Psychological Sequelae in Coeliac Disease:

Cross-Sectional and Longitudinal Studies of Mood, Cognition, and Quality of Life

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Statement of Authorship

Except where explicit reference is made in the text of the thesis, this thesis contains no material published elsewhere or extracted in whole or part from a thesis by which I have qualified for or been awarded another degree or diploma. No other person's work has been relied upon or used without due acknowledgment in the main text and reference list of the thesis.

Signature: _____

Date: _____

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Abstract

In coeliac disease (CD), dietary gluten – a ubiquitous protein in wheat, rye and barley derived foods – degrades intestinal absorptive function. Untreated CD involves a cascade of autoimmune modulated health effects in genetically predisposed individuals, with a worldwide CD prevalence in European origin populations of about 0.3% to 1%. Resultant physical problems in undetected or sub-optimally treated cases include anaemia and reduced bone density, with the risk of intestinal lymphoma and overall mortality increased. Depression and reduced life quality are also commonly reported pre- and post-diagnosis. Gut restitution and general health restoration is incumbent upon strict, lifelong avoidance of gluten ingestion and maintaining the diet is a challenge in itself. At any time only around one in five to ten probable CD cases are actually diagnosed, owing to an insidious onset in minimal-symptomatic cases and a kaleidoscopic clinical presentation. Studies of the psychological ramifications of CD comprise a small proportion of burgeoning international research into the pathogenesis and genetic underpinnings. The goal of the thesis was to investigate psychological functioning in CD at different stages of treatment with the gluten-free diet (GFD), both cross-sectionally and longitudinally.

Study 1 involved a clinically heterogeneous biopsy-confirmed Australian CD group aged 16 to 84 (mean 41 years; n = 110; 60% female). Mean age at diagnosis was 36.9 years (range 1-84, SD = 15.4), occurring after the age of 19 years in 87% of cases. Participants with CD undertook 5-6 hours of clinical interviewing and assessment. They were compared with two age-, sex-, education-, socioeconomic status-and IQ-matched comparison groups; 69 healthy volunteers, termed normal controls (NCs) and 53 people with diabetes mellitus (DM; Type-1 = 36; Type-2 = 17). The normal and chronic illness comparison groups were recruited in an analogous way to the CD group and subject to identical assessment procedures. Individual evaluation across key demographic, health-related, affective, cognitive and behavioural domains involved use of the *Beck Depression Inventory, 2nd Edition* (BDI-II; 1996), the full *Wechsler Adult Intelligence Scale, 3rd Edition* (WAIS-III; 1997), Spielberger's *State-Trait Anxiety* (1983) and *State-Trait Anger Expression* (1988) *Inventories* and the *Quality of Life Questionnaire* (QLQ; Evans & Cope, 1989). Results: In neuropsychological (WAIS-III) testing, the CD sample had reduced working memory (WM) and processing speed (PS) compared to NCs. These differences held when the CD sample was subdivided into low, medium or high subgroups, based on total IQ, age at study entry, age or number of symptoms at CD diagnosis and time on or compliance with the GFD. The results were also significant irrespective of gender, although the clear processing speed difference was accentuated in male, compared to female, participants with CD. A subgroup of two thirds of the CD sample, retrospectively assessed at study commencement as clinically multisymptomatic at the time of CD diagnosis, had significantly higher BDI-II depression (of somatic-affective origin), trait anxiety and state anger, as well as reduced quality of life (QOL), compared to the healthy (but not chronic illness)

comparison groups. State anxiety was higher in the multisymptomatic CD subgroup vis-à-vis both comparison groups, regardless of gender. Across the full CD sample, retrospective self-reported health status was markedly lower prior to diagnosis in relation to each comparison group. Unlike participants with DM, whose self-rated health status declined slightly pre- to post-diagnosis, a significant increase in subjective health status was reported in the CD group following diagnosis. Nevertheless, the multisymptomatic subgroup still rated their health status following diagnosis (i.e., at study enrolment) as below healthy control levels. Upon gender partitioning, statistical significance only held for females. The lack of perceived health improvement in the chronic illness comparison group pre- to post-diagnosis was attributed to the almost inevitable, eventual deterioration of health associated with DM, as distinct from CD, in which a remission of health problems is generally observed following consistent adherence to the GFD. Nevertheless, almost one in three participants who were multisymptomatic at CD diagnosis were at least mildly depressed at study entry. Discriminant function analysis, using equally weighted static and dynamic diagnostic, dietary and temporal correlates, was undertaken to determine if a combination of readily available or obtainable clinical information was useful in predicting psychological functioning. This process correctly predicted group membership of three in four CD participants, each classified beforehand as either non-depressed or above the minimum cut-score conferring BDI-II depression at study entry. Of major clinical relevance was the high reliability and reasonable specificity of this straightforward procedure. Seven out of ten non-depressed CD participants were correctly classified, with identification of more than eight out of ten who were depressed. Since only easily procurable clinical information was utilised and false positives could be screened via psychometric assessment or clinical interviewing, this accurate, brief, cost-effective analysis would appear to have significant practical utility as an adjunct in mental health intervention considerations in the care of CD patients.

Study 2 involved the reassessment, one year later (i.e., at T_2), of one quarter of the full cross-sectional CD sample ($n = 27$; 14 females, 13 males) who had been diagnosed with CD for less than nine weeks at initial assessment (T_1) in Study 1. These participants were reassessed using an identical protocol. A subgroup of ten healthy volunteers was also reassessed, principally to monitor inherent retesting effects in the WAIS-III and test-retest stability of other measures used. In general, the longitudinal CD group reported initial GFD compliance, which had been sustained at T_2.

Results: Perceived health status pre-to post-diagnosis increased, verifying the same finding at study entry. State anxiety decreased between T_1 and T_2 and a trend towards a decrease in mean BDI-II scores (underpinned by change in the somatic, as opposed to the cognitive, dimension of self-reported depression) was observed, in addition to slight decreases in trait anxiety, state and trait anger. The *Profile of Mood States* (POMS; McNair, Lorr, & Droppleman, 1971) was administered to the longitudinal CD group at T_1 and T_2, to corroborate any shifts in affect identified by the primary

aforementioned measures. Changes between T_1 and T_2, in order of descending strength of significance, were decreases in fatigue-inertia (which held across gender), confusion-bewilderment and anger-hostility A total mood disturbance score, based on the summation of all six POMS subscales, was also found to significantly decrease, although depression-dejection did not significantly change. One year on the GFD was not associated with a significant improvement in QOL and one third still exhibited low QOL. A 3-point rise in full IQ, not above a level that could be accounted for by a practice effect, occurred within the CD group, with residual index-specific weaknesses in WM and PS compared to NCs.

Summary: Each study detailed in the thesis highlighted that the psychological sequelae observed in CD are typically juxtaposed with markers of clinical severity at diagnosis and physical symptomatology post-diagnosis. For many – but not all – of those newly diagnosed, mood state ameliorates in concert with recession of physical symptoms in response to a strict GFD sustained over the passage of time. However, the specific neuropsychological deficits may be relatively refractory to dietary change. Increased symptomatic duration prior to diagnosis significantly impacted on the degree of impairment, underlining the essence of early detection. Furthermore, self-reported depression affected about one third of multisymptomatic CD participants at study enrolment and remained elevated in almost one-quarter of all newly diagnosed CD study entrants at one year follow-up. Multisymptomatic members of this longitudinal group did not quite attain, on average, the same QOL as NC participants, with a significantly greater proportion reporting low QOL. These results suggest that, following CD diagnosis, psychological intervention should be considered in conjunction with ongoing specialist medical advice and expert dietary assistance.

Chapter 1: Introduction to Coeliac Disease

The National Heart Foundation of Australia, state anti-cancer councils and various government bodies have advised the public of the dangers of contemporary Western eating habits (Craig, 1988). These include excessively high saturated fat, salt and refined sugar consumption and inadequate fibre intake (Stanton, 1995). Australians in at-risk groups, including people with hypertension, raised low-density lipoprotein (LDL) cholesterol and diabetes mellitus, have also been alerted to the benefits of modified nutritional regimens (Lester, 1994). Campaigns financed by the business sector have advocated the inclusion of particular foods. For example, women have been encouraged by the beef industry to eat more red meat in advertisements highlighting purported links between a wide range of frequently experienced, everyday symptoms (e.g., tiredness), anaemia and low dietary iron (e.g., "Red Meat, Feel Good"; Gardiner, 2001).

Similarly, osteoporosis has been coupled with inadequate dietary calcium by the Australian Dairy Corporation (2001). This link contrasts with current medical opinion that "the long-term effect of a high dietary calcium intake on bone health is unclear" (Delmas, 2002, p. 2022). Evidence exists that, in adults, increased calcium ingestion per se, whether from milk or other foods, does not actually reduce the incidence of hip fracture and may even be counterproductive (Feskanich, Willett, Stampfer, & Colditz, 1997). The reality may sound extraordinary, against the powerful resonance of pro-dairy messages to the contrary, which saturate advertising space, seduce and profoundly influence consumer choice (Schelling, 1996). These campaigns include; "Milk. Are you getting enough?" (1994-98) and "Milk, Legendary Stuff" (1998-99), both highly successful Australian marketing promotions (Davey, 2000).

At the base of the food guide pyramid advocated by health educators and nutritionists (Baron, 2002, p. 1269), are breads and cereals, with 6-11 daily servings recommended, ahead of even fruit or vegetables (2-4 and 3-5 servings respectively). Bread, whether in a loaf or sliced, in rolls, buns, muffins, pastries and even rusks for babies, remains the venerated "staff of life". This is attributable

to historic, economic and social – as well as health – considerations. Naturally low in fat, high in complex carbohydrates if unrefined, and full of, or fortified with, fibre, wheat-based breads are especially inexpensive to mass-produce. They are palatable, readily available, versatile and convenient, having been embraced by European culture since Biblical times. Pasta was a homemade, mostly ceremonial food in Middle Ages Europe (Greco, 1991), but, like bread, became gluten-enriched after the Renaissance (Greco, 1997) and more widely available after the Industrial Revolution (Feldman & Sears, 1981).

Vegetarianism's mid-late twentieth century resurgence (Waerland, 1979; Whorton, 1994), underpinned by ecological, ethical, religious and health concerns (Worsley & Skrzpiec, 1998), was contemporaneous with the Pritikin-inspired diet, based on grains, pasta and plant-based foods. Each movement was buoyed by associations between saturated fat and elevated cholesterol, weight gain and atherosclerosis (Hetzel & McMichael, 1989). A lynchpin of the low glycaemic index (G.I.) solution for blood sugar control, weight loss, diabetes and heart disease management, pasta was again popularised during the preceding decade as a "...fabulous low G.I. food...to eat more of" (Miller, Foster-Powell, Colagiuri, & Leeds, 1996, pp.143-144). Miller et al.'s international best-selling book, based on sixty research papers addressing the glycaemic index of foods, was strongly endorsed by Zimmet (1996), director of Melbourne's International Diabetes Institute. These influences have heralded the revived promotion of pasta, cereal and bread, as part of a low G.I., cholesterol-free, environmentally friendly and low-cost panacea for many of the Western world's major health problems associated with dietary imbalances and excesses.

