACT processes (k = 9, 64% manuscripts reporting). Given that pilot/feasibility trials do not have adequate power to detect statistically significant effects, results from statistical significance testing are reported for non-pilot trials only. Within-group effect sizes are reported to assess preliminary efficacy in pilot/feasibility trials.

Functioning and related domains. Thirteen manuscripts (93%) reported 27 outcomes in this domain, including daily functioning, functioning in specific life domains, disability, QoL, healthcare utilization, pain interference, medication use and cessation, and disease self-

management, all of which were measured using self-report instruments. Specific constructs and measures are listed in *Table 3.2*. Of the 27 outcomes assessed across all studies, approximately half were condition-specific and half were general to health and functioning. In the three non-pilot trial manuscripts that assessed this domain, 4/7 outcomes (57%) showed significantly greater improvement in the ACT group than the control group, and one (14%) showed a trending significant (p = .06) outcome. In the 10 pilot/feasibility trial manuscripts that assessed this domain, 20/20 outcomes (100%) showed medium-to-large effect sizes. Effect sizes varied within and across studies (see *Table 3.2*). In total, 24/27 outcomes in this domain (88%) showed results favoring ACT.

Mental health. Eleven manuscripts (79%) reported 24 mental health outcome effects total, including depression (n = 10), anxiety (n = 7), stress (n = 2), PTSD symptoms (n = 1), GI-specific anxiety (n = 1), and general or composite mental health status (n = 3). In two non-pilot trial manuscripts, 1/6 outcomes (17%) showed significantly greater improvement in the ACT group (depression symptoms in Dindo et al., 2020b). In nine pilot/feasibility trial manuscripts, 15/18 outcomes (83%) showed medium-to-large effect sizes. Those that did not were depression and anxiety in breast cancer patients (Hadlandsmyth et al., 2019) and general mental health status in adults with multiple sclerosis (Sheppard et al., 2010). In total, 16/24 outcomes in this domain (67%) showed results favoring ACT.

Physical health. Ten manuscripts (71%) reported 13 physical health outcome effects total, including general physical health status (k = 3), raw HbA1c and diabetes control as assessed by HbA1c (k = 1), headache frequency and severity (k = 1), inflammatory bowel disease symptoms (k = 1), irritable bowel syndrome symptom severity (k = 1), pain cessation (k = 1), and pain severity (k = 2). In three non-pilot trial manuscripts, 1/5 outcomes (20%) was statistically

significant in favor of the ACT group (greater increase in proportion of glycemic control in Gregg et al., 2007). In seven pilot/feasibility trial manuscripts, 3/8 outcomes (38%) showed medium-to-large effect sizes: headache frequency and severity (Dindo et al., 2014), inflammatory bowel disease activity (Hou et al., 2017), and irritable bowel syndrome symptoms severity (Ferreira et al., 2018). In total, 4/13 outcomes in this domain (31%) reported results favoring ACT.

ACT processes. Eight manuscripts (57%) reported 11 ACT process outcomes, including experiential avoidance, acceptance, psychological flexibility, and engagement in values-consistent behavior. Two studies administered the general Acceptance and Action Questionnaire-II (Bond et al., 2011), and six administered condition-specific AAQ variants. Two manuscripts examined three ACT-adjacent process constructs: thought suppression, "mindful attention awareness," and pain catastrophizing (Hadlandsmyth et al., 2019; Sheppard et al., 2010). In one non-pilot trial, the ACT group reported significantly greater increases in diabetes acceptance at three-month follow-up than a diabetes management education condition (Gregg et al., 2007). In eight pilot/feasibility trial manuscripts, 7/10 outcomes (70%) showed medium-to-large effect sizes. Small effects were detected for pain acceptance and values-consistent behavior among Veterans who underwent orthopedic surgery, despite greater rates of pain cessation and opioid cessation (Dindo et al., 2018), and for pain acceptance in female breast cancer patients who underwent breast surgery (Hadlandsmyth et al., 2019). Medium-to-large effect sizes were shown for thought suppression among patients with multiple sclerosis and patients with diabetes mellitus type 2 (Sheppard et al., 2010; Welch, 2014). Small effects were shown for mindful attention awareness among patients with multiple sclerosis (Sheppard et al., 2010) and pain

catastrophizing among breast cancer patients (Hadlandsmyth et al., 2019). In total, 8/11 outcomes in this domain (73%) showed results favoring ACT.

Three manuscripts conducted some form of mediational analyses using ACT process measures. Gregg et al. (2007) found that changes in diabetes acceptance and self-reported self-management behavior mediated impact of treatment on changes in HbA1c in patients with diabetes mellitus type 2. Using a proxy mediation method, Dindo et al. (2015) found that psychological flexibility (measured by the Experiencing Questionnaire) partially mediated reductions in depressive symptoms among individuals at risk for vascular disease with clinically significant anxiety or depression. Finally, Ferreria et al. (2018) used hierarchical multiple regression to examine the unique contribution of changes in irritable bowel syndrome acceptance (pre-treatment to post-treatment) in accounting for variance in change in outcome measures (pre-treatment to follow-up). They found that changes in irritable bowel syndrome acceptance significantly predicted changes in all outcomes, even when accounting for symptom severity.

Meta-analysis: Outcomes Assessed and Intervention Efficacy

Five out of eight controlled studies (63%) reported a functioning-related outcome. Four studies assessed general functioning using the World Health Organization Disability Assessment Schedule II (WHODAS; Rehm et al., 1999), which assesses illness-related functioning in six domains: cognition; mobility; activities of daily living; interacting with others; activities at home, work, school, and leisure; participation in community activities. The fifth study (Dindo et al., 2015) assessed general well-being using the World Health Organization Quality of Life-BREF (WHO-QoL-BREF; Skevington, Lotfy, & O'Connell, 2004), from which scores on the psychological well-being subscale were used. Effects were estimated using data from three-month follow-up for four studies and six-month follow-up (the shortest available) for one study

(Pedersen et al., 2019). Random effects meta-analysis found that ACT did not significantly outperform comparator groups on these outcomes (mean Hedges' g = -0.51, 95% CI [-1.19, 0.16], p = .14) (see *Figure 3.2*). The pooled effect size was medium. Study effects displayed considerable heterogeneity (I^2 = 86%; Q [df=4]: 28.84, p < .001; τ^2 = 0.50). The prediction interval shown in *Figure 3.2* crossed 0, which does not suggest that future effects are expected to favor ACT. Examination of a funnel plot showed no evidence for publication bias.

The nine within-group effects for functioning and related domains across all trial types are depicted graphically in *Figure 3.3*. Of nine effects, five were from the WHODAS (Dindo et al., 2012; Huddleston et al., 2018; Pedersen et al., 2019; Dindo et al., 2020a; Dindo et al., 2020b), one was from WHO-QoL-BREF (Dindo et al., 2015), one was from the Quality of Life Inventory (Sheppard et al., 2010), and two were from measures of condition-specific health-related QoL (the Short IBD Questionnaire in Hou et al., 2017; IBS Impact on Quality of Life Scale in Ferreira et al., 2018). Effect sizes were generally medium to large, with two studies clearly favoring ACT.

Discussion

The purpose of this systematic review with meta-analysis was to describe the state of the literature and estimate the efficacy of single-session ACT interventions for CHC populations. Our search yielded 14 manuscripts (from 13 unique studies) for inclusion, nine of which were not included in prior reviews. Ten of the 13 included studies were pilot/feasibility trials and quality of all studies was variable, underscoring the nascent nature of this literature. Overall, efficacy results were promising, but varied by condition and population as well as specific outcome type. Narrative review of ACT efficacy found significant results in RCTs or medium-to-large effect sizes in pilot/feasibility trials for the majority of outcomes (69%) across four

domains. Consistent with the theory and treatment targets of ACT, the greatest benefits were in functioning and related domains, followed by ACT processes. Physical health outcomes did not improve at comparable rates to other outcomes, likely because symptom improvement is not the primary goal of ACT and may not have been addressed directly. However, physical health outcomes tended to improve for conditions with substantial behavioral (e.g., diabetes control), or psychosomatic components (e.g., headache severity, irritable bowel syndrome symptom severity).

We found that all four studies that required participants to meet DSM diagnostic criteria for a psychiatric condition reported significant or large effect size improvements in mental health symptoms and significant or medium-to-large effect size improvements in functioning and related domains (Dindo et al., 2012; Huddleston et al., 2018). This is contrary to Graham et al. (2016), which noted that intervention dose is important to consider as CHC can be long-standing, severe, and accompanied by significant psychiatric issues. It is possible that clinically significant psychiatric distress may indicate a greater need for behavioral intervention and therefore greater responses to treatment.

For ACT process outcomes, acceptance, psychological flexibility, and values-consistent behavior were most commonly assessed, and often measured with condition-specific measures, which is in line with recommendations (Ong, Lee, Levin, & Twohig, 2019). Although the current review focused on direct influences of treatment on ACT process outcomes, the three studies that conducted some form of mediational analyses (Dindo et al., 2015; Ferreira et al., 2018; Gregg et al., 2007), found evidence for partial or proxy mediation. Assessing purported mechanisms is essential for optimizing behavioral interventions for CHC populations, especially in RCTs where multiple active intervention types may be compared.

Results from meta-analysis suggested a medium effect of single-session ACT on functioning and well-being, though the pooled estimate was not statistically significant. These results should be interpreted tentatively, since two of the five meta-analyzed effects came from pilot/feasibility trials, and the five effects displayed considerable heterogeneity. Ultimately, pilot trial results inform treatment acceptability and feasibility rather than efficacy (Bowen et al., 2009). Thus, results from pilot RCTs should be reproduced in fully powered RCTs. Data from additional RCTs will better inform the efficacy of single-session ACT for people with CHC.