Maintaining the bread group as a foundation stone of healthy eating has been an overwhelming success. It would therefore surprise many health-conscious people that, over time, "as people put more pasta and bread in their diets, they increased their risk of diabetes by two-and-a half times" (Fuhrman, 1998, p. 123). Furthermore, the ingestion of these foods is immediately and acutely toxic for a significant minority of people. Affecting 0.3% to 1.1% of European origin populations (Greco, 1997; Meloni, Dore, Fanciulli, Tanda, & Bottazo, 1999) is a disease often overlooked as a possible

cause of gastronomic distress, anaemia, skin inflammation, osteoporosis, depression, infertility and even neurological disorders, lymphoma, and increased mortality if undetected (Nielsen et al., 1985; Club del Tenue Study Group, 2001; Catassi et al., 2002).

This readily treatable illness has largely escaped the glare of public health campaigns, and a degree of scrutiny in general medical practice commensurate with its prevalence and seriousness. While reliable testing exists, at least six out of seven people in the developed world and a higher proportion in non-Western nations probably escape diagnosis (Catassi et al., 1996). For all of these reasons, coeliac disease (CD) qualifies as a major identifiable worldwide health problem. It remains "hard to imagine that the single most common food intolerance to the single most common staple food in our environment might provoke such a variety of adverse immuno-mediated reactions in any part of the human body" as those medically documented in CD (Greco, 1997, p. 19).

Given the dearth of research in Australia investigating the psychological impact of CD in the small proportion of detected cases and the aforesaid social forces and culinary conventions that exacerbate the problem, CD is the consummate challenge for health educators and uncharted terrain for clinical/ health psychology. At an annual state meeting for health psychologists[1], lack of CD awareness in these circles was apparent. The author observed that few people amongst those present had actually heard of CD. Only one person later identified herself as being familiar with the condition in any detail. Her older sister had, quite coincidentally, been diagnosed just a week earlier.

Public and professional nescience may both contribute to the likelihood of missed or mis-diagnosis, but, combined with increased awareness, has also lead to the significant percentage of CD cases identified in recent times in adulthood, often following long periods of unspecified ill health throughout life (Sollid & Lundin, 2001). The old adage that "doctors do not diagnose diseases they do not know" is often applicable to CD. For those affected, a delay or absence of an accurate diagnosis and treatment may be catastrophic in health terms. This chapter briefly reviews the historical

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[1] Victorian Section of the Australian Psychological Society College of Health Psychologists, AGM, Melbourne; Australia, September, 1998

aspects, aetiological underpinnings, pathogenesis and worldwide epidemiology of CD, its heterogeneous clinical presentation, current diagnosis and treatment guidelines, contemporary research trends, food labelling practice standards, diagnostic screening and other micro- and macro-level issues pertaining to the interface with clinical and health psychology.

History

References to gastrointestinal (GI) maladies were written in Sanskrit as long ago as 1500 BC (Hunter, 1987). The earliest known description of a CD-like malabsorption condition was made by a second century AD physician, Aretaeus (Adams, trans. 1856; cited in Thomas, 1948). Aretaeus was from Cappadocia, an eastern department of the Roman Empire and today part of Turkey, where the first traces of wild wheat and barley were originally cultivated (Greco, 1997). Within Adams' translation (Thomas, 1948), signs of "atony" throughout the GI tract – familiar nowadays in classic CD cases – were noted, including "eructations" (belching) and flatulent "evacuations", as well as observations of "the patient [as] emaciated and atrophied, pale [and] feeble" (p. 600). The illness itself was described as "very protracted and intractable", being found in children, older people and in "women rather than to men" (p. 601). The accompanying diarrhoea in children was attributed to an "ephemeral [i.e., transitory] intemperance to food" (p. 601). Aretaeus has also been credited with coining the term *coeliac*, from the Greek word *koilia* (meaning "belly"), to denote the abdominal distension and diarrhoea experienced by those afflicted (Ciclitira & Ellis, 1997). Further descriptions of GI syndromes consistent with CD symptomatology ensued, with various unsavoury or chimerical remedies offered, including one recorded by Oxford's Robert Lovel, quoting Pliny in 1661 (Rawcliffe & James, 1985): "The hee-goot spleen rosteth, helpeth the coeliak" (p. 17).

The Dutch physician Vincent Katelaer described the ailment "Stomatitus Aphthous" in a 1669 treatise on "spruw" [*sic*], noting small ulcers in the intestines and mouths of diarrhoea sufferers (Hunter, 1987). Sprue came to refer to chronic enteritis encountered in the tropics, with CD sometimes designated "non-tropical sprue". It was more than two hundred years later, in his 1888 paper "On the

Coeliac Affection", that Samuel Gee of London provided the first clear description of CD as a specific condition, as documented by Walker-Smith (1988) at the 5th Coeliac Meeting in London:

> There is a kind of chronic indigestion, which is met with in persons of all ages, yet is especially apt to affect children between 1 and 5 years old ... Signs of the disease are yielded by the faeces, being loose, but not watery, bulky and pale. The onset of the disease is usually gradual ...Cachexia[2] is a constant symptom. The belly is mostly soft, often distended (p. 1).

Gibbons (1889) described the characteristic emotional symptoms of a child with CD a year later (cited in Gardiner, Porteous, & Walker-Smith, 1971, p. 39): "The temper of the child seems variable, most frequently he is extremely irritable, fretful, capricious or peevish. Nothing seems to please him and altogether he is unlike himself". Despite Gee's unmistakable description and an archetypal limn illustrated by Gibbons, the cause of what became known as chronic intestinal infection, or recurrent diarrhœa in childhood (see Still, 1918), remained obscure. The most prominent cases usually appeared in infancy and typically succumbed to acute infantile diarrhoea (Visakorpi, 1997).

Dutch paediatrician Willem Dicke made a curious observation half a century after Gee's initial description of CD. Dicke (1950) found that children with chronic intestinal infection in Nazi-occupied Holland improved under conditions of near starvation, when Dutch wheat was sent to Germany, but deteriorated again after World War II, as wheat became readily available. Suggesting that grains might be a causative factor, Dicke (1950) became the first person to show that flour from wheat and other grains produced CD symptoms in children with the illness, generalising his finding to all ages. This was to prove the aggiornamento of CD research and patient care. The hybrid term "coeliac sprue", synonymous with gluten intolerance, thus emerged.

With a team of researchers at the University of Birmingham, the late Australian pioneer Charlotte Anderson, described variously by peers as the "mother" (Myers, 2002, p.1) and "grandmother of paediatric gastroenterology"; Walker-Smith, p. 589), subsequently isolated gluten as the noxious component of wheat flour in those susceptible. Anderson et al. (1952) had their results verified by van

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[2] Cachexia is a condition of extreme malnutrition, with chronic disability of body or mind

de Kamer, Weijers and Dicke (1953), who established that the gliadin fraction of gluten in wheat protein was especially toxic for people with CD. Paulley (1954) noted atrophy of the villi in the intestines of untreated CD cases. Anderson shared the new CD results with sceptical paediatricians on a tour of hospital centres in the United States, during which she found gastroenterologists working with adults more easily persuaded by the Dutch and English results (Allen, 1996). On her return to Australia, Anderson instigated small intestinal bioptic testing for CD and prescribed diets free of wheat gluten to CD patients at the Royal Children's Hospital in Melbourne (Anderson, Townley, Messer, & Hubbard, 1962). With various commercial millers and bread makers, she pioneered the development of local gluten-free breads suitable for CD sufferers (Allen, 1996).

Prior to the introduction of the gluten-free diet (GFD), published mortality rates in CD ranged from 10-30% (Hardwick, 1939; Ciclitira, 2001). Sakula and Shiner (1957) were the first to demonstrate, via histological examination of an upper intestinal biopsy, proof of mucosal atrophy in a child with CD similar to that found in "thirteen adult cases of ideopathic steathorrhœa", which these authors said "may be one and the same disease" (p. 877). "For many decades" – until this finding – "anatomical lesions of the small intestine in children with cœliac disease [had] been suggested by some authors and denied by others" (p. 876). Margot Shiner's pioneering work (Hancock & Shiner, 1958; Shiner, 1956, 1959) consequently opened the way for modern diagnostic techniques.

Definition, Aetiology, Heredity and Pathogenesis

In CD, also known as gluten-sensitive enteropathy, and still referred to as celiac sprue in most North American medical texts, the intestinal absorptive surface in susceptible individuals is damaged by dietary gluten, a ubiquitous protein in foods derived from wheat, rye, barley and various combinations of these grains (e.g., triticale/ spelt; Farrell & Kelly, 2002). The intolerance to ingested gluten is permanent (Troncone, Greco, & Auricchio, 1996), appearing classically in infancy upon exposure to gluten after weaning, or in early childhood. However, CD may manifest clinically at any age. Breast feeding duration, age at which gluten is introduced into the infant diet, length of period

during which both breast milk and gluten are given, amount of gluten consumed and infectious agents (e.g., adenovirus type 12) are all early environmental factors of apparent importance in disease onset (Ascher, Krantz, Rydberg, Nordin, & Kristiansson, 1997; Fälth-Magnusson, Franzén, Jansson, Laurin, & Stenhammar, 1996; Sollid, 2002). Pre-diagnostically silent (i.e., symptomless), latent or mild cases often emerge insidiously – or recur in many instances of undiagnosed childhood CD – after adolescence and throughout adulthood (Duggan, 1997; Gracey & Anderson, 1969). Adult-detected cases may have been preceded by months, years or decades of very subtle to severe CD-related symptoms or unspecified ill-health, with non-specific or atypical (non-GI) coeliac features.

Untreated CD involves a cascade of autoimmune modulated health effects in genetically predisposed individuals, with a subtle interplay between genes and environment (Sollid et al., 2001). An "...inappropriate T-cell mediated immune response against ingested gluten" that jeopardises the tight, intercellular junctions in the intestinal epithelium, characteristically increases gut permeability in the "early phase of CD" and "may be responsible for the increased incidence of autoimmune disorders reported in untreated CD...", as elucidated by Allesio Fasano (2000, p. 769), Professor of Pediatrics, Medicine, and Physiology and Director of the Center for Celiac Research, Baltimore, Maryland (see also Fasano et al., 2000).