Recommendations for Future Studies

While current review findings suggest promise for the utility of single-session ACT for CHC, additional high-quality trials are needed to better establish this treatment approach. Below we offer multiple considerations for enhancing the literature in this area, from general strategies to those specific to the single-session ACT format.

1. Given the variability of study quality and the preponderance of pilot/feasibility studies, additional well-designed RCTs are needed to fully examine the efficacy of single-session ACT for CHC. Such studies should include pre-specified hypotheses and outcomes, *a priori* power calculations, adequate sample size, blinded assessors, and therapist adherence and competency ratings. RCTs should also compare single-session ACT to an active control condition (e.g., education, relaxation) and ensure equivalence in length, intensity, therapist proficiency, and any additional treatment components (e.g., booster sessions).
2. Only four of the reviewed studies included follow-up periods beyond three months. Future studies would benefit from multiple follow-up assessments (perhaps up to one year) to better examine the long-term efficacy of single-session ACT. Other ACT research has emphasized the importance of longer-term follow-up periods for capturing unexpected increases in

improvement over time as well as maintenance of treatment effects compared to comparator conditions (Clarke, Kingston, Wilson, Bolderston, & Remington, 2012; Gifford et al., 2011; González-Menéndez, Fernández, Rodríguez, & Villagrá, 2014).Increasing the follow-up period will inform the relative efficacy of single-session ACT and whether it can be offered as a standalone intervention or should be offered as part of a more comprehensive treatment package.

3. Several studies used general measures of functioning that assess outcomes less amenable to behavioral interventions such as ACT (e.g., mobility and self-care in the WHODAS), whereas others used condition-specific measures, which are ostensibly more sensitive to outcomes of interest to patients and providers. Selecting validated and appropriate measures of functioning and QoL as the primary outcome for single-session ACT studies of CHC is critical to establishing the efficacy of this intervention. Future studies should use both general and condition-specific measures when possible. Further, all included studies used self-report measures of functioning, most of which rely on retrospective recall. Investigators may consider using novel assessments of functioning that are ecologically valid and less prone to social desirability and recall biases, such as ecological momentary assessment (EMA) and accelerometry or other behavioral measures relevant to the CHC.
4. There was variability in participation and dropout rates across the reviewed studies, especially high for conditions with psychiatric comorbidity or greater levels of disability (e.g., multiple sclerosis). Given that single-session ACT interventions for CHC can facilitate access to treatment, they could be delivered virtually to further enhance their reach. Virtual delivery may increase willingness and ability to participate and may be less distressing for some individuals. Virtual delivery may also increase access among underserved populations.

5. Single-session interventions deliver a great amount of information in a short period. Further, traditional post-treatment assessments were uncommon in included studies and may not be psychometrically appropriate. Therefore, incorporating a participant comprehension check should be considered. Instituting a comprehension check both immediately following the intervention and at follow-up may provide information that can be used to optimize single-session delivery. A recently developed measure that may be suitable for this purpose is the ACT-SQ, which captures how well ACT processes were realized during a treatment session (Probst et al., 2020).
6. Patient characteristics and the clinical complexity of CHCs varied widely across the studies and may have contributed to the modest outcomes in some of the studies. Examining clinical variables as moderators of treatment outcome can shed more light on whether single-session ACT is adequate for those with greater disease burden. Additionally, the majority of participants in most studies were white. Given the higher prevalence of some CHCs in racial and ethnic minority groups, future studies should assess these variables as potential moderators to inform culturally sensitive approaches.
7. Only nine of the 14 manuscripts included ACT process measures, despite the importance of examining the impact of treatment on the purported processes of change. We strongly encourage all future single-session ACT studies to include multiple measures of ACT processes, preferably both condition-specific and general measures, and conduct adequately powered mediation analyses where possible. Newer measures such as CompACT (Francis, Dawson, & Golijani-Moghaddam, 2016) can also be included to measure multiple ACT processes. This is an important step to identifying underlying treatment processes that predict treatment outcomes.

8. Only two of the included studies delivered additional components (i.e., booster session in Dindo et al., 2018; bibliotherapy and support calls in Ferreira et al., 2018) and both demonstrated robust treatment findings. Future studies should specifically test whether adjunctive intervention components increase efficacy. This may include telephone- or text-based booster sessions, ACT-based apps or websites, and/or peer-support groups. Future studies also may consider implementing a multiphase optimization strategy (MOST; Collins, 2018) to better understand the briefest and most cost-effective intervention that still achieves efficacy. Relatedly, stepped-care approaches for treatment of non-responders could evaluate outcomes following a single-session intervention and provide additional intervention (e.g., full-length ACT) as indicated.

Additionally, future pilot or feasibility studies should consider the recommendations of Bowen et al. (2009) to assess outcomes in eight domains: acceptability, demand, implementation, practicality, adaptation, integration, expansion, and limited-efficacy testing. Future randomized controlled trials incorporating the above recommendations will answer important questions regarding for whom single-session ACT may be efficacious, the optimal delivery method and intervention design for specific populations, and the role of single-session ACT in treatment of CHC populations (e.g., as "first-line" treatment in stepped-care approach).

Review Limitations

This is the first systematic review with meta-analysis of single-session ACT interventions in CHC populations. In terms of assessing study quality, there is no ideal tool for evaluating single-session psychotherapy studies, nor are we aware of a single tool that adequately assesses the quality of both pilot/feasibility studies and RCTs. The POMRF was chosen because its items assess a range of nuanced design and reporting features that are important for establishing strong

evidence for efficacy of behavioral interventions specifically. We also modified the POMRF for our purposes, following precedent from a related review (Graham et al., 2016). However, the reliability and validity of the POMRF have not been rigorously evaluated and it has been criticized for not assessing process-based therapy variables that are especially important in ACT interventions (Atkins et al., 2017). We encourage the development of validated quality assessment tools appropriate for brief psychotherapy interventions.

Outcomes across various domains were reported in the present review, though meta-analysis was limited to outcomes related to functioning. Further, only between-group meta-analysis was conducted due to concerns about overestimation biases inherent in within-group effect size calculations. Not all controlled studies reported functioning-related outcomes, which limited the size of the meta-analysis to five effect sizes. These five effects demonstrated considerable heterogeneity, which could not be explored using meta-regression or subgroup analyses due to the small size of the analysis. Four of the five meta-analyzed effects came from studies conducted by the same primary author, which may also introduce bias. As evidence continues to accumulate, future meta-analyses should explore possible sources of heterogeneity based on both clinical and methodological factors. For example, Hadlandsmyth et al. (2019) was an outlier among studies included in the review both in terms of delivery method (individualized rather than group-based) and duration (2 hours versus the modal 5 hours), and showed small effects across all outcomes. Meta-regression of multiple studies with varying design qualities will allow for broader conclusions about efficacy and optimal delivery.

It is also important to note that general measures of functioning and related domains (rather than condition-specific measures) were chosen to meta-analyze to reduce statistical heterogeneity. However, condition-specific measures may be more sensitive to change. Future

studies and larger meta-analyses should include both condition-specific and general measures of functioning that are sensitive to the intervention.

We calculated between- and within-group effect sizes for studies where these were not reported in the manuscript. However, these within-group effect sizes did not account for the dependence between pre- and post-test scores, which may lead to inflated estimates (Cuijpers et al., 2017; Cheung, 2019). Future studies should report appropriate effect sizes in addition to statistical significance testing. Finally, the present review did not formally assess risk of bias across studies. Of the 13 studies reviewed, only one was pre-registered, which precludes assessment of selective reporting. A funnel plot of meta-analyzed effects did not suggest publication bias, and the inclusion of grey literature should reduce publication bias in the present review. However, it will be important to systematically assess whether all data collected and pre-specified analyses were reported as more RCTs are conducted.

Despite these limitations, the current review has a number of strengths. It provides an up-to-date synthesis of single-session ACT studies for CHC and is the first to meta-analyze treatment outcomes. We also included grey literature, broad reporting of outcomes types and results, and detailed description of study design and intervention characteristics.

Conclusion

Brief interventions hold promise for increasing access and use of behavioral interventions among CHC patients, who tend to have a greater burden of healthcare needs than other psychotherapy consumers Our systematic review identified 13 studies collectively assessing the feasibility, acceptability, and efficacy of single-session ACT interventions in CHC populations, which were successfully delivered to samples with various conditions. Studies generally reported positive results favoring ACT, especially in functioning and related domains, which is the

primary target of ACT interventions. However, there were few RCTs, and sample sizes were relatively small. Given the relatively limited dose of treatment delivered in a single session and the likelihood that patients with CHCs have complex clinical presentations, it is critical to further evaluate the efficacy of brief interventions to better inform treatment design and delivery, especially in traditional and integrated healthcare settings.

Paper 3, in full, is a reprint of the material as it appears in *Journal for Contextual Behavioral Science*, 2021, Dochat, Cara; Wooldridge, Jennalee S.; Herbert, Matthew S.; Lee, Michael W.; Afari, Niloofar. Elsevier, 2021. The dissertation author was the primary investigator and author of this paper.