A genetic predisposition to CD has long been recognised (Ebbs, 1950). Concordance between identical twins, believed to be at least 70% (Susi, Holopainen, Mustalahti, Mäki, & Partenen, 2001; Trier, 1991), is probably higher, given that some discordant individuals later diagnosed appear to have had latent (i.e., clinically quiescent) CD (Mäki & Collin, 1997). Recent Italian research in fact revealed concordance rates between (genetically identical) monozygotic twins of 0.86 proband wise and 0.75 pair wise, versus dizygotic rates of 0.20 proband wise and 0.11 pair wise (Greco et al., 2002). Since dizygotic twins are not more alike genetically than other siblings, but share a common environmental background, these authors noted that their research design afforded a "powerful means of assessing the weight of genetic and environmental factors...with substantial evidence for a very strong genetic component in CD" (p. 624). Approximately one third of siblings

and 10% of first degree relatives of people with CD are usually affected (Partanen, 1997).

At least nine out of ten CD patients carry a combination of two human leukocyte antigen (HLA) alleles on chromosome 6 (HLA-DQA1*0501 and HLA-DQB1*02), but so do about 20% of healthy European controls (Peña, Garrote, & Crusius, 1998). Based on the familial clustering of CD, non-HLA genes may collectively have more influence upon who develops CD (Sollid & Lundin, 2001). Although individual contributions from each single, hypothesised, predisposing non-HLA gene are relatively small (Zhong et al., 1996), evidence is accumulating for the role of CTLA4 on chromosome 2, a regulator of T-cell function, in susceptibility to CD (Djilali-Saiah et al., 1998; Holopainen et al., 2000, 2001; King et al., 2002; Popat, Hearle, Bevan et al., 2002).

Small bowel villous atrophy, crypt hyperplasia and decreased villous height-to-crypt depth ratio are morphological changes observed at the small intestinal mucosal surface, in the duodenum and proximal jejunum, at CD diagnosis (Fasano & Catassi, 2001). There is also a proliferation of intraepithelial lymphocytes (Selby, 2001). Figure 1 overleaf shows images of villi pre- (top) and post-diagnosis (bottom) sourced from www.gesa.org.au publications – professional CD guidelines. The severity of mucosal inflammation, damage at pathologic sites, length of intestine and extent of intestinal surface involved are highly variable (Barr & Grehan, 1998). Mucosal changes range from minor villous blunting or partial atrophy (with patients often presenting clinically as oligo[3]symptomatic or asymptomatic), to subtotal or total villous atrophy, in classic and multisymptomatic cases (see Fasano & Catassi, 2001, p. 645, for a pictorial display of the range of histological grades of atrophy).

Cells constituting normal, frond-like functional villi (microscopic intestinal projections) are involved in the digestion and absorption of all nutrients, including vitamins, minerals, proteins, fats and simple carbohydrates. In CD, widespread or even patchy damage to the absorptive surface of the intestines thus results in various degrees of malabsorption of most nutrients. Impaired assimilation of lipids significantly limits uptake of the fat-soluble vitamins (A, D, E, and K), also forcing the body to

[3] General (Greek-derived) medical prefix; useful in describing CD cases with few or slight symptoms of illness (from Gk. *oligos*: small, *oligios*: few); used by Aldao del Rosario (1992) and other CD researchers

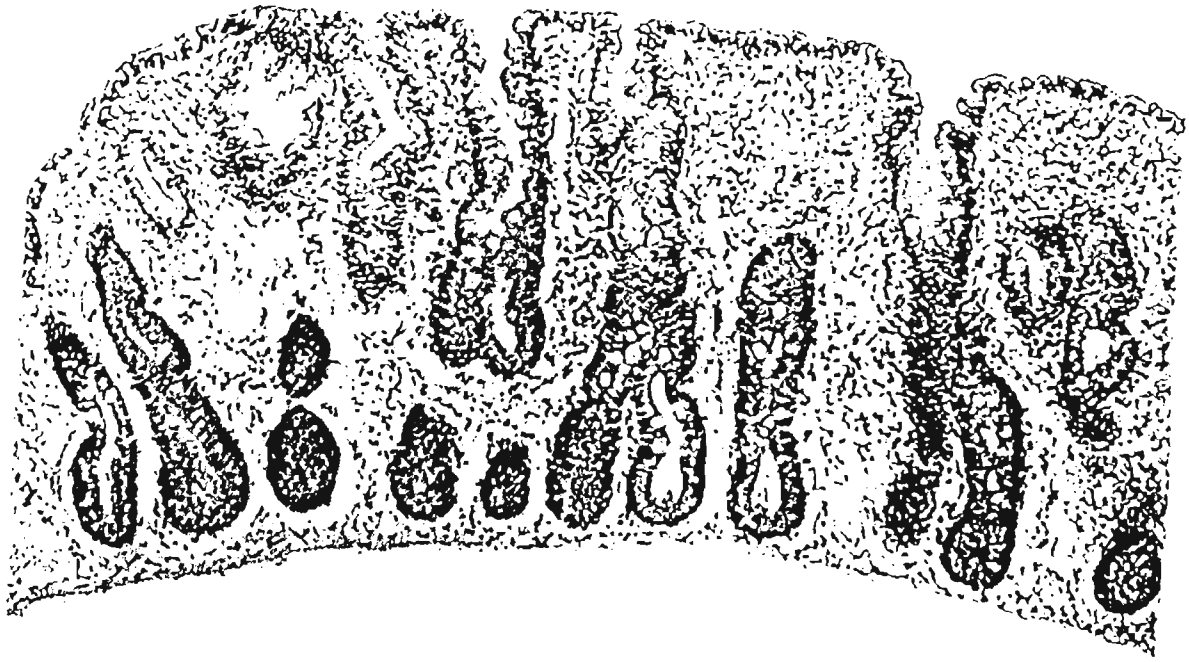
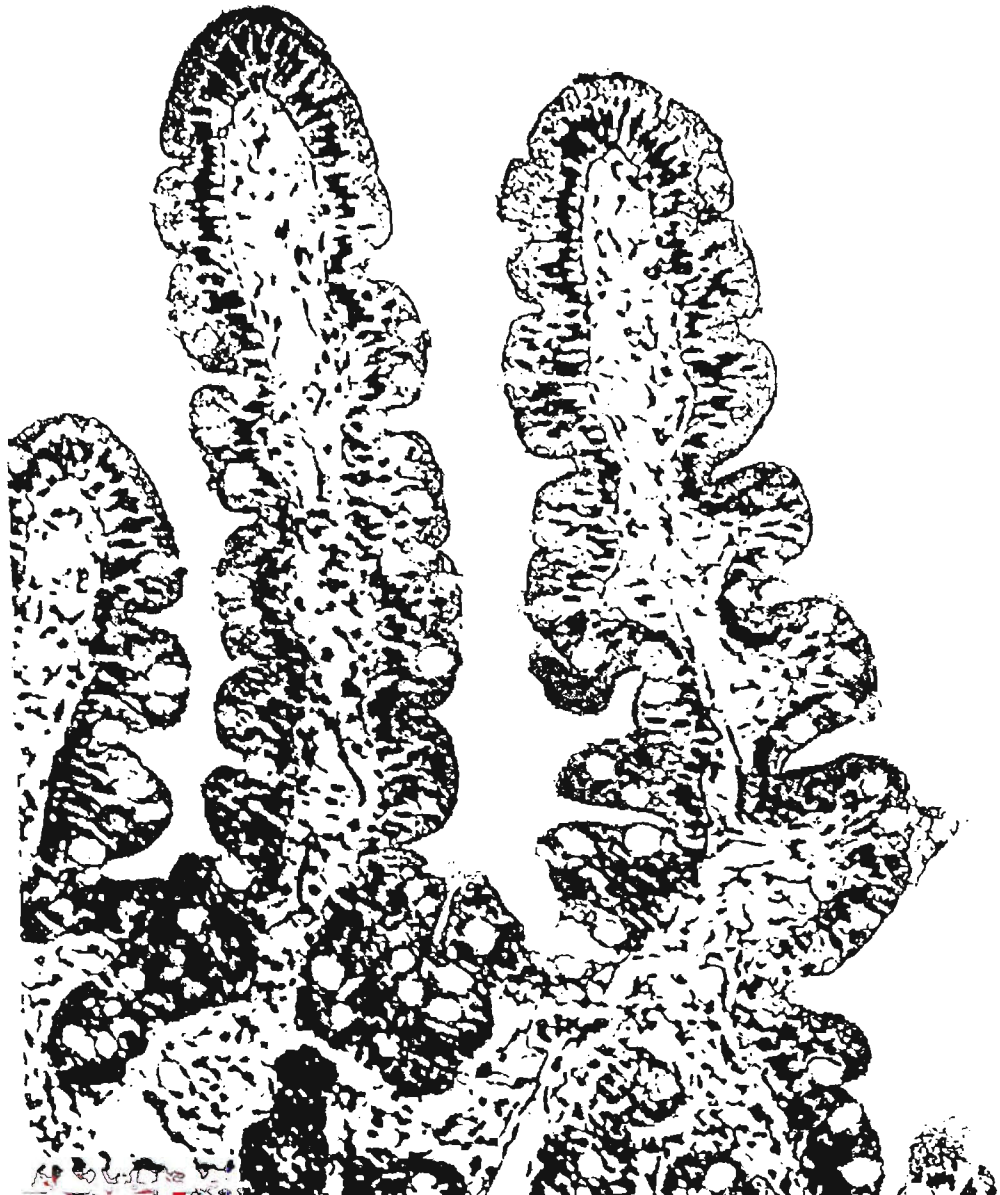


Figure 1: Images sourced from www.gesa.org.au publications – professional CD guidelines;

Damaged mucosal surface (appearing flattened) shown above; Functional villi below



utilise essential amino acids as an energy source. Given that protein metabolism in the gut contributes about one third of whole-body protein turnover (van der Schoor et al., 2002), impaired mucosal activation may unduly compromise extra-visceral amino acid requirements. Degraded uptake, utilisation or retention of the major electrolytes (including potassium, magnesium and calcium) and micronutrients (e.g., vitamin B_6, copper and iron; all precursors of haemoglobin formation and neurotransmitter production; Hallert, 1987) may also impact on bone metabolism and many other physiological processes (Selby & Faulkner-Hogg, 1998). In severe CD cases, "the absorptive surface of the small intestine may shrink from the size of a tennis court[4] to that of a household door" (Ryan, 2000, p. 835). Intake of nutrients in the upper intestinal area (e.g., iron and folate) is most affected. Reduced intellectual performance and behavioural alterations are both associated with iron deficiency alone (Lozoff, 1989). Sideropenic anaemia accompanies most CD diagnoses (Barr & Grehan, 1998).

Secondary metabolic problems, arising from nutritional deficiencies and immunological reactions caused by or associated with CD, exert stress on digestion-related, ancillary and remote body organs. Systemic effects and perturbations ensue (Howdle, 1997). Ramifications for an affected person's general health and well-being may be substantial, cumulative and even life-threatening, with the risk of intestinal lymphoma and overall mortality increased (Club del Tenue Study Group, 2001), especially in untreated or sub-optimally managed CD patients.

Gut restitution and restoration of general health are incumbent upon strict, lifelong avoidance of gluten ingestion. Following gluten withdrawal, clinical improvement occurs within weeks in just over two thirds of cases (Pink & Creamer, 1967; Selby & Faulkner-Hogg, 1998). An almost immediate remission of nettling symptoms of chronic ill-health or acute GI pain is often described (see Greco, 1997; Lohiniemi, 2001). Internally, complete healing of the intestinal mucosa may take six to twelve months in children (Mulder, Wahab, Moshaver, & Meijer, 2000) and up to a year or longer in adults and the elderly (Grefte, Bouman, Grond, Jansen, & Kleibeuker, 1988; O'Mahony, Howdle, &

[4] Total area of adult mucosal epithelial surface ≡ 400m^2 or ≈ 200 times entire skin surface area (Brandtzaeg, 1997)

Losowsky, 1996). Ongoing nutritional deficiencies, especially early in treatment, are not uncommon. For example, magnesium depletion, which may contribute to osteoporosis, has been noted in clinically asymptomatic CD patients on the GFD (Rude & Olerich, 1996). Full histological restitution is compromised by incomplete removal of gluten, with subsequent dietary lapses causing re-inflammation. Numerous, often related, aetiologies have been proposed for the pathogenic changes observed, including enzymopathic theories, membrane glycoprotein- and mucosal permeability-defect hypotheses (Cornell, 1996). Increasingly, unequivocal support and evidence supporting immunological pathways (Fasano, 2000; Schuppan, 2000; Sollid, Lundin, Sjöström, Molberg, & Thorsby, 1997) has emerged. Gluten proteins form complexes with an enzyme in the small bowel architecture known as tissue transglutimase (tTG), instigating "an antigenic response from the mucosal T cells" (Ryan, 2000, p. 835). The "resultant antitransglutimase autoantibody damages [the] intestinal mucosa" (p. 835).

Redefinition of CD as an auto-immunological reaction to gluten has occurred within the last decade (Peña et al., 1998). In acute or active CD, intestinal damage is almost always demonstrable, however slight, and GI symptomatology is a common, but not exclusive, physical indicator of illness (Mulder, Rostami, & Marsh, 1998). Indeed, in the preceding generation, close to half of all new CD cases worldwide have presented with non-GI symptoms at diagnosis, as noted by Fasano and Catassi (2001) in an overview of present day diagnosis-treatment protocols in CD (see also Catassi & Fasano, 2002, or Hallert, 1984, for an earlier overview of all clinical aspects).

Extra-intestinal manifestations, which may present with or without obvious mucosal atrophy, include dermatitis herpetiformis (see Fry, 1997/ 2002), a blistering skin disorder and the "classical non-GI disorder associated with CD" (Selby & Falkner-Hogg, 1998, p. 32) and dental enamel hypoplasia (Aine, 1996), each of which often receive treatments unrelated to CD recognition. In fact, without an active case-finding strategy in risk groups, most people with CD are unlikely to be detected (Hin, Bird, Fisher, Mahy, & Jewell, 1999; Mustalahti et al., 2002; Sanders, Hurlstone et al., 2002), owing to a preponderance of unapparent or unheeded symptomatology. On the basis of CD identified via screening data versus actual clinical diagnosis, Fasano and Catasasi (2001) remarked

that, "worldwide, CD *out of the intestine* is 15 times more frequent than CD *in the intestine*" (p. 641). Even at the symptomatic level, the Norwegians Sollid and Lundin (2001) noted that many of the likeliest signs of CD "including anaemia, fatigue, osteoporosis, depression, and infertility...are not especially suggestive of a disorder of the gut" (p. s13).

Classic versus Atypical Presentation

The classic presentation of CD involves a failure to thrive and significant weight loss, or failure to gain weight, in infancy or early childhood, as well as lassitude, pallor (due to anaemia) and GI distress, signs of which include bloating (resulting in abdominal distension), diarrhoea, flatulence or constipation and steatorrhoea (fat malabsorption), with increased faecal fat traditionally the barometer (Trier, 1991). Nevertheless, these clinical features are highly variable and characteristic of the acute phase or more severe cases of CD, now widely recognised as not confined to early life (Tursi et al., 2001). Moreover, none of these features are pathognomic to CD (Pham & Barr, 1996).

Iron-deficiency anaemia is perhaps the most frequent concomitant or antecedent symptom, extra-intestinal manifestation or atypical feature (in absence of GI symptoms) of CD at diagnosis. This often manifests as a loss of vitality or pallor in children (Abdullah, 1994). Menstrual irregularity or amenorrhea during the child-bearing years, especially if refractory to supplementation of iron and folic acid, may also indicate CD (Barr et al., 1993). Various skeletal pathologies (e.g., osteoporosis[5], osteopaenia[5], and osteomalacia[5]; Basu, Elmer, Babu, & Kelly, 2000; Marsh, 1994, and dental enamel defects/ mineralisation disturbances of permanent teeth; Rasmusson & Eriksson, 2001) are common, with significant osteopaenia usually accompanying adult CD diagnosis (Selby & Faulkner-Hogg, 1998). Recurrent oral aphthous ulceration is not rare and cutaneous disorders (e.g., psoriasis, dermatitis herpetiformis) are seen in one quarter of CD patients (Fry, 1997).

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[5] *Osteoporosis*: Defined as hip bone mineral density (BMD) T score 2.5 standard deviations (SDs) or more < young adult female mean using Dual Energy X-ray Absorptiometry (DEXA); Osteopaenia: BMD T score < -1, > -2.5 SD on DEXA; *Osteomalacia*: Adult version of rickets (vitamin D/ Ca ↓).

Professor Claes Hallert and his colleagues, of the Coeliac Centre at Linköping University, Sweden, have found depression to be the most common psychological problem in people with CD pre- and post-diagnosis (Hallert & Åström, 1982; Hallert & Derefeldt, 1982; see Hallert, 1984, 1987, and 1997, for comprehensive reviews). Pyridoxine (vitamin B_6) deficiency, then supplemental repletion, was linked to a decrement, followed by a significant amelioration of mood state (Hallert, Åström, & Walan, 1983). Increased depressive symptoms in CD were also identified by Ciacci, Iavarone, Mazzacca, and De Rosa (1998) and dysthymia was the most frequent psychological symptom post-diagnosis in a small CD series, affecting 23% (Rebaudengo et al., 1997). Most recently, Carta et al. (2002) found a high prevalence of major depressive and panic disorder in adult CD patients compared to healthy controls.

Headaches and migraine are often reported (Perniola et al., 1997; Roche Herrero et al., 2001), sometimes with bioccipital calcification and epilepsy (Piattella et al., 1997). Subtle neuropsychological deficits have also been identified (Grech, Richards, McLaren, & Winkelman, 2000). Serological evidence of CD was found in just over half of a cohort of patients with cryptic neurological dysfunction (Hadjivassiliou et al., 1996) and neurological complications occurred in 7% of another newly diagnosed CD series (Luostarinen, Pirttilä, & Collin, 1999). These include polyneuropathy, ataxia and epilepsy (Gobbi, Andermann, Naccarato, & Banchini, 1997). Suggestions CD "can be associated with severe neurological symptoms" (Bruzelius, Liedholm, & Hellblom, 2001, p. 3538) prompted those authors to call for CD screening "in suspected cases" (p. 3538). "Atypical neurological involvement associated with CD" (Hanagasi Gurol, Sahin, & Emre, 2001, p. 67) may sometimes result from a long-term deficiency of nutrients essential to neural function (see also Holmes, 1997), but is chiefly understood to have an immunological basis (Alaedini et al., 2002; Burk et al., 2001, Williamson et al., 2000), independent of malabsorption in CD (Fasano & Catassi, 2001; Hadjivassiliou et al., 1998).

Thyroid conditions are often synchronous with CD (Hakanen, et al., 2001) and subclinical thyroid disease may be an underlying factor in the increased risk of psychiatric morbidity in CD patients (Carta et al., 2002). Other atypical CD symptoms or complications are alopecia (Corraza et al., 1995) and arthritis. Onset occurs as early as adolescence (Mäki et al., 1988). Rickets and short stature,

linked to malabsorption and once a primary manifestation of CD (Groll, Candy, Preece, Tanner, & Harries, 1980), is not as common nowadays (Visakorpi, 1992), but less severe or subclinical signs of physical under-development are reported (Visakorpi, 1997). Children with untreated CD typically fail to grow satisfactorily, appearing thin or wasted, with undulating symptoms and subtle progression in milder cases (Anderson, 1969). George et al. (1997) detailed the clinical picture at the time of CD diagnosis in 193 Dutch children, identified in 1993-4. Growth failure[6] was the most common presenting symptom. In Australia, "plotting of growth percentiles is [deemed] mandatory in the assessment of suspected coeliac disease [in conjunction with other investigations] and is very helpful in the differentiation of this condition from other diarrhoeal diseases" (Barr et al., 1993, p. 4).

Adult-detected patients routinely present as weak and listless. Anaemia and low bone mineral density (BMD) occurs in at least two thirds of those newly diagnosed (Barr & Grehan, 1998). Retrospective histories of persistent, long-standing ill health, often accepted as normal by the unsuspecting patient, or intermittent symptoms intensifying prior to diagnosis, rather than true clinical silence, are usually readily uncovered (Johnston, Watson, McMillan, Sloan, & Love, 1998).

Many adult patients realise after diagnosis that they "have been unwell all their lives" (Barr et al., 1993, p. 10) and may have been "shopping around trying to understand what is wrong with them, not knowing they are celiac" (Fasano, 1998, p. 3). Emotionally, this realisation may evoke relief at the possibility or novel experience of vigorous health, despair or embitterment at newly discovered ill-health (e.g., osteoporosis) or lost physical condition (e.g., infertility), fear of future complications, or various combinations and intensities of these and other sentiments, at different times (Lohiniemi, 2001). All reactions, whether negative or positive, pessimistic, optimistic or realistic, mirror the clinical heterogeneity of CD and other illnesses with delayed recognition and an uncertain course, such as type-2 diabetes (see Edelwich & Brodsky, 1986) or Huntington's disease (HD). In HD, lowered mood often precedes the definitive choreic movements, with "signs of a mental disorder among the first manifestations of a systemic or cerebral disease" (American Psychiatric Association

[6] Defined as a decrease of ≥ two SDs below their growth line, either in height, weight or both.

[APA], 1994, p. 167). That psychiatric treatment may be attempted prior to awareness of the presence of Huntington's disease (Grech, 1993) is reminiscent of clinical judgments about and treatment of depressive illness in unrecognised CD, noted decades ago (see Hallert & Derefeldt, 1982).