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** References marked with an asterisk indicate studies included in the meta-analysis*

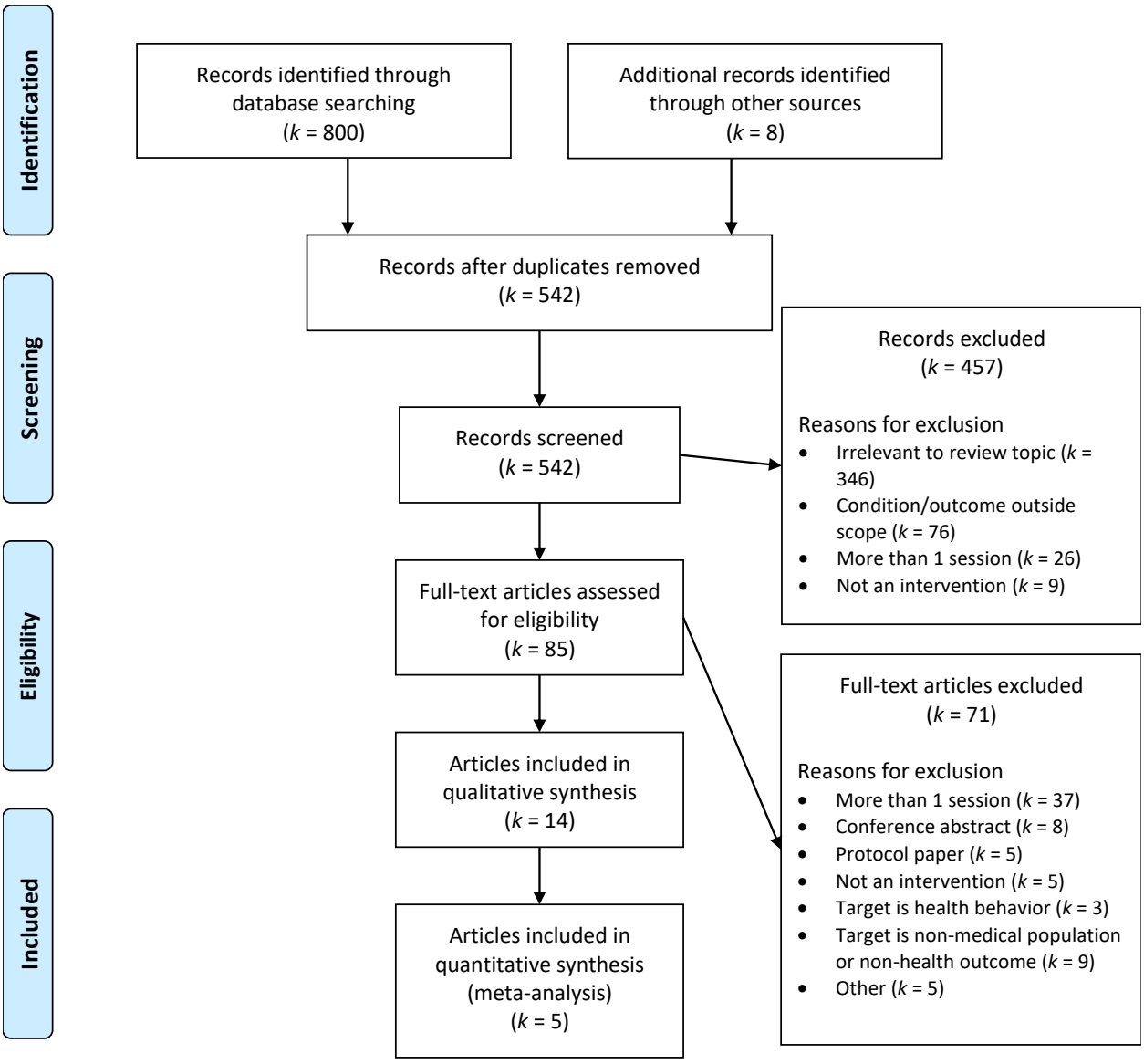

Figure 3.1. *Study Screening Flowchart. Note:* Adapted from Moher et al., 2009.

Table 3.1

Study Quality Assessment using the Psychotherapy Outcome Study Methodology Rating Scale (POMRF)

Study: First Author Year	Gregg 2007	Sheppard 2010	Dindo 2012	Dindo 2014[†]	Welch 2014	Dindo 2015	Hou 2017	Dindo 2018	Ferreira 2018	Huddleston 2018	Hadland smyth 2019	Pedersen 2019	Dindo 2020a	Dindo 2020b
Pilot/ Feasibility	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	N
Controlled	Y	N	Y	Y	N	Y	N	Y	N	N	Y	Y	Y	Y
1: Clarity of sample description	2	1	1	1	2	1	1	1	1	1	1	2	2	2
2: Severity/ chronicity of disorder	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
3: Represent-ativeness of sample	2	1	2	2	1	2	2	2	2	2	2	2	2	2
4: Reliability of diagnosis	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
5: Specificity of outcome measures	2	2	2	2	2	2	2	2	2	2	2	2	2	2
6: Reliability and validity of outcome measures	2	2	2	0	2	2	2	1	2	2	2	2	2	2
7: Use of blind evaluators	1	n/a	0	0	n/a	0	n/a	1	n/a	n/a	n/a	0	0	2
8: Assessor training	1	0	2	2	0	0	0	0	0	0	n/a	0	0	0
9: Assignment to treatment	1	0	0	0	0	1	0	1	0	0	1	1	1	2
10: Design	1	0	0	0	0	0	0	1	0	0	0	1	1	2
11: Power analysis	2	0	n/a	n/a	n/a	n/a	0	n/a	n/a	n/a	n/a	2	n/a	0

Table 3.1 (continued)

Study Quality Assessment using the Psychotherapy Outcome Study Methodology Rating Scale (POMRF)

Study: First Author Year	Gregg 2007	Sheppard 2010	Dindo 2012	Dindo 2014†	Welch 2014	Dindo 2015	Hou 2017	Dindo 2018	Ferreira 2018	Huddleston 2018	Hadlandsmyth 2019	Petersen 2019	Dindo 2020a	Dindo 2020b
12: Assessment points	0	0	1	1	0	1	0	1	1	1	0	2	0	1
13: Manualized, replicable, specific treatment programs	2	0	0	0	2	0	0	0	2	0	1	0	2	2
14: Number of therapists	1	1	1	1	0	0	0	1	1	0	1	1	1	1
15: Therapist training/ experience	1	2	2	2	0	0	0	2	2	0	2	2	2	2
16: Checks for treatment adherence	0	0	0	0	0	0	0	0	0	0	1	0	1	0
17: Checks for therapist competence	0	0	0	0	0	0	0	0	0	0	1	1	2	0
18: Control of concomitant treatments	0	0	1	1	0	1	0	0	0	1	0	0	0	0
19: Handling of attrition	2	1	1	1	0	1	0	2	1	0	0	2	1	1
20: Statistical analyses and presentation of results	2	2	2	2	2	1	2	1	2	2	2	1	2	2
21: Clinical significance	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
22: Equality of therapy hours	2	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	0	n/a	2

Note. Pilot/feasibility determination made based on source author's use of the terms to describe study. †Same parent study as Dindo (2012)

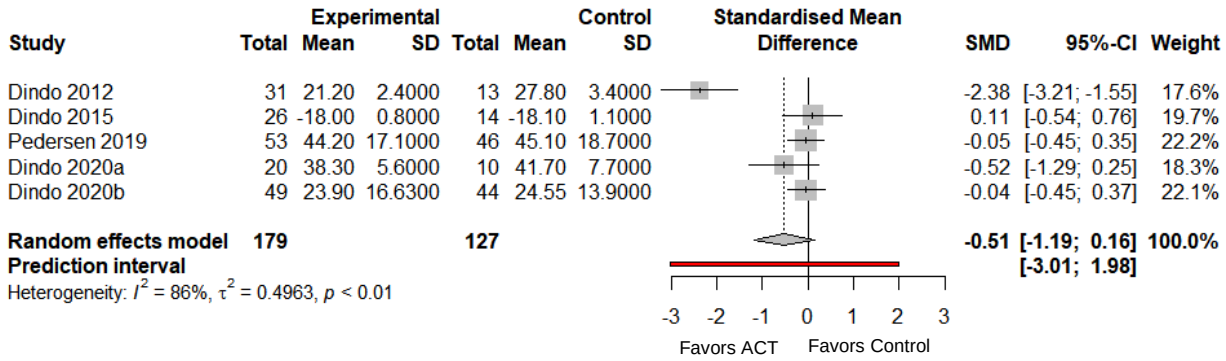

Figure 3.2. *Between-group Meta-analysis Results and Forest Plot. Note:* Error bars are 95% confidence intervals; dashed line is mean effect size from the random effects meta-analysis; red line is prediction interval. *SD* = standard deviation. Standardized mean difference is calculated as Hedges' *g*.

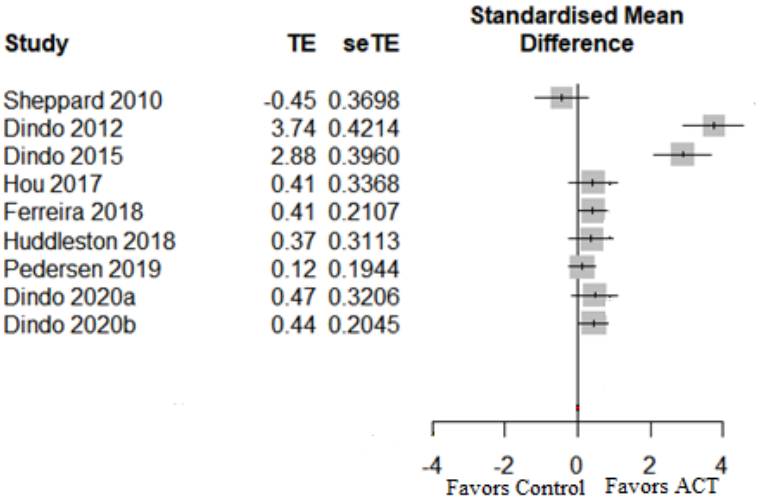

Figure 3.3. *Within-group Effect Sizes and Forest Plot. Note*: Error bars are 95% confidence intervals. TE = Hedges' *g*; seTE = standard error of Hedges' *g*.

Table 3.2

*Manuscripts Reporting Studies of Single-session ACT Interventions for Chronic Health Condition Populations (*K *=14)*

	First author (year)	Population/ Condition	Participant characteristics	Study design, setting, intervention duration, assessment schedule	Intervention and comparator conditions	Outcomes and measures	Key Findings
1	Gregg (2007)	Adults with diabetes mellitus type 2	N = 81; M_{age} = 50.9 years; female = 46.9%; white = 23.5%; employment = 10% working full-time, 9% working part-time, 25% unemployed looking for work, 6% unemployed not looking for work, 8% retired, 28% disabled/unable to work; education = 57% with some education greater than High School; income not reported; M_{BMI} = 32.6	Randomized controlled trial; 7-hour workshop; Setting: community health center; Baseline, 3-month FU	(1) ACT + diabetes management education (n = 43) (2) Diabetes management education (n = 38)	(a) HbA1c (b) Diabetic Control (HbA1c < 7.0%) (c) Diabetes self-management (3 self-report items based on exercise, diet, glucose monitoring) (d) Diabetes acceptance (Acceptance and Action Diabetes Questionnaire/ AADQ)	(a) Nonsignificant trend for greater improvement in HbA1c in Group (1) > Group (2) at FU; Cohen's d = 0.35 (b) Significant increase in rate of diabetic control in Group (1) at FU, p < . 01, but not Group (2); Cohen's d = 0.61 (c) Group (1) increase > Group (2) increase at FU, both p < .05; Cohen's d = 0.68 (d) Group (1) increase significant (p < .01) and > Group (2) increase at FU; Cohen's d = 0.78

Table 3.2, continued

	First author (year)	Population/ Condition	Participant characteristics	Study design, setting, intervention duration, assessment schedule	Intervention and comparator conditions	Outcomes and measures	Key Findings
2	Sheppard (2010)	Adults with multiple sclerosis (MS)	N = 15; M_{age} (SD) = 53.13 years (7.68); female = 80%; white = 66.7 %; employment = 46% unemployed or receiving disability payments; education = 60% with Bachelor's degree or higher; income not reported	Uncontrolled feasibility trial; 5-hour workshop; Setting: local hotel conference venue; Baseline, 3-month FU	ACT + MS education	(a) Depression (Beck Depression Inventory-II/BDI-II) (b) Impact of Fatigue (Modified Fatigue Impact Scale/MFIS) (c) Pain Effects on mood/behavior (Pain Effects Scale/PES) (d) Physical Health (SF-36) (e) Mental Health (SF-36) (f) Quality of Life (Quality of Life Inventory/QOLI) (g) Thought Suppression (White Bear Suppression Inventory/WBSI) (h) Mindful Attention Awareness Scale (MAAS)	(a) Baseline to FU mean difference = -8.31; Hedges' g = -0.73 (b) Baseline to FU mean difference = -11.21; Hedges' g = -0.50 (c) Baseline to FU mean difference = 4.98; Hedges' g = -0.98 (d) Baseline to FU mean difference for physical health = -0.86; Hedges' g = -0.10 (e) Baseline to FU mean difference for mental health = 4.23; Hedges' g = 0.36 (f) Baseline to FU mean difference = 1.11; Hedges' g = 0.45 (g) Baseline to FU mean difference = 5.35; Hedges' g = -0.33 (h) Baseline to FU mean difference = 0.22; Hedges' g = -0.22

Table 3.2, continued

	First author (year)	Population/ Condition	Participant characteristics	Study design, setting, intervention duration, assessment schedule	Intervention and comparator conditions	Outcomes and measures	Key Findings
3	Dindo (2012)	Adults with migraine and depression (current depressive episode)	N = 45; M_{age} (SD) = 32.8 years (13.2); female = 94%; white = 92%; employment = 89% working or in school; education = 89% > 12 years; income not reported	Non-randomized controlled pilot trial; 5-hour workshop; Setting: university hospital and clinics; Baseline, 2-, 6-, 12-week FU	(1) ACT + migraine psychoeducation (n = 31) (2) Waitlist/TAU (n = 14)	(a) Depression Sx (Hamilton Rating Scale for Depression/HRSD) (b) General functioning (World Health Organization Disability Assessment Schedule II/WHODAS) [M] (c) Migraine-related disability (Headache Disability Inventory/HDI)	(a) Group (1) decrease > Group (2) decrease at 12-week FU; Cohen's d = 1.18 (b) Group (1) increase > Group (2) increase at 12-week FU; Cohen's d = 0.98 (c) Group (1) decrease > Group (2) decrease at 12-week FU; Cohen's d = 1.03

Table 3.2, continued

	First author (year)	Population/ Condition	Participant characteristics	Study design, setting, intervention duration, assessment schedule	Intervention and comparator conditions	Outcomes and measures	Key Findings
4	Dindo (2014)[†]	Adults with migraine and depression (current depressive episode)	N = 45; M_{age} (SD) = 31.4 years (12.3); female = 94%; white = 87%; employment = 90% working or in school; education = 92% > 12 years; income not reported	Non-randomized controlled pilot trial; 5-hour workshop; Setting: university hospital and clinics; Baseline, 2-, 6-, 12-week FU	(1) ACT + migraine psychoeducation (n = 38) (2) Waitlist/TAU (n = 22)	(a) Headache frequency/severity (b) Acute headache medication use (c) Leisure and work disability (d) Visit to healthcare professional Note: all outcomes measured using daily headache diary	(a) Group (1) decreased in frequency (OR=0.57) and severity (OR=0.41) at 12-week FU, no change for Group (2) (OR=0.84, 1.0) (b) Group (1) decreased in acute medication use (OR=0.64) at 12-week FU, no change for Group (2) (OR=0.97) (c) Group (1) decreased in leisure disability (OR=0.56) and work disability (OR=1.0) at 12-week FU, no change for Group (2) (OR=0.78, 1.8) (d) At baseline, 20% of Group (1) and 22% of Group (2) attended medical visit in last month; at 12-week FU, 3% of Group (1) and 33% of Group (2)

Table 3.2, continued

	First author (year)	Population/ Condition	Participant characteristics	Study design, setting, intervention duration, assessment schedule	Intervention and comparator conditions	Outcomes and measures	Key Findings
5	Welch (2014)	Adults with diabetes mellitus type 2 with significant distress (either diabetes management regimen distress or emotional burden)	N = 31; M_{age} (SD)= 43 years (9.1); female = 70%; white = 45%; employment status not reported; M_{years} education (SD) = 13.9 (1.2); income not reported	Uncontrolled pilot trial; 8-hour workshop; Setting: psychology graduate school; Baseline, post-treatment, 2-week FU	ACT	(a) Self-care behavior (Summary of Diabetes Self-Care Activities scale revised version/SDSCA) (b) Diabetes-related distress (Diabetes Distress Scale 17/DDS17) total (c) Diabetes acceptance (AADQ) (d) Thought suppression (WBSI) (e) Depression (DASS-21) (f) Anxiety (DASS-21) (g) Stress (DASS-21)	(a) Baseline to FU mean difference on subscales: (1) General diet = 0.82; Cohen's d = 0.52 (2) Diabetes-specific diet = 0.62; Cohen's d = 0.61 (3) Exercise = -2.12; Cohen's d = 1.62 (4) Blood-glucose testing = 0.58; Cohen's d = 0.29 (5) Foot care = -1.29; Cohen's d = 0.76 (6) Smoking status = -0.9; Cohen's d = 0.22 (b) Baseline to FU mean difference on total score = -1.51; Cohen's d = 1.74 (c) Baseline to FU mean difference = 18.85; Cohen's d = 1.95 (d) Baseline to FU mean difference = 19.15; Cohen's d = 1.58 (e) Baseline to FU mean difference = -3.1; Cohen's d = 0.57 (f) Baseline to FU mean difference = -4.4; Cohen's d = 0.42 (g) Baseline to FU mean difference = -5.7; Cohen's d = 0.72

Table 3.2, continued

	First author (year)	Population/ Condition	Participant characteristics	Study design, setting, intervention duration, assessment schedule	Intervention and comparator conditions	Outcomes and measures	Key Findings
6	Dindo (2015)	Adults at risk for vascular disease* with clinically significant anxiety or depression Sx	N = 44; M_{age} = 45 years; female = 67%; white = 74%; employment not reported; education = 70% completed college; income not reported	Randomized controlled pilot trial; 6-hour workshop; Setting: university hospital and clinics; Baseline, 12- and 24-week FU	(1) ACT + psychoeducation (n = 30) (2) TAU (n = 14)	(a) General wellbeing (World Health Organization Quality of Life-BREF/WHOQOL-BREF) [M] (b) Depression (HRSD) (c) Anxiety (Hamilton Rating Scale for Anxiety/HSRA) (d) Psychological Flexibility/decentering (Experiencing Questionnaire/EQ)	(a) In Group (1), all four domains (physical, social, psychological, environment) improved at 24-week FU; in Group (2), only psychological domain was improved (b) Group (1) decrease > Group (2) decrease at 12- and 24-week FU; unspecified effect size = 1.4 at 24-week FU (c) Group (1) decrease > Group (2) decrease at 12- and 24-week FU; unspecified effect size = 1.5 at 24-week FU (d) Increase in Group (1) at unspecified FU; Group (2) results not reported