Initial CD diagnosis is correlated with lowered body mass index (e.g., Capristo et al., 1997), partly attributable to nutrient malabsorption, especially lipids. Increasingly though, CD patients may be overweight at diagnosis (Franzese et al., 2001). Those authors reported atypical cases presenting with obesity-related liver dysfunction. Smallness of the liver in young children with CD was noted long ago by Still (1918), with mild liver abnormalities common at diagnosis (Davison, 2002; Sjöberg, Lindgren, & Eriksson, 1997). The GFD may, however, reverse hepatic failure (Kaukinen et al., 2002). Slight, albeit clinically relevant neuropsychological impairment is, in turn, prevalent in liver disease (Elass, Lund, & Ranek, 1978; Watanabe, Tuchida, Yata, & Kuwabara, 1995). This relationship's pert- inence to neuropsychiatric functioning in CD is not yet established. It is known that the severity of the aforementioned neurological complications may be associated with a later age of diagnosis (Hadjivassiliou et al., 1998), but CD is also widespread among children with neurological dysfunction (Salur et al., 2000). The atypical aetiology or inadequate response (pre-CD diagnosis) of these conditions to standard medical interventions may lead to further investigations that uncover underlying gluten sensitivity. At different centres in a small number of countries, including Sweden, Finland, Italy and Ireland, routine screening for CD in high-risk paediatric and adult groups is increasingly occurring.

The "experience [of] miscarriage or an unfavourable outcome of pregnancy" occurs in up to half of untreated women with CD, but "no excess of unfavourable outcomes are observed" after 6-12 months of the GFD (Martinelli et al., 2000, p. 332). These authors showed CD is more common than most diseases for which pregnant women are routinely screened, affecting 1.4% of their group. They demonstrated that many of the avoidable outcomes of untreated CD in pregnancy (including a nine-fold increased risk of miscarriage and low birth weight) are reversible following timely diagnosis and GFD treatment, supporting suggestions of CD screening during pregnancy (Greco, 2001).

Associated Health Problems

The list of physical health problems often comorbid, or significantly associated, with CD is extensive (James & Scott, 2001). These may result from the chronic or acute effects of malnutrition due to malabsorption in CD, covalent genetic underpinnings, or the direct and remote immunological sequelae cognate to gluten ingestion (see Maki, Collin, & Visakorpi, 1997). Patent or implicit haematological, osteological, endocrinological or dermatological signs are commonplace. Hyposplenism, indicated by Howell-Jolly bodies on a blood film, is not uncommon in CD (Duggan, 1997; Selby, 2001) and frequently persists despite gluten withdrawal" (Barr et al., 1993). Conditions that Fasano and Catassi (2001) noted as possibly gluten-dependent include autoimmune hepatitis (Sjöberg et al., 1997), Addison's disease (in case reports; e.g., Collin & Mäki, 1994) and Sjögren's syndrome, which affects 3-5% of adult CD patients in Tampere, Finland (Collin & Kaukinen, 1998). Immunoglobulin A (IgA) deficiency, not in itself harmful, is a gluten independent association that affects about one in thirty people with CD (Cataldo, Marino, Ventura, Bottaro, & Corrazza, 1998) and invalidates serological testing using IgA antigliadin (AGA) and antiendomysium antibodies (EMAs) as markers for CD, generating false negatives (Prasad, Thomas, Nicholas, Sharer, & Snook, 2001).

An increased duration of gluten exposure is connected with a correspondingly enhanced risk of other autoimmune diseases in CD (Ventura, Magazzù, & Greco, 1999). It has been proposed that increased age at CD diagnosis, as well as gluten exposure per se, may partly explain this observation (Sategna Guidetti, Solerio, Scaglione, Aimo, & Mengozzi, 2001). Ebbs et al. (1950) noticed an increased incidence of diabetes mellitus in CD – a finding since confirmed (Cronin & Shanahan, 1997). Recently, people with insulin-dependent diabetes mellitus were found to be about twenty times more likely to have or develop CD, with a 6.2% overall prevalence of biopsy-confirmed CD in a northern Italian cohort of children and adolescents with type-1 diabetes (Barera et al., 2002).

The major gluten independent condition associated with CD – or vice versa – is Down's syndrome (Zubillaga, Vitoria, Arrieta, Echaniz, & Garcia-Masdevall, 1993), but the reasons "remain unexplained" (Hill, Fasano, Schwartz, Counts, Glock, & Horvarth, 2000, p. 89). In an Australian

institutionalised Down's syndrome adult group, CD prevalence was increased more than one hundred-fold (Gale, Wimalaratna, Brotodiharjo, & Duggan, 1997; see also Carlsson et al., 1998). Book et al. (2001) recently recommended that children with Down's syndrome be screened for CD, after also finding an increased prevalence in a Utah-based, United States Caucasian population.

An interesting question is the overall association, if any, between CD and cardiovascular health. Correlates of potential atherosclerosis have been investigated in CD (e.g., elevated homocysteine; Hallert, Lilliecreutz, Fridell, & Grant, 1999). Banco (2000) noted that "heart disease (10.83%) was twice as prevalent as [in] the general population" (p. S28) in an international survey of 835 people with CD. Prati et al. (2002), who investigated "a possible link between CD and dilated cardio-myopathy" found that end-stage heart failure patients "are at increased risk for CD as compared to the general population" (p. 39). Conversely, in a longitudinal study of dermatitis herpetiformis patients, "mortality from ischaemic heart disease was significantly below national rates...and was similar in patients who had followed a [GFD] and those who had not" (Swerdlow, Whittaker, Carpenter, & English, 1993, p. 140). West et al. (2002) actually found "a favourable cardiovascular profile which is likely to afford substantial protection from ischaemic heart disease and stroke" (p. A18), in middle-aged English people with undetected CD identified via serological screening. These authors highlighted a common finding of hypocholesterolemia in newly identified CD. Could it be that a malabsorption of lipids and iron, in untreated CD, guards against an inordinately high intake of saturated (and trans) fat, as previously alluded (Whorwell, Alderson, Foster, & Wright, 1976), and, perhaps, a tendency towards iron overload in the modern diet?

One of the most disturbing complications of undetected or poorly managed CD, regardless of other symptoms or presenting features, is an increased risk of intestinal lymphoma, which is partly responsible for a two-fold overall increase in mortality in CD (Logan, Rifkind, Turner, & Ferguson, 1989). This outcome was essentially replicated by the Club del Tenue Study Group (2001), but – in terms of pattern of clinical presentation – only found to apply to CD patients with GI symptomatology at diagnosis, as opposed to those detected with minor symptoms or via

antibody screening. Whilst malignancies have been previously reported in at least one in ten adult CD patients (Harris, Cooke, Thompson, & Waterhouse, 1967), strict GFD adherence sustained from childhood reduces risk to a level comparable with the general population (Logan et al., 1989). Poor compliance and delay in diagnosis significantly increases mortality, with non-Hodgkin lymphoma the main cause of death (Club del Tenue Study Group, 2001).

In patients adhering to the dietary restrictions, BMD may eventually reach the level of healthy controls, with significant increases in the first year of treatment (see Valdimarsson, Toss, Ross, Löfman, & Ström, 1994), but this not a universal finding (McFarlane, Bhalla, Reeves, Morgan, & Robertson, 1995). Half of McFarlane et al.'s (1995) treated adult patients had osteoporosis (see also Scott, Gaywood, & Scott, 2000, for a detailed review of guidelines for osteoporosis in CD). Indeed, GFD treatment was insufficient to resolve osteopaenia in Turkish children with CD one year post-diagnosis (Kalayci, Kansu, Girgin, Kucuk, & Aras, 2001), or bone size in asymptomatic Hungarian children and adolescents many years after commencement of a GFD (Szathmari et al, 2001). Adult-detected patients have even less of an opportunity to overcome low peak bone mass.

A problem in symptomless CD detected via screening protocols is that the likelihood of compliance "with a very restricted lifelong diet in the hope of avoiding a distant complication defies logic" (Duggan, 1997, p. 315). Similar observations of adherence to treatment being centred on the existence of current symptoms or regimen difficulty, rather than long-term benefits, have been noted in diabetes (Jacobsen, de Groot, & Samson, 1995). In many serious and sometimes irreversible CD-related complications, such as osteoporosis or lymphoma, there may be few, if any, noticeable symptoms of these diseases until the advanced stages.

Diagnosis and Screening for Coeliac Disease

None of the clinical features, archetypal abnormalities of the duodenojejunal junction of the small bowel or problems of malabsorption in CD are unique to this illness (Pham & Barr, 1996; Ryan, 2000), as alluded earlier. Other clinical conditions sharing the histological changes seen in CD include eosinophilic enteritis, Crohn's disease, cow's milk protein intolerance, tropical sprue, bacterial

overgrowth, infection with Giardia lamblia and kwashiorkor (Barr et al., 1993; Troncone, Maurano, Iovine, Petrone, & Paparo, 1998). Furthermore, "one form of intestinal malabsorption does not rule out another" (Hallert, 1984, p. 98). Clear evidence of gluten intolerance, with documentation of a clinical response to gluten withdrawal, has therefore remained a primary consideration following Dicke's (1950) observations (Anderson, 1953; Barr et al., 1993; Walker-Smith, 1997).

A 1969 meeting of the European Society of Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) in Interlaken, Switzerland, universally established the criteria required for the definition and diagnosis of CD (Meeuwisse, 1970). A series of small intestinal biopsies[7] to establish evidence of gluten-induced damage in the presence of GI elimination and mucosal re-injury after a gluten "challenge" (and reappearance of CD symptoms) represented the exhaustive (and invasive) process of CD identification. At the first international CD conference in London that year, only the first two steps were deemed essential (Walker-Smith, 1997). The third phase involving the gluten challenge was questioned, given the increasing acceptance of CD as a permanent condition, and practical considerations regarding tracking patients and implementing the gluten challenge. Nevertheless, the three-stage ESPGHAN or Interlaken criteria, for definitive CD confirmation, changed little for the next two decades (Marsh, 1995).

The gluten-dependant mucosal damage, resolution upon dietary exclusion and, preferably, demonstration of disease permanence via histological relapse after gluten exposure, were accepted as key steps in diagnosis. Although diagnoses continued to be precipitated by the recognition of classic CD signs and symptoms observed to resolve after dietary treatment, the clinical criteria became vestigial or even redundant in many cases, as the proportion of identified subclinical or oligosymptomatic cases rose with advances in screening technology and interpretation.

Use of increasingly reliable and accurate serological (blood) testing techniques resulted in greater detection of CD, as well as influencing assessment protocols, with a progressive simplification of the

[7] The biopsy involves taking a sample of tissue from the lining of the small intestine, normally the duodenum, using a gastroscope, fed mechanically from the mouth into the bowel of a conscious or sedated patient. The bioptic procedure may be called a "gastroscopy", "upper GI endoscopy" (UGIE) or "esophagogastroduodenoscopy" (EGD)

diagnostic guidelines in the preceding decade (see Walker-Smith, 1997). In 1990 the ESPGHAN criteria were revised, with a good clinical response to the GFD confirmatory given a clinical presentation, serological screening profile and histological findings compatible with CD from the outset (Walker-Smith et al., 1990). A repeat, control biopsy, to confirm histological resolution after dietary intervention, was determined to be requisite only in the event of an equivocal clinical response to the GFD or in patients symptom-free at diagnosis, often the case in identification via screening (Fasano & Catassi, 2001). Various grades of intestinal lesions were acknowledged as possibly indicative of CD, from patchy and partial epithelial damage to total villous atrophy. The gluten challenge, with bioptic evidence of histological relapse – also no longer considered mandatory – was reserved for cases involving doubt about the initial diagnosis. These include instances in which an initial biopsy specimen is atypical of CD, otherwise inadequate or was not performed at the time of diagnosis (Troncone et al., 1998). Other circumstances in which a gluten challenge is recommended include diagnoses made prior to the age of two years, or when the possibility, or suspicion, of a differential diagnosis may be heightened (e.g., in communities with a high incidence of other causes of enteropathy; Troncone et al., 1998). A planned gluten challenge may also be useful in the event that an adolescent intends to depart from the GFD (Walker-Smith, 1997).