Table 3.2, continued

	First author (year)	Population/ Condition	Participant characteristics	Study design, setting, intervention duration, assessment schedule	Intervention and comparator conditions	Outcomes and measures	Key Findings
7	Hou (2017)	Adults with inflammatory bowel disease (IBD) and clinically significant anxiety or depression symptoms	N = 20; M_{age} = 51 years; female = 30%; % white not reported; employment not reported; education not reported; income not reported; n=9 with Crohn's disease, n=10 with ulcerative colitis, n=1 IBD unclassified	Uncontrolled feasibility study; 5-hour workshop; Setting: Veterans Affairs medical center and university medical school; Baseline, 3-month FU	ACT + IBD education	(a) Health-related Quality of Life (the Short IBD Questionnaire/ SIBDQ) (b) Depression (DASS-21) (c) Anxiety (DASS-21) (d) Stress (DASS-21) (e) IBD activity (Harvey Bradshaw Index for pts. with Crohn's/HBI) (f) IBD activity (partial Mayo score for pts with Ulcerative Colitis/pMayo)	(a) Baseline to FU mean difference = 0.5; Hedges' g = 0.41 (b) Baseline to FU mean difference = -2.1; Hedges' g = -0.39 (c) Baseline to FU mean difference = -2.6; Hedges' g = -0.65 (d) Baseline to FU mean difference = -1.9; Hedges' g = -0.39 (e) Baseline to FU mean difference = -0.5; Hedges' g = -0.15 (f) Baseline to FU mean difference = -1.2; Hedges' g = -0.47

Table 3.2, continued

	First author (year)	Population/ Condition	Participant characteristics	Study design, setting, intervention duration, assessment schedule	Intervention and comparator conditions	Outcomes and measures	Key Findings
8	Dindo (2018)	Veterans receiving orthopedic surgery at risk for chronic pain or prolonged opioid use**	*N* = 88; M_{age} (*SD*) = 63 years (10); female = 7%; white = 82.5%; employment not reported; education = 68% with some education greater than High School; income not reported	Randomized controlled pilot trial; 5-hour workshop; Setting: Veterans Affairs medical center; Baseline and 3-month FU for CPAQ and CPVI; DLPM submitted weekly for 14 weeks post-treatment	(1) ACT workshop + 1 individualized "booster" session by phone 2-4 wks following workshop (*n* = 44) (2) TAU (*n* = 44)	(a) Pain cessation (Daily Log of Pain and Pain Medication/ DLPM) (b) Opioid use/ cessation (DLPM) (c) Pain acceptance (Chronic Pain Acceptance Questionnaire total/CPAQ) (d) Values-based behavior (Chronic Pain Values Inventory/ CPVI)	(a) Median days to pain cessation was 66 for Group (1) and 74 for Group (2); HR = 1.42 [95% CI: 0.68, 2.95] (b) 29% of Group (1) taking opioids at 7 weeks v. 52% of Group (2); HR = 1.44 [95% CI: 0.74, 2.78] (c) Mean difference between Group (1) and (2) at FU = 2.07 [95% CI: -7.46, 11.61]; HR = 1.42 [95% CI: -7.11, 9.57] (d) Mean difference between Group (1) and (2) on 'mean success' at FU = -0.50 [95% CI: -1.01, 0.01]; HR = 0.13 [95% CI: -0.33, 0.59]; mean difference between Group (1) and (2) on 'discrepancy score' at FU = 0.21 [95% CI: -0.23, 0.65]; HR = -0.42 [95% CI = -0.85, 0.01]

Table 3.2, continued

	First author (year)	Population/ Condition	Participant characteristics	Study design, setting, intervention duration, assessment schedule	Intervention and comparator conditions	Outcomes and measures	Key Findings
9	Ferreira (2018)	Adults with refractory irritable bowel syndrome (IBS)	N = 79; M_{age} (SD) = 48 years (13); female = 93%; race/ethnicity not reported; employment not reported; education = 68% with post-secondary education; income not reported.	Uncontrolled pilot trial; 6-hour workshop followed by 2 months of bibliotherapy and 2 FU support calls; Setting: gastroenterology outpatient clinic; Enrollment, pre-treatment, post-treatment (2 months following pre-treatment), 6-month FU	ACT + IBS education workshop, bibliotherapy, 2 individualized support calls	(a) IBS Acceptance (IBS Acceptance and Action Questionnaire; IBSAAQ) (b) Symptom severity (IBS Symptom Severity Scale; IBSSSS) (c) Quality of life (IBS Impact on Quality of Life Scale; IBS36) (d) IBS avoidant behaviors (Behavioural Responses Questionnaire; IBS-BRQ) (e) Gastrointestinal specific anxiety (Visceral Sensitivity Index; VSI)	(a) Pre- to post-treatment mean difference = 7.24; Cohen's d = 0.32; Pre-treatment to FU mean difference = 9.82; Cohen's d = 0.50 (b) Pre- to post-treatment mean difference = -41.48; Cohen's d = 0.41; Pre-treatment to FU mean difference = -49.78; Cohen's d = 0.47 (c) Pre- to post-treatment mean difference = -17.41; Cohen's d = 0.41; Pre-treatment to FU mean difference = -23; Cohen's d = 0.55 (d) Pre- to post-treatment mean difference = -8.57; Cohen's d = 0.32; Pre-treatment to FU mean difference = -10.18; Cohen's d = 0.39 (e) Pre- to post-treatment mean difference = -6.3; Cohen's d = 0.76; Pre-treatment to FU mean difference = -8.73; Cohen's d = 1.10

Table 3.2, continued

	First author (year)	Population/ Condition	Participant characteristics	Study design, setting, intervention duration, assessment schedule	Intervention and comparator conditions	Outcomes and measures	Key Findings
10	Huddleston (2018)	Veterans with migraines and co-occurring depression (current depressive episode)	*N* = 32; Age = 36% under 45, 36% 45-55 years, 24% 56-65 years, 1% over 65 years; female = 36%; white = 24%; employment = 25% employed full- or part-time, 6% retired, 34% unemployed, 22% disabled, 13% student; education = 56% with some education greater than High School; income not reported	Uncontrolled pilot trial; 5-hour workshop; Setting: Veterans Affairs medical center; Baseline, 3-month FU	ACT + migraine education	(a) Depression Sx (HRSD) (b) Anxiety Sx (HRSA) (c) General functioning (WHO Disability Assessment Schedule II/WHODAS) (d) Headache-related disability (HDI) (e) Pain acceptance (CPAQ) (f) Values-based behavior (CPVI) (g) Psychological flexibility (Acceptance and Action Questionnaire/ AAQ-II)	(a) Baseline to FU mean difference = -7.95; Cohen's *d* = -1.93 (b) Baseline to FU mean difference = -6.57; Cohen's *d* = -1.84 (c) Baseline to FU mean difference = -5.38; Cohen's *d* = -0.38 (d) Baseline to FU mean difference = -7.44; Cohen's *d* = -0.39 (e) Baseline to FU mean difference = 8.48; Cohen's *d* = 0.48 (f) Baseline to FU mean difference = 0.5; Cohen's *d* = 0.48 (g) Baseline to FU mean difference = -5.53; Cohen's *d* = -0.71

Table 3.2, continued

	First author (year)	Population/ Condition	Participant characteristics	Study design, setting, intervention duration, assessment schedule	Intervention and comparator conditions	Outcomes and measures	Key Findings
11	Hadlandsmyth (2019)	Adult women undergoing surgery for breast cancer or ductal carcinoma in situ at risk for persistent postsurgical pain***	N = 62; M_{age} (SD) = 53 years (12); female = 100%; white = 87%; employment not reported; education not reported; income = 17% <$40,000, 24% $40,000-79,999, 59% $80,000+	Randomized controlled pilot trial; 2-hour individual session 2 weeks post-surgery; Setting: comprehensive cancer center; Baseline, 3-month FU	(1) ACT therapy + TAU (n = 24) (2) TAU (medical care) (n = 30)	(a) Pain intensity (0-10 scale) (b) Pain catastrophizing (Pain Catastrophizing Scale/PCS) (c) Depression (Patient Health Questionnaire-8) (d) Anxiety (Generalized Anxiety Disorder-7) (e) Pain acceptance (CPAQ)	(a) At FU, 8.3% in Group (1) reported moderate-to-severe pain v. 13.3% in Group (2); phi = 0.08 (b) At FU, 4.2% in Group (1) reported elevated pain catastrophizing v. 3.3% in Group (2); phi = 0.02 (c) At FU, 12.5% in Group (1) reported elevated depression v. 13.3% in Group (2); phi = 0.01 (d) At FU, 4.2% in Group (1) reported elevated anxiety v. 13.3% in Group (2); phi = 0.16 (e) Mean difference at FU = 1.66, favoring Group (1); Cohen's d = 0.10

Table 3.2, continued

	First author (year)	Population/ Condition	Participant characteristics	Study design, setting, intervention duration, assessment schedule	Intervention and comparator conditions	Outcomes and measures	Key Findings
12	Pedersen (2019)	Adults with multiple functional somatic syndromes (FSS)	*N* = 121 (for conditions of interest); M_{age} (*SD*) = 39 years (9); female = 83%; race/ ethnicity not reported; employment = 26% employed or student, 31% unemployed, 31% disability pension or flexible work; education = 31% greater than basic school (Denmark); income not reported; Functional Somatic Syndromes: 29% Irritable Bowel Syndrome, 79% Chronic Fatigue Syndrome, 74% Fibromyalgia, 74% tension headaches, 55% non-cardiac chest pain; average number of FSS = 3.9	Randomized, controlled, 3-arm trial; Setting: university general hospital; Baseline, 6-, 14, and 20-month FU	(1) ACT (6-hour workshop) + Enhanced Care (1-1.5 hour psychoeducation consultation with a physician 1-2 weeks after randomization) (*n* = 61) (2) Enhanced Care only (*n* = 60) (3) Extended ACT (nine 3-hr group sessions) + Enhanced Care (*n* = 59) Note: this review reports results comparing Groups (1) and (2) only	(a) Patient-rated overall health (5-pt clinical global improvement scale/CGI) (b) Physical Health (SF-36) (c) Mental Health (SF-36) Note: total of 18 secondary outcomes assessed, including: depression Sx, anxiety and somatic Sx (Hopkins Symptom Checklist/SCL-92; BDS checklist); illness worry (Whiteley-7); disability (WHODAS 2.0) [M]	(a) No difference between Groups (1) and (2) at 14-month FU (b) No difference between Groups (1) and (2), *p* = .98 at 14-month FU (c) No difference between Groups (1) and (2), *p* = .59 at 14-month FU Note: no significant differences between Groups (1) and (2) in change over time on the 18 secondary outcomes

Table 3.2, continued

	First author (year)	Population/ Condition	Participant characteristics	Study design, setting, intervention duration, assessment schedule	Intervention and comparator conditions	Outcomes and measures	Key Findings
13	Dindo (2020a)	Veterans with chronic pain, mild Traumatic Brain Injury (mTBI), and current diagnosis of MDD, GAD, or PTSD	*N* = 39; M_{age} (*SD*) = 36.6 years (6.2); female = 0%; white = 42%; employment = 51% employed full- or part-time; M_{years} education (*SD*) = 14.2 (1.7); Past month diagnoses: 68% PTSD, 54% MDD, 16% GAD; most severe TBI = 26% Stage 1 mTBI, 55% Stage 2 mTBI, 19% Stage 3 mTBI	Randomized controlled pilot trial; 5-hour workshop; Setting: Veteran Affairs medical center; Baseline, 3-month FU	(1) ACT + psychoeducation (*n* = 20) (2) TAU (*n* = 12)	(a) PTSD (Posttraumatic Stress Disorder Checklist; PCL-C) (b) Depression, Anxiety, and Stress (DASS-21 total) (c) Reintegration (Military to Civilian Questionnaire/ M2C-Q) (d) Disability (WHODAS 2.0) [M] (e) Pain Severity (Brief Pain Inventory/BPI) (f) Pain Interference (BPI) (g) Psychological flexibility (AAQ-II)	(a) Group (1) decrease > Group (2) decrease at FU; Cohen's *d* = 0.33 (b) Group (1) decrease > Group (2) increase at FU; Cohen's *d* = 0.68 (c) Group (1) improved, Group (2) worsened at FU; Cohen's *d* = 0.47 (d) Group (1) decrease > Group (2) decrease at FU; Cohen's *d* = 0.44 (e) No difference in Group (1) and Group (2) decrease at FU; Cohen's *d* = 0.10 (f) Group (2) decrease > Group (1) decrease at FU; Cohen's *d* = 0.78 (g) Group (1) increase > Group (2) increase at FU; Cohen's *d* = 0.56

Table 3.2, continued

	First author (year)	Population/ Condition	Participant characteristics	Study design, setting, intervention duration, assessment schedule	Intervention and comparator conditions	Outcomes and measures	Key Findings
14	Dindo (2020b)	Adults with migraines and co-occurring depression (current depressive episode)	*N* = 136; M_{age} (*SD*) = 35.8 years (13.9); female = 83%; white = 76%; employment = 81% employed or in school; education = 57% with more than 12 years of education; age of onset of migraines *M* (*SD*) = 19 (10.6); 31% taking antidepressants; number of migraine/headache days during month prior to baseline *M* (SD) = 7.4 (3.4); 87% taking abortive anti-migraine medication; 35% taking preventative anti-migraine medication	Randomized controlled trial; 5 to 6-hour workshop; Setting: hospital; Baseline, 3-, and 6-month FU	(1) ACT + migraine education (*n* = 56) (2) Support + migraine education (*n* = 47)	(a) Depression Sx (Hamilton Rating Scale of Depression/HRSD) (b) Current depressive episode (depression module of SCID-IV) (c) Anxiety (Structured Interview Guide for the Hamilton Anxiety Rating Scale/SIGH-A) (d) Headache-related disability (HDI) (e) General Functioning (WHODAS 2.0) [M] (f) Social relationship functioning (World Health Organization Quality of Life/WHO-QOL)	(a) Group (1) proportion of treatment responders > Group (2) at 3-month FU, $p < .05$, OR = 3.10 (b) Nonsignificant result for group (1) proportion of participants meeting criteria < Group (2) at 3-month FU, $p = .33$, OR = 0.54 (c) Nonsignificant result for group (1) proportion of treatment responders > Group (2) at 3-month FU, $p = .11$, OR = 2.45 (d) Group (1) proportion of treatment responders (i.e., ≥ 29 decline in total score) mean decrease > Group (2) at 3-month FU, $p < .05$, OR = 4.47 (e) Nonsignificant difference in mean improvement at 3-month FU, $p = .23$, Cohen's $d = 0.33$ (f) Group (1) increase > Group (2) increase at 3-month FU, $p = .01$, Cohen's $d = 0.62$

Table 3.2, continued

First author (year)	Population/ Condition	Participant characteristics	Study design, setting, intervention duration, assessment schedule	Intervention and comparator conditions	Outcomes and measures	Key Findings
14					(g) Environment (WHO-QOL) (h) Psychological well-being (WHO-QOL) (i) Physical health (WHO-QOL)	(g) Group (1) increase > Group (2) increase at 3-month FU, p = .05, Cohen's d = 0.47 (h) Nonsignificant trend for Group (1) increase > Group (2) increase at 3-month FU, p = .06, Cohen's d = 0.46 (i) Nonsignificant difference in mean increase at 3-month FU, p = .40, Cohen's d = 0.27

Note. *N* reflects the number of participants randomized (for studies with > 1 condition) or assigned to treatment (for single-arm studies); FU = follow-up; Sx = symptoms; *M* = mean; *SD* = standard deviation; TAU = treatment as usual; OR = odds ratio; HR = hazard ratio; SCID-IV = Structured Clinical Interview for DSM-IV; PTSD = posttraumatic stress disorder; MDD = major depressive disorder; GAD = generalized anxiety disorder. Unable to calculate effect sizes for Pedersen (2019). Effect sizes reported for studies with comparison conditions are between-group effects; effect sizes reported those studies without comparison conditions are within-group effects.

[†]Subsample from Dindo (2012) study, focused on headache outcomes
*At-risk defined as having hypertension, diabetes mellitus or impaired fasting glucose, dyslipidemia, or obesity
**At-risk defined as having high levels of preoperative pain and clinically significant anxiety or depression
***At-risk defined as under the age of 50, having a preexisting chronic pain condition, elevated anxiety, elevated depression, or elevated pain catastrophizing, assessed pre-surgery
M Included in meta-analysis

Table 3.3

Qualitative Description of Intervention Conditions

First author (year)	ACT condition	Comparison condition

1. Gregg (2007)	• Type: ACT + diabetes management education
	• Duration: 4 hours ACT, 4 hours education
	• Format: group
	• Content
	  o Education component included abbreviated version of the content described under 'comparison condition'
	  o ACT ("mindfulness and acceptance training") component included addressed difficult thoughts and feelings about diabetes, exploration of personal values related to diabetes, and a focus on the ability to act in a valued direction while contacting difficult experiences
	• Facilitator: doctoral student
		• Type: Diabetes management education
		• Duration: 7 hours
		• Format: group
		• Content: from patient education manual based on ADA diabetes education principles, including: diabetes disease process; nutritional management; importance of physical activity; diabetes medications; blood glucose monitoring; use of glucose results; and the prevention, detection, and treatment of complications
		• Facilitators: doctoral-level clinician or one of four master's-level graduate students

2. Sheppard (2010)	• Type: ACT + multiple sclerosis (MS) education
	• Duration: 5 hours
	• Format: group
	• Content: Didactic and experiential components
	  o Didactic components included: (1) psychoeducation about MS, (2) identifying the costs associated with the struggle to control unwanted thoughts, feelings, and physiological reactions linked with MS, (3) the importance of balancing acceptance and behavior change strategies, (4) values-clarification exercises, (5) using mindfulness and acceptance strategies to foster psychological flexibility when faced with MS-related barriers, and (6) using cognitive defusion techniques to reduce the behavioral impact of negative thoughts and feelings
	  o Experiential components not explicitly described
	• Facilitators: two licensed clinical psychologists
		n/a

Table 3.3, continued

First author (year)	ACT condition	Comparison condition

3. Dindo (2012)	• Type: ACT + migraine education
	• Duration: 4 hours ACT, 1 hour education
	• Format: group
	• Content
	  ○ Education component included: education about the pathology of migraine, risks for migraine chronification, migraine triggers, treatment of migraines, medication overuse migraine, and lifestyle factors contributing to migraine
	  ○ ACT component included both acceptance and behaviour change components, targeting: new ways of managing troubling thoughts, feelings, and pain sensations (e.g., learning how to recognize, and develop cognitive distance from, unhelpful thoughts and learning how to willingly face experiences that cannot be changed), teaching patients how to recognize ineffective patterns of behavior and habits, exploring and setting life goals and those related to health, and promoting effective and committed actions to achieve these goals
	• Facilitators: ACT component led by two licensed clinical psychologists; education component led by medical doctor specializing in headache medicine (neurology)
		• Type: Waitlist/TAU
		• Duration: Patients in the Waitlist/TAU group waited at least 12 weeks before receiving treatment
		• Note: no treatment was provided by the investigators during this time, but participants in the Waitlist/TAU group completed the same clinical assessments as the ACT-ED group. They also continued to take any medications they had been on at entry to the study.