The present day gold standard of CD diagnosis "remains histologic confirmation of the intestinal damage in serologically positive individuals" (Fasano & Catassi, 2001, p. 636). Even so, serological screening devices available to the general practitioner are becoming very reliable in identifying clinically suspected CD and diagnostic tests are imminent (e.g., Baldas et al.'s (2000) highly accurate dot blot assay). With each passing year, the zero biopsy goal envisaged by Schmitz (1997) inevitably moves closer to reality. For the time being, use of combinations of assays, including the highly specific AGA IgA and very sensitive AGA IgG, plus the antiendomysium antibody (AEA, or its antigen tTG) results in excellent positive and negative predictive value for identifying CD, particularly in high risk groups, but is in reality limited by a range of clinical, practical, interpretative and cost considerations, outlined in detail by Fasano & Catassi (2001). Those authors reviewed current

diagnostic protocols and outlined an "algorithm for the definitive diagnosis of CD" (p. 644) in reference to ESPAGHN criteria (Walker-Smith, et al., 1990). In biopsy-proven cases, serological testing may provide useful collateral information in monitoring compliance with the GFD (Valletta & Mastella, 1990) and, of course, "is often crucial for how far an investigation [of CD] is pursued" in the first place (Ludvigsson, Fälth-Magnusson, & Ludvigsson, 2001, p. 1279).

Since strict, lifetime avoidance of all gluten containing foods represents a lifestyle alteration involving considerable sacrifice for the patient, false-positive CD diagnoses, albeit uncommon, must be minimised via bioptic confirmation of intestinal damage in serologically positive cases. Conversely, a serious consequence of under diagnosing a genuine case of CD by forgoing bioptic testing is that the level of GFD compliance is likely to be diminished. Realistically, "the picture of a damaged intestine" (Fasano, 1997, p. 7) is likely to project a greater impression on a CD patient of the seriousness of their illness, and importance of following the GFD, than a less-invasive serological procedure, especially in people who are relatively asymptomatic.

People suspected of having a gluten intolerance, but who have not been definitively assessed, are strongly advised against self-trialling a GFD (Barr et al. 1993; Kaukinen et al., 2000; Selby, 2001), as suggested in some otherwise useful books advocating rotation or elimination diets (e.g., Buist, 1990; Savill & Hamilton, 2001). Transitory or ongoing wheat sensitivities and other cereal or otherwise dietary-related intolerances may exist (Selby & Faulkner-Hogg, 1998; Kaukinen et al., 2000), as do alternative reasons for reducing or avoiding gluten-containing foodstuffs (e.g., CD-like, or irritable bowel, symptoms, due to wheat starch fermentation in the gut). A food additive commonly used as a mould inhibitor in bread (calcium propionate) has also recently been linked to irritability in Australian children, most of whom had attention-deficit hyperactivity disorder (ADHD)-type behaviours (Dengate, 2002). However, the GFD is an absolute medical necessity for people after confirmation of CD. As noted in a *Gluten-Free Living* guide (1999), "gluten sensitivity is not a casual diagnosis". Serological tests for CD may be invalidated by pre-test avoidance of gluten (Selby, 2001). Murray (1999) noted that "both the general public and practitioners of alternative medicine commonly ascribe a vast

collection of ill effects to dietary gluten and prescribe wheat-free or gluten-free diets for many complaints without any attempt to confirm the existence of celiac disease or even without an awareness of the disease", which "can lead to diagnostic difficulties" (p. 356). Given the lifelong implications of CD and following the GFD, it is crucial to determine whether CD or another condition is the underlying health problem and, by corollary, to be certain that strict adoption of the GFD is necessary.

In Australia, Victorian Coeliac Society support centre staff are periodically contacted by confused, ostensibly newly diagnosed CD patients who have, "on their own initiative" (Ryan, 2000, p. 836), or encouraged by health care professionals – sometimes their general, or alternative, health practitioner – to "trial" a "low or no gluten diet" (without a preceding biopsy; Ryan, p. 836) and judge for themselves if they feel better. Referral to a gastroenterologist for upper GI endoscopy or even serologic testing may not have occurred, a fear also expressed elsewhere (Green, 1998). Parents of children with CD have also reported receiving medical opinion that their children will probably "grow out of it [CD]" by adolescence or adulthood, based on previous observations of spontaneous clinical remission prior to the use of the GFD (Sheldon, 1959) and histological recovery upon a gluten challenge (e.g., Schmitz, Jos, & Rey, 1978; see also McNeish, 1980).

A very small percentage of health care professionals may even doubt that CD is a legitimate medical condition, with some still expressing scepticism that certain foodstuffs are a legitimate and documented etiological factor in physical illnesses in the absence of classic allergic mechanisms. Others perhaps regard the GFD as a fad, still perceive the illness due to CD as a "transient" food intolerance (see Berg & Lindberg, 1979), or rely on outdated medical information, which in past decades has catalogued genuine cases of CD to be a rare intestinal disease confined to childhood, as reported by Visakorpi (1992, 1997). Poor knowledge of CD among family doctors has also been noted previously in Italy (Catassi, 1997), where CD awareness is relatively high. Certainly, the "limited expertise of health care professionals regarding the celiac diet and absence of federal regulations [in the United States and other countries] for accurate food and drug labelling both represent significant challenges for patients with newly diagnosed CD" (Fasano & Catassi, 2001, p. 647).

A 1995 survey of 1,887 Australian Coeliac Society members (out of a total national membership at that time of about 5,000), declaring themselves to have medically diagnosed CD (Stuart, 1997a and 1997b; see also Stuart, Faulkner-Hogg, Selby, & Loblay, 1997), revealed that 92% of respondents had been referred for and undertaken at least one small bowel biopsy to confirm the diagnosis, but 8% had not. Of those having a small bowel biopsy, 58% had only one biopsy (which, as mentioned, is now often regarded as adequate), 31% had two and 11% had three (or more) over time. Of the 8% (i.e., 151 people) surveyed who were not biopsy-confirmed only 39% had actually undertaken serologic testing. It is conceivable that people who are proactive about their illness – in becoming members of self-help or support associations (such as the Coeliac Society) – might be over-representative of the proportion of people with CD community-wide who have been diagnosed according to the gold standard, inclusive at least one biopsy.

Given that nearly 90% of Australians see a general practitioner at least once a year (Harris & Penrose-Wall, 2001), a unique opportunity for early intervention exists in general practice to facilitate investigation of many common, under-recognized conditions, including CD, a point stressed by Ventura et al. (2001). The high prevalence of CD now verified in an Australian population-based study (Hovell et al., 2001) and the frequent non-specificity of symptoms in CD detected locally, akin to the worldwide experience, presents a persuading case for wider screening of CD.

In a Melbourne-based study, Ryan (2001) demonstrated that about 5% (5 in 97) of patients undergoing gastroscopy had CD, but none of the patients presenting with diarrhoea and only one of six with anaemia had CD, showing that restricting biopsy to this group would have missed most patients with CD. He recently suggested that "people presenting for gastroscopy represent a high-yield group for histological screening for CD in Australia" (Ryan, 2002, p. 298), arguing the case for routine duodenal biopsy at the time of gastroscopy, regardless of the indication. Differential diagnoses to CD, not mentioned earlier, also include lactase deficiency or cystic fibrosis in children and irritable bowel syndrome, pancreatic insufficiency or GI blood loss in adults (Selby & Faulkner-Hogg, 1998).

Epidemiology of Coeliac Disease Since 1950

Many health care professionals in Australia and North America may be unfamiliar with CD, but the illness is now recognized as the "second most common chronic disorder of children" in Sweden (Popat et al., 2002b, p. 28) and "one of the commonest lifelong disorders in Italy" (Catassi et al., 1996; Parnell & Ciclitira, 1999, p. 2), if not the Western world, in adults and children (Catassi et al., 2002; Catassi & Fasano, 2002). However, this has been a relatively recent acknowledgement. Prior to the identification of gluten as the causative environmental factor in CD, few paediatric cases survived infancy, often succumbing in early childhood due to a combination of nutritive factors (i.e., uncorrected malabsorption plus general under-nutrition as a result of poverty) and reduced resistance to a variety of other illnesses, including concomitant GI infections (Greco, 1997).

Contemporaneous with Dicke's identification of the toxicity of certain farinaceous elements in CD, the cumulative incidence of "sprue syndrome" was estimated to range from one in four to eight thousand in the United Kingdom (Davidson & Fountain, 1950). Despite the advent of simple devices enabling intestinal biopsy soon afterwards, CD was regarded as a relatively rare condition originating in infancy or early childhood for the best part of the succeeding two decades, with detection based on classic GI symptoms. Green and Wollaeger (1960) noted that only 4% of new CD diagnoses in the United States at that time were made in patients aged over sixty years.

During the 1960s in Finland, around eight or nine out of each ten new CD cases were diagnosed in infants below the age two years, with a mean age of ten months (Mäki, 1998). Gluten had, on average, been introduced just over four months before the onset of symptoms. The development of more sophisticated diagnostic techniques in that period was accompanied by increased awareness of CD among gastroenterologists, as well as paediatricians. A study reporting a relatively high CD incidence of one in six hundred people in Ireland (Mylotte, Egan-Mitchell, McCarthy, & McNicholl, 1973) three decades ago sparked an explosion of interest in the true incidence and prevalence of CD throughout Europe, which was found to be higher than previously believed. Paradoxically, increased CD awareness, contributing to the practice of delaying gluten exposure

after weaning in the belief that sensitivity to gluten may not develop, was sequelled by a real decrease in the incidence of childhood CD. This trend was documented in Britain (Littlewood, Crollick, & Richards, 1980) and Ireland over a twenty year period, beginning in the early-mid 1970s (Gumaa, McNicholl, Egan-Mitchell, Connolly, & Loftus, 1997). On the other hand, the childhood CD incidence remained constant, then increased in the Netherlands (George et al., 1997) and Sweden (Hallert, 1998) in the 1980s. This phenomenon was attributed to a slight postponement of gluten introduction (Cavell, 1992), with reduced onset of illness in infancy, offset by a minor drift upwards in age at diagnosis. Greater awareness of CD by paediatricians and general practitioners and the advent of more sensitive serological screening were other contributing factors, increasing the likelihood of diagnosis at any time in childhood (Hallert, 1998).