4. Dindo (2014)[†]	Same as Dindo (2012)	Same as Dindo (2012)
5. Dindo (2015)	• Type: ACT + education • Duration: 6 hours • Format: group • Content: (1) education (cardiovascular risk factors, diet and lifestyle recommendations, and self-monitoring), (2) acceptance (new ways of managing troubling thoughts, feelings, and sensations), and (3) behavioral change (how to recognize ineffective patterns, set goals, and commit to action) • Facilitators: not described	• Type: TAU in the community

Table 3.3, continued

First author (year)	ACT condition	Comparison condition
6. Hou (2017)	• Type: ACT + inflammatory bowel disease education • Duration: 4 hours ACT, 1 hour education • Format: group • Content: not described • Facilitators: not described	n/a
7. Dindo (2018)	• Type: ACT workshop + 1 individualized "booster" session (+ TAU) • Duration: 5 hour workshop; "booster session" duration not specified • Format: group, individual • Workshop content: (1) Acceptance and Mindfulness Training emphasizing new ways of managing troubling thoughts, feelings, and physical sensations (e.g., learning how to recognize, and develop cognitive distance from, unhelpful thoughts such as "I can't take this pain anymore" or "This is too much to bear") and learning how to willingly face experiences that cannot be changed; and (2) Behavioral Change Training involving (a) teaching patients how to recognize ineffective patterns of behavior and habits, (b) exploring and setting life goals and goals related to mental and physical health, and (c) promoting effective and committed actions to achieve these goals despite the urge to do otherwise • Individualized "booster" session conducted over-the-phone with one of the workshop facilitators; delivered by phone 2-4 wks following workshop; content of individualized session not described in manuscript • Facilitators: two clinical psychologists • Note: participants in the ACT intervention condition also received TAU	• Type: TAU • Duration: not described • Format: group • Content: patient education class covering the post-operative course and what to expect for pain control and recovery • Facilitators: nurse(s)

Table 3.3, continued

First author (year)	ACT condition	Comparison condition
8. Ferreira (2018)	• Type: ACT + irritable bowel syndrome psychoeducation workshop; + 2 months of self-guided bibliotherapy; + 2 individual support calls • Duration: 6 hour workshop, 2 months of self-guided bibliotherapy, duration of support calls not specified • Format: group, individual • Content: (a) irritable bowel syndrome symptoms and diagnosis; (b) creative hopelessness; (c) acceptance; (d) values; (e) defusion; (f) defusion observer-self, present-moment awareness; (g) committed action; see manuscript for detailed description of exercises and metaphors • Facilitators: two clinical psychologists	n/a
9. Huddleston (2018)	• Type: ACT + migraine education • Duration: 4 hours ACT, 1 hour education • Format: group • Content: o ACT components: (1) behavioural change training (2 hr) involving (a) teaching patients how to recognize ineffective patterns of behavior and habits, (b) exploring and setting life goals and goals related to mental and physical health, and (c) promoting effective, committed actions to achieve these goals, despite the urge to do otherwise; and (2) acceptance and mindfulness training (2 hr) emphasizing (a) new ways of managing troubling thoughts, feelings, and physical sensations (e.g., "I can't take this pain anymore" or "I am not good enough") and (b) learning how to willingly face experiences that cannot be changed. o Migraine education components: information about symptoms of migraine, triggers for symptom worsening, risk for migraine chronification, how to use acute and preventive migraine medications, medication overuse, medical and psychological treatments of migraine, and migraine comorbidity • Facilitators: not described	n/a

Table 3.3, continued

First author (year)	ACT condition	Comparison condition
10. Hadland-smyth (2019)	• Type: ACT (+ TAU) • Duration: 2-hour individual therapy session 2 weeks after surgery (on the day of their surgical follow-up) • Format: see above • Content: (a) check-in about experiences in treatment, (b) values clarification, (c) brief mindfulness exercise, (d) differentiating between private events (thoughts, emotions, physical sensations) and behaviors, (e) acceptance and willingness exercises, (f) cognitive defusion exercises, and (g) committed action (including goal-setting) • Facilitator: either clinical psychologist or advanced counselling psychology doctoral student • Note: participants in the ACT intervention condition also received TAU	• Type: TAU • Content: medical care as indicated based on a combination of their pathology results, staging, hormone receptor status, genetic risk, discussion at tumor board, and stated patient preferences • Note: treatment involved surgery for all participants, radiation for most who underwent lumpectomy, chemotherapy as indicated, and frequently hormone therapy
11. Pedersen (2019)	• Type: ACT + bodily distress syndrome (BDS) education (+ enhanced care) • Duration: 6 hours • Format: group • Content: information about multi-organ BDS and introduction to ACT concepts such as acceptance, mindfulness, and life values • Facilitators: three therapists trained in ACT and management of BDS • Note: participants in the ACT intervention condition also received enhanced care	• Type: Enhanced care • Duration: 1-1.5 hours • Format: individual • Content: manualised follow-up consultation with the physician conducting the clinical assessment 1–2 weeks after randomisation; aimed at enhancing the patient's understanding of the BDS diagnosis, optimising further treatment initiatives in the healthcare system, increasing awareness of stress factors and motivation for lifestyle changes • Facilitator: medical doctor

Table 3.3, continued

First author (year)	ACT condition	Comparison condition
12. Dindo (2020a)	• Type: ACT + psychoeducation • Duration: 4 hour ACT, 1 hour education • Format: group • Content: ACT portion of the workshop included Behavioral Change Training (2 h), which involved 1) teaching Veterans how to recognize ineffective patterns of avoidant coping and behaviors; 2) exploring and identifying personal values; 3) setting specific, trackable goals aimed at fostering these values despite adversity and challenges, as well as Acceptance and Mindfulness Training (2 h), which involved 1) teaching new ways to manage troublesome thoughts, feelings and physical sensations to prevent their interference with valued life directions; and 2) teaching ways to cultivate present moment awareness. The psychoeducational component of this workshop included 1) reviewing the symptoms, and overlap of symptoms, of common problems among OIF/OEF Veterans (i.e., mTBI, PTSD, major depressive disorder, anxiety, chronic pain); 2) discussing resources available to Veterans. • Facilitator: two clinical psychologists • Note: recruitment was specifically single-gender (all male)	• Type: TAU • Format: standard care through the Veterans Health Administration system, including continued utilization of VHA psychiatric and medical services
13. Dindo (2020b)	• Type: ACT + migraine education • Duration: 5-6 hours • Format: group • Content: ACT component of the workshop emphasized approaches to managing troubling thoughts, feelings and pain sensations (e.g., learning how to recognize and develop cognitive distance from unhelpful thoughts, such as "I can't take this pain anymore," and learning how to willingly face experiences that cannot be changed), while promoting effective and committed actions to achieve life goals. The education component (1 h), developed by a headache specialist, involved educating participants about triggers and prodromes, risk factors for migraine chronification, effective use of medical treatments, and psychological and lifestyle factors known to contribute to migraine. • Facilitator: two psychologists	• Type: Support + migraine education • Duration: 5-6 hours • Format: workshop • Content: Same migraine education components as active treatment condition. Additionally, diaphragmatic breathing and passive progressive relaxation were taught and practiced. • Facilitator: two psychologists

Table 3.3, continued

First author (year)	ACT condition	Comparison condition
14. Welch (2014)	• Type: ACT • Duration: 8 hours • Format: group • Content: Protocol specifically targeted emotional distress symptoms; present-moment process, values identification, defusion, committed action, barriers to valued living, acceptance/willingness • Facilitator: doctoral student	n/a

Note. TAU = treatment as usual.
[†]Same parent study as Dindo (2012)

Integrated Discussion

The present research addressed gaps in the literature regarding measurement of quality of life and behavioral treatment considerations for adults with celiac disease. The first two studies demonstrated that (a) the CD-QOL is an acceptable measure of celiac disease-specific quality of life, and (b) there are subgroups of adult celiac disease patients with different patterns of persisting physical symptoms whose psychiatric wellbeing, functioning, and quality of life vary, who may benefit from behavioral intervention. The third study demonstrated that single-session ACT interventions are acceptable and feasible for addressing psychiatric symptoms, functioning, and quality of life in chronic health conditions broadly, suggesting these interventions may be appropriate for adults with celiac disease.

Specifically, Study 1 demonstrated that the CD-QOL assesses celiac disease-specific quality of life as a single construct and as four subconstructs: functional impact/limitations, stigma and mood, celiac disease-related health concerns, and perceptions of inadequate celiac disease treatment. CD-QOL total score and subscale scores demonstrated good internal consistency reliability, convergent validity, and known-groups validity. CD-QOL subscale scores showed limited incremental concurrent validity compared to SF-36 scores for predicting gluten-free diet adherence. Nevertheless, the CD-QOL assesses unique aspects of celiac disease-specific quality of life that would be appropriate targets for behavioral intervention, and therefore the CD-QOL may have incremental clinical utility as a screening and outcomes measure, which should be examined empirically.