Compared to neighbouring Nordic countries, the incidence of CD recorded in Danish children has been very low, at about one in 10,000 between 1962 and 1987 (Weile & Krasilnikoff, 1992, 1993). Although retrospective reviews of clinical diagnoses, as well as the national diagnostic register were used, these figures were still much lower than Europe in general. Of significance, Danish children are introduced gradually and comparatively late in infancy to much smaller amounts of gluten than Swedish children. At the age of nine months Swedish children were reported to have an intake of 50.6 g wheat/ day compared to only 7.9 g wheat/ day for Danish infants (Michaelsen, Weile, Larsen, Samuelsson, & Krasilnikoff, 1993). Interestingly, the adult prevalence of CD in Denmark of about 0.2% approaches that seen in neighbouring countries (Sjöberg & Eriksson, 1999).

Modified infant feeding practices, as well as a greater appreciation and detection of clinically silent, oligosymptomatic or atypical cases (Tursi et al., 2001), especially in later life, has led to a much higher estimate of the overall prevalence of CD in the preceding decade or so. Catassi (1997) noted that the first reported community screening study of CD (undertaken by Hed et al., 1986) was apparently overlooked for several years. This investigation showed a 1 in 256 prevalence of un-diagnosed CD, based on serological markers, among Swedish blood donors. Other population-based screening studies in the preceding two decades verified that the overall CD prevalence was at least one

in several hundred in Scotland (Logan, Rifkind, Busutti, Gilmour, & Ferguson, 1989), Denmark (Weile et al., 1996) and Norway (Hovdenak et al., 1996, 1999), and as high as 1:130 in Finland (Kolho, Färkkilä, & Savilahti, 1998). The prevalence of CD in a large, recent series of healthy 2.5 year old Swedish children was 1.3%, but if the already known cases of symptomatic, biopsy-verified CD in that birth cohort were added, the prevalence reached 2% (i.e., 1 in 50). Following a large scale multi-centre collaborative study, CD prevalence in Italy was determined to be 1 in 184 (Catassi, 1997), with a ratio of known to undiagnosed CD cases of 1 to 7. This determination, and others according similar estimates, are based on comparisons between the number of actual CD diagnoses in given geographic areas versus research-based screening data pertaining to the general local population.

The iceberg model (Logan, 1992; see also Catassi et al., 1994; Fasano & Catassi, 2001, and Figure 2; a representation courtesy of Mäki & Collin, 1997, reprinted on next page) is a useful way of conceptualising the varying CD prevalence rates temporally and geographically, obtained by a variety of methodologies. In this model, the total coeliac population may be conceptualised as a floating iceberg, in which the visible portion represents the known or detected CD cases at any given time point. The submerged part depicts unrecognised CD, with the undiagnosed cases (typically silent or asymptomatic) just below the surface. Latent or potential cases complete the iceberg (Ferguson, Arranz, & O'Mahoney, 1993). Latent CD refers to either "existing but not manifest" illness (Holm, 1998, p. 19), including a pre-biopsy CD history or "...the situation where serology is positive but biopsy [is] negative" (Ryan, 2000, p. 836), in which case "some but probably not all of these individuals will develop clinical [CD]" (p. 836). Potential CD may be considered either synonymous with CD latency, or inclusive of a larger population pool with any abeyant markers or even correlates of illness. At one extreme this may extend to all people with predisposing genotypes, involving up to one in five people of European heritage, most of whom will never develop CD (Holmes, 2001). The overall size of the iceberg is dependent primarily on genetic susceptibility (not unknown in Mongoloid/ Negroid races, but consistently higher in Caucasians; Pham & Barr, 1996), and the definitional threshold of CD, given the enormous continuum of histologic, immunologic

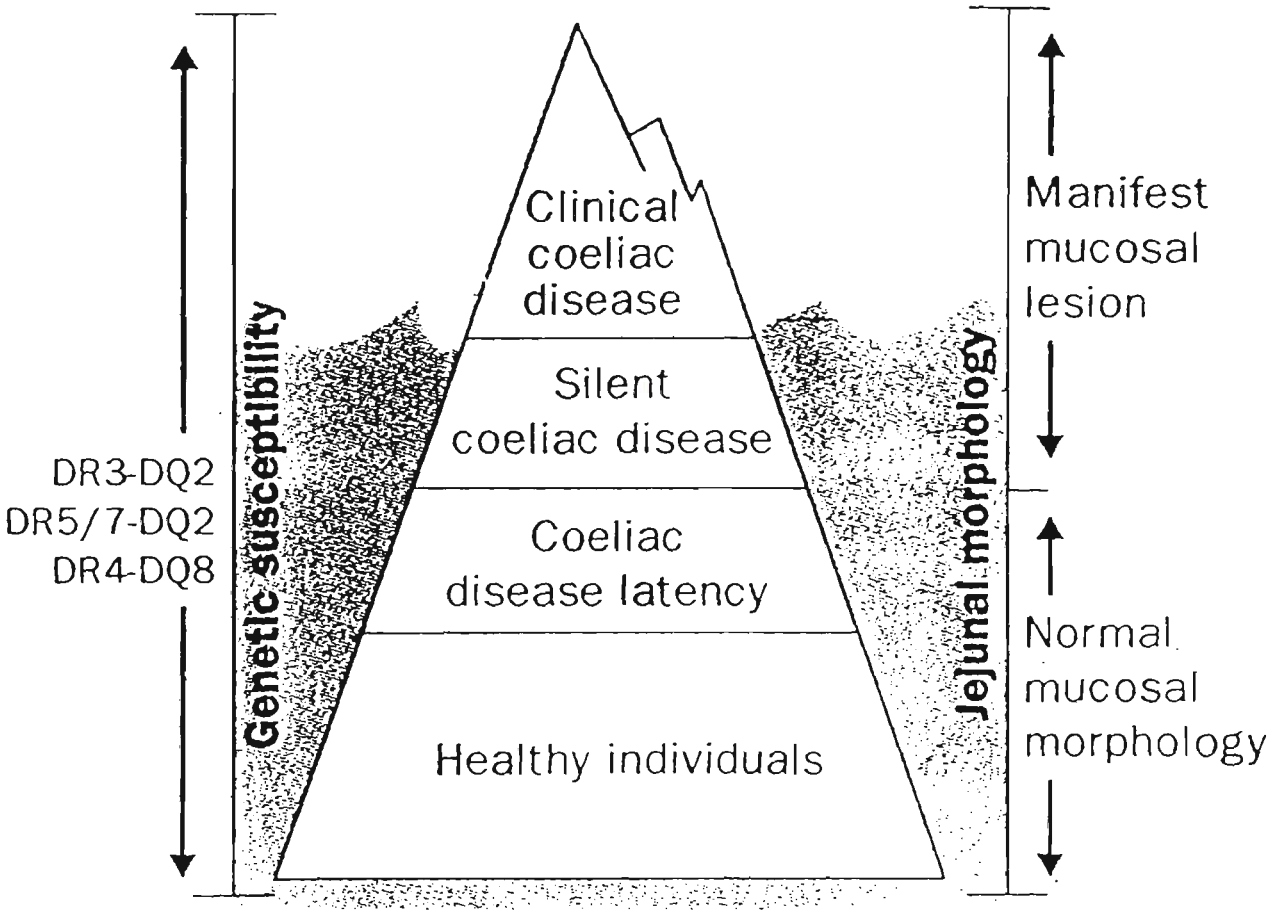

Figure 2: The coeliac iceberg and spectrum of gluten sensitivity

(representation courtesy of Mäki and Collin, 1997)

and clinical heterogeneity and severity observed.

At what point the CD iceberg floats above or lies below the waterline is influenced by numerous factors. These include average gluten intake (which is highest, with wheat intake, in latitudes remote from the equator), CD awareness (public and professional) and the quality and accessibility of medical care generally and CD diagnostic facilities in particular, including the sensitivity of serological markers, assay methods, cut-off values and interpretation (Catassi, 1997). In Western countries the visible part of the iceberg (i.e., clinically diagnosed cases) is by and large five to ten times smaller than the submerged portion (Fasano & Catassi, 2001), as revealed by prevalence studies entailing current diagnostic procedures and representative samples from the general population. In incidence studies, the age sampled and historical and regional context are also highly relevant, as demonstrated by the Nordic experience.

Finally, the population sampling method utilised is germane to the evident prevalence. For instance, the use of blood donors is a convenient way to mass screen for CD with sensitive serological markers. However, blood donors actually represent a selected, relatively healthy subgroup from the general population, from which people with a range of symptoms of ill health, deficiency states or CD-related conditions (e.g., anaemia, very common in untreated CD) are not permitted to give blood (Australian Red Cross Blood Service, 2002). In Australia, an increasingly restrictive screening protocol, involving detailed interviewing, pre-donation finger-prick haemoglobin testing (entailing strict cut-criteria) and post-donation testing, is used in selection. Although one's exclusion as a blood donor may not be indefinite, records of volunteers are kept and the resolution of health issues, with medical clearances, is a pre-condition of future donating. A net result is that many people, for the sake their own – as well as blood recipients' – health, are discouraged or barred from ongoing blood donation. It is conceivable that people with untreated CD, who are more likely to have a range of health problems, may be less likely to initially present to make blood donations.

Of people already diagnosed with CD (some of whom may be detected as a direct consequence of being initially barred from donating due to anaemia), serological testing for CD becomes negative

with strict adherence to the GFD. In addition, only 3% of the Australian population are regular donors (Australian Red Cross Blood Service, 2002) and a higher proportion of males donate blood, but a greater proportion of women usually have CD (Sjöberg & Eriksson, 1999). Overall, notwithstanding the imposition of stricter exclusionary criteria in recent years and variations in restrictions pertaining to different countries, it appears prevalence rates based on blood donors, whilst useful, are likely to significantly underestimate CD prevalence, or yield minimal to lower limits.

In Australia, a reported CD prevalence of one in 2,900 (Porter & Duggan, 1990), based on clinical diagnosis, has been superseded by a recent study which retrospectively analysed stored serum samples from 3,011 participants from the Busselton health study (Hovell et al., 2001), then tracked serologically positive individuals. Seven (out of ten) participants who were IgA and AEA positive had bioptic results compatible with CD, with three not tested (one subject had died, another could not be traced and a third refused small-bowel biopsy). Two other participants already had a CD diagnosis, resulting in a prevalence of 1 in 251 if all ten AEA-positive participants are included.

Used as a rough guide, this prevalence figure, if extrapolated to the Australian population of 19.5 million (ABS, 2002), would suggest that there are in the order of 80,000 Australians with CD. The latter, hypothetical number is obviously greatly in excess of approximately 8,000 current members of the Australian Coeliac Society who are medically diagnosed CD patients (G. Price, personal communication, July 9, 2002), even acknowledging that about one third of members fail to renew their annual membership. Propinquity regarding national CD association membership numbers in relation to the total population and the estimated prevalence of CD, are observed elsewhere in the world, including New Zealand [8] (with analogous circumstances and food labelling laws to Australia), and, to a lesser degree, the United Kingdom[9].