Study 2 demonstrated that adults with celiac disease vary in overall persisting symptom severity, specific persisting symptoms, and perceptions of health. Patient subgroups derived from latent profile analysis differed significantly with respect to anxiety and depression symptoms,

limitations due to physical and emotional health, social functioning, and sleep disturbance. Across profiles, lower symptom burden did not necessarily translate to better mental health and quality of life. Even profiles with lower overall symptom burden demonstrated elevations in fatigue, headaches, food cravings, and physical pain, which were associated with significantly greater role limitations due to physical health and sleep disturbance, and lower general health, social functioning, and emotional wellbeing. Fatigue and pain are nonspecific extraintestinal symptoms common across various chronic illnesses, and are known to negatively impact mental health, functioning, and quality of life (Creed et al., 2013; Jaime-Lara, Koons, Matura, Hodgson, & Riegel, 2020; Matura, Malone, Jaime-Lara, & Riegel, 2018; Swain, 2000; Zautra, Fasman, Parish, & Davis, 2007). Given the frequency of persisting fatigue and pain, their impact on functioning and mental health, and the high prevalence of co-occurring health conditions in adults with celiac disease (96.5% in this sample), this population would likely benefit from adjunctive behavioral intervention.

ACT interventions have been shown acceptable, feasible, and effective for addressing functioning and quality of life deficits in chronic illness generally. Study 3 explored whether truncated, single-session ACT interventions are similarly effective. As reported in Study 3, systematic review and meta-analysis results suggest that single-session ACT is acceptable, feasible, and potentially effective for improving functioning, quality of life, and mental health across a variety of chronic illnesses, and well-designed RCTs are warranted. Results support the development and pilot testing of a brief ACT intervention to promote functioning, psychiatric wellbeing, and quality of life in adults with celiac disease.

Physical Symptoms and Celiac Disease-Specific Quality of Life

There was no association between symptom severity or patterns of persisting symptoms and celiac disease-specific quality of life in the present sample. This finding is consistent with research showing that quality of life is more strongly related to psychiatric symptoms, gluten-free diet adherence, and perceived difficulty of following a gluten-free diet than gastrointestinal symptoms (Barratt et al., 2011; Sainsbury et al., 2013b). Prior research has examined the relationship between overall gastrointestinal symptom burden and generic health-related quality of life, whereas the present research examined the relationship between total symptom burden and celiac disease-specific quality of life. The absence of association between total symptom burden and celiac disease-specific quality of life may be due to the nature of the domains assessed by the CD-QOL. That is, overall symptom severity may not be linearly associated with celiac disease-specific impacts on mood, social and lifestyle limitations, concerns about celiac disease-specific health implications, and perception of inadequate available treatment. In the present sample, difficulties maintaining a gluten-free diet may be more likely to impact celiac disease-specific cognitive, behavioral, and affective quality of life domains, as reflected by the positive associations between CD-QOL and CDAT scores.

Additionally, research suggests that the relationship between symptoms and quality of life may change over time, such that the relationship is stronger at diagnosis and weaker as years since diagnosis increase (Nachman et al., 2010). The present sample had a mean diagnostic latency of 6 years, with 8% within a year of diagnosis, 25% within 2 years of diagnosis, and 50% within 3 years of diagnosis. Thus, the strength of relationship between symptom severity and celiac disease-specific quality of life may be lower in the present sample than in samples of newly diagnosed individuals. Future research should consider time since diagnosis in examining

these relationships, especially as they relate to making recommendations for adjunctive behavioral or medical intervention.

Clinical Implications

It is well established that adults with celiac disease experience mental illness at higher rates than the general population (Alkhayyat et al., 2021; Clappison et al., 2020). In the present sample, mean anxiety and depression symptom scores were within one standard deviation of the U.S. adult population, but half reported lifetime diagnosis of a mental health condition and a quarter reported significantly elevated ($t \geq 60$) anxiety and depression symptoms, respectively. Findings about relative quality of life deficits in adults with celiac disease have been mixed (Ciacci et al., 2003; Roos et al., 2006). Mean generic health-related quality of life scores in this sample were within normal range; however, half the sample reported significantly elevated fatigue, and a smaller proportion (15-20%) reported significant pain interference, physical function, reduced ability to participate in social roles/activities, and sleep disturbance. Because there are no established cut-offs for the CD-QOL, it is unclear whether this sample presented with clinically significant celiac disease-specific quality of life deficits.

As shown in the present and prior studies, mental health and functioning are not linearly associated with overall symptom burden in adults with celiac disease. Rather, mental health and functioning are likely more strongly associated with other aspects of managing celiac disease (e.g., lack of social support for gluten-free diet adherence and perceived social isolation) and/or frequency of specific persisting symptoms. ACT interventions may be effective for improving psychiatric symptoms and functional limitations in celiac disease, regardless of symptom burden. For example, mindfulness and present moment awareness practices may reduce distress related to risk of gluten exposure. Values and committed action exercises may reduce avoidance of

personally-valued activities. Additionally, given that greater celiac disease-specific quality of life was associated with greater gluten-free diet adherence in Study 1, ACT interventions designed to improve celiac disease-specific quality of life may improve gluten-free diet adherence, and vice versa. Greater celiac disease-specific quality of life was also associated with lower anxiety and depression symptoms and greater generic health-related quality of life, and therefore behavioral interventions improving any of these variables may improve others. Intervention research would provide valuable insight into the longitudinal and causal nature of these relationships and possible moderators (e.g., time since diagnosis).

Cultural Considerations

The sample used in Studies 1 and 2 represents a cross-section of the U.S. celiac disease patient population that is mostly white, middle-aged, and female, with access to the internet and interest in research participation. While white women make up the majority of known celiac disease cases in the U.S. (Caio et al., 2019; Choung et al., 2015; Mardini, Westgate, & Grigorian, 2015; Singh et al., 2018; Stahl et al., 2021), they may nevertheless be overrepresented in the present sample. Moreover, there are known disparities in celiac disease testing, diagnosis, and treatment in the U.S. People of color, men, older people, and people of lower social economic means are systematically underdiagnosed and therefore underrepresented in public health data and celiac disease research (Anyane-Yeboa et al., 2021; Lebwohl et al., 2012). It should also be noted that in studies reviewed for Study 3, the average inclusion rate of female participants was 61% and the average inclusion rate of participants identifying as white was 61%. Mean sample age ranged from 33 to 63 years (median: 46.5; M = 46, SD = 8.5). Thus, the present findings may not generalize to other sociodemographic groups in the U.S. (Krigel et al., 2016) and abroad.

In Study 2, the group with the highest symptom burden reported lower education level and household income than the two lowest overall symptom burden groups. Education level and income may relate to symptomology and subjective health through access to healthcare, systemic bias, accessibility of nutrient-dense gluten-free food, knowledge about gluten exposure risk, and social support for gluten-free diet adherence. There is also a demonstrated relationship between food insecurity and lower gluten-free diet adherence (Ma et al., 2021). Thus, the relationship between symptoms, gluten-free diet adherence, and quality of life may differ in strength and mechanism among people of greater and lesser socioeconomic means, and these differences may require distinct intervention approaches.

Future Research

Together, findings from Studies 1-3 support the development and pilot testing of a single-session ACT intervention for addressing functional limitations, psychiatric symptoms, and behavioral aspects of managing celiac disease. Such a pilot study should assess treatment acceptability, demand, implementation, practicality, adaptation, integration, and expansion, and conduct limited-efficacy testing (Bowen et al., 2009). Such a study could administer the CD-QOL and a generic health-related quality of life instrument to further examine psychometric properties of the CD-QOL (e.g., test-retest reliability, sensitivity to change, incremental predictive validity), and examine preliminary efficacy of the intervention. The study could also administer ACT process measures to explore the purported mechanisms underlying outcome changes (e.g., acceptance and committed action). Such a pilot study should recruit adult celiac disease patients from diverse backgrounds in order to (1) increase representation and (2) allow for examination of cross-cultural equivalence of the psychometric properties of CD-QOL scores. Strategies for increasing diversity might include recruiting from rural and urban primary care

clinics rather than recruiting only from tertiary treatment centers or patient advocacy groups and ensuring financial compensation for participation.

Limited qualitative studies describe the lived experience of U.S. adults managing celiac disease, and those results should be used in the design and implementation of novel behavioral interventions (Leffler et al., 2017). However, due to underrepresentation of patients of color, male patients, and patients from lower socioeconomic backgrounds in all types of celiac disease research thus far, it is recommended to conduct novel qualitative research among these groups to inform development of a culturally-sensitive and effective intervention. Ultimately, such an intervention could be delivered through primary care or specialty clinics, in a single visit, and perhaps virtually to increase access.

Conclusion

Adults with celiac disease report negative impacts of the condition and its management on mental health, functioning, and quality of life. These individuals may be particularly concerned about negative impacts of adhering to a gluten-free diet on social and lifestyle functioning, stigma, the impact of celiac disease on their long-term health, and inadequacy of the gluten-free diet as the sole treatment for celiac disease, regardless of physical symptom burden. Many celiac disease patients would likely benefit from the development and implementation of accessible behavioral interventions to address these concerns. In screening to determine possible need for adjunctive behavioral intervention, it is crucial to directly assess psychiatric symptoms and various aspects of quality of life rather than using overall symptom burden as the sole indicator. Screening for psychiatric symptoms and quality of life in routine clinical encounters would provide opportunity for referral to behavioral healthcare providers, which may reduce disparities in mental health among adults with celiac disease.

It is imperative that healthcare systems improve identification of celiac disease cases in diverse populations, and that public health and behavioral researchers intentionally recruit and retain celiac disease patients of various cultural identities to participate in both observational and experimental research. Partnerships between advocacy groups and non-governmental organizations like that of *Beyond Celiac* and the National Minority Quality Forum are an initial step toward addressing celiac disease health inequities and improving outcomes for underserved celiac disease patients.

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