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[8] Coeliac Society membership in New Zealand, a country in which gluten-free food is partly government subsidised, numbers approximately 2,000 (C. Chambers, personal communication, May 21, 2002) in a population of just under 4 million (Brunner, 2002), an equivalent membership rate to neighbour, Australia, on a per capita basis.

[9] The United Kingdom national membership of just over 50,000 (J. Willis, personal communication, June 5, 2002), in a nation of about 60 million people (Brunner, 2002), is somewhat higher per head of population.

Australian Coeliac Society membership has grown more than five-fold since 1990, with steady increases recently replacing the rapid growth previously observed. A plateau in new monthly membership figures, presently hovering at around 200 nationally (D. Baker, personal communication, May 20, 2002), has been counterbalanced by slightly increased annual retention, perhaps reflective of an ever-increasing and up-to-date range of resources provided by local state coeliac Societies.

Future medical screening for CD, as part of the management of very common, but often obstinate, health problems associated with the illness (e.g., reduced bone density, depression, reproductive disorders and type-1 diabetes mellitus), would involve millions of Australians (Wall, Wood, & Holman, 1999), but probably lead to vastly improved health in at least tens of thousands, if the Australian CD prevalence is comparable to Europe's, as appears likely. There is also an increasing recognition and prioritisation, by the Australian federal and state governments, of disease entities associated with the greatest overall community morbidity (e.g., diabetes, musculoskeletal problems and depression), and calls to identify underlying causes and associations (Wall, Wood, & Holman, 1999). Clearly, CD – as one potential underlying factor or condition associated with all of these common health problems – appears to be a prime candidate for future inclusion.

Recent estimates of the true CD prevalence have converged on an upper figure of about 1% of the general population (Cook, Burt, Collett, Whitehead, Frampton, & Chapman, 2000; see also Fasano & Catassi, 2001; Greco, 1997). Prevalence rates of this magnitude, let alone smaller ones, require large population samples to give stable and reliable results (Catassi, 1997; Karvonen, 2000). However, firm evidence in support of this figure is accumulating. In two separate Italian studies, biopsy-proven CD prevalence in Sardinian children was ascertained. For 6-14 year olds, this figure was determined to be at least 1.1% (Meloni et al., 1999) and, in those aged 11-15 years, 0.86-0.91%, if a repeatedly AEA-positive subject with normal mucosal architecture was included (Catassi et al., 2000). The prevalence of CD in the United States, where the disorder was previously believed to be rare, has been found to be as high as in the Caucasian European general population, at 0.9% in adults and 0.6% in children, with the CD prevalence in various risk groups also similar (Gerarduzzi et al., 2000).

In Northern Ireland, serological screening of a randomly selected adult population of 1,823 (not blood donors) led to a biopsy-proven prevalence of at least 0.8%, of which only two of fifteen detected CD cases had been previously diagnosed (Johnston, Watson, McMillan, Sloan, & Love, 1997). Sanders et al. (2002) found 12 new biopsy-proven cases in a sample of 1200 volunteers from five general practices in South Yorkshire, the "first study to establish the prevalence of undiagnosed CD in a general population from England" (p. A18). Prevalence rates close to 0.8% in Finland and 1-2% in Sweden (as noted), 0.6% and 1.2% respectively in Argentina (Gomez et al., 2001) and New Zealand (Cook et al., 2000) have also been documented. Applied to the Australian population, a 1% CD prevalence would increase the aforementioned estimate of 80,000 people to almost 200,000.

A prevailing belief that CD was rare in the United States was questioned in the preceding decade (Fasano, 1996). In fact, CD "...may be as common as in Europe" (Hill et al., 2000, p. 86), as demonstrated by ongoing, multi-centre, epidemiological US research. Gerarduzzi et al. (2000) found a CD prevalence of 1:167 and 1:111 in healthy children and adults respectively and 1:30/ 40 in symptomatic children/ adults.

Of major significance, the prevalence of IgA-AEA positivity found in 989 Arab Saharawi children in Northern Africa is at least five-fold higher than in European populations (Catassi et al., 1999). These authors also found that serum IgA-AEA positivity appeared to be a very reliable marker of biopsy-confirmed CD in this group. Further evidence of its specificity in children with chronic malnutrition and diarrhoea has been demonstrated (Gandolfi et al., 2001). Catassi (2001) proposed that the high prevalence of CD in the Saharawi children may be due to a protective role of the coeliac enteropathy against intestinal infections in the context of both low gluten intake and poor sanitary conditions in that region. This possibility is reminiscent of West et al.'s (2002) favourable cardiovascular profile in screening-detected, untreated CD. The notion of CD conferring one or more selective advantages in certain environments may help to explain its persistence in European populations, given the conjoint circumstances of limited control of sanitation and a much lower comparative gluten intake relatively recently in human history.

Demographic Findings: Age and Gender

The median age at CD diagnosis is rising worldwide as CD awareness increases, screening methods become more accurate and widely used and minimal-symptomatic CD cases are recognised, especially later in life (Barr & Grehan, 1998; Beaumont & Mian, 1998). Previous researchers have demonstrated a bimodal peak for age at diagnosis in adults, with the first crest in the fourth decade (mainly in women) and a later one in the sixth and seventh decades, principally in males (Swinson & Levi, 1980). Although these trends may not be universal, middle-aged adults in the 45 to 54 age bracket were the highest-prevalence subgroup in a comprehensive Swedish series aged greater than 15 years, with one quarter detected due to coexisting dermatitis herpetiformis and over one third having a history of childhood CD symptoms (Hallert, Gotthard, Norrby, & Walan, 1981). Similarly, in Hovell et al.'s (2001) Australian epidemiological study there was significant clustering of CD cases in the 30 to 50 year age range.

Where CD awareness is relatively high and active case finding is increasingly applied (e.g., Italy, Sweden, Finland, Norway and Britain/ Ireland), CD detection is generally amplified across most age groups, irrespective of disease severity. Therefore, the age at diagnosis for a person having CD in these countries may be expected to be lower than elsewhere. However, a lower anticipated mean age at diagnosis in the overall population is counterpoised by the soaring rate of middle-aged to elderly adult cases systematically unearthed, many of whom are oligosymptomatic, or unresponsive to treatment for any of the wide range of related illnesses aforementioned. Many researchers have touched on or explored these trends (see Ascher, 1997; Catassi, 1997, Ciclitira, 2001; Cooke & Holmes, 1984; Hallert, 1998; Kelly, Phillips, Elliot, Dias, & Walker-Smith, 1989, Mäki et al., 1998, Mäki & Collin, 1997, and Visakorpi, 1997).

No gender-related genetic differences in people diagnosed with CD have been identified to date, but women typically make up a greater percentage of identified CD cases in adult series (e.g., Corrao et al., 1996). In children, the ratio is usually closer to unity (McConnell, 1981; cited in Logan, Tucker,

Rifkind, & Heading, 1983). Two of three CD patients in a population-based Spanish study were female, which the authors ascribed "to a greater genetic risk of immunologic disease" in women (Riestra, Fernández, Rodrigo, Garcia, & Ocio, 2000, p. 401). The consistent inter-study finding is that about two (and up to three) times as many females as males are diagnosed with CD in adulthood (Beaumont & Mian, 1998; Collin, Reunala, et al., 1997), with the ratio ranging from 1:1 to 2.8:1 (Bodé & Gudmand-Høyer, 1996). These findings are mostly attributable to women being more susceptible to, or likely to be investigated for, a number of medical conditions that are CD-related, such as anaemia (with amenorrhoea uniquely affecting women), osteoporosis and mood disorders (including depression), as well as the increased frequency of females visiting doctors (Wright, 1995). Ciacci, Cirillo, Sollazzo, Savino, Sabbatini, and Mazzacca (1995) examined the relationship between gender and clinical presentation in adult celiac disease. Unsurprisingly, females outnumber males in Coeliac Society membership figures worldwide, with a ratio of 2:1 noted in the United Kingdom (McConnell, 1981; cited in Logan et al, 1983). Females comprised three quarters of respondents in Stuart's (1997) survey of 1,887 Australian Coeliac Society members and the mean age overall was 48 years (range: 3 to 89 years), with the ages of children responding via a parent included in that calculation.

A potentially gender-related selection advantage that has been surmised to be associated with CD, and may partially explain the prevalence and stability of CD in modern populations, is a low male sex ratio in the offspring of women with CD (see Hozyasz, 2002; James, 2001). Hozyasz (2002) made intriguing observations of historical mechanisms that may have counterbalanced an increased overall morbidity and mortality in CD. These partly related to a higher proportion of female births to women with CD, based on the finding by Norgard, Fonager, Sorenson and Olsen (1999) that the male sex was proportionately lower than an expected value in a Danish cohort.

Anecdotal observations among general practitioners, gastroenterologists and Coeliac Society staff in Victoria suggest that more males than females who are referred to the state support centre (for CD and GFD information) fail to make initial contact, or quickly lose touch with their local support group. Furthermore, the author's direct observations, accrued during years of involvement

as a Victorian Coeliac Society committee member and reinforced during the extensive interviewing of 110 CD patients involved in the present study, are that adult female CD patients often report having brothers and sons with a range of unexplained health problems, depressive symptoms or even classic features of CD. The males in these women's lives often refuse to be tested for CD or, even if diagnosed, regard the GFD as effeminate. These males are unlikely to persevere with the GFD consistently, if at all. This problem may be somewhat exacerbated in countries like Australia, where relatively high wheat and beer consumption is interwoven within the local social milieu. Australian males are also typically discouraged from expressing concerns about ill-health, contextual to a macho undercurrent which permeates an otherwise laid-back local culture that may not be conducive to inquisitiveness about one's health, or a resolve to follow dietary restrictions.

Relevance of Gender to Depression in CD

Periodically, initial calls are received at the local Coeliac Society support centre from newly diagnosed patients who present as severely depressed and sometimes acknowledging suicidal ideation. Despite the fact "psychiatric morbidity is a leading cause of disability among adult celiacs" (Hallert, 1987, p. 127), suicidality in CD patients is only occasionally reported (e.g., Pellergrino, 1995). Even so, eight cases of self-poisoning (equating to 2.1% of the sample) were recorded in a large British CD series (Holmes, 1997) and suicide was the cause of mortality in three out of twenty-three (i.e., 13% of) deaths recorded among 98 Danish non-tropical sprue patients diagnosed in the two decades (1964-1982), before they were traced via the national Central Person Registrar (Nielsen et al., 1985). The three reasons cited were depression, severe abdominal pain and osteoporosis (due to chronic back pain/ steroid treatment), with various health complications noted in other surviving and deceased patients.

In Australia, the first-time callers to the Victorian support centre mentioned above are not uncommonly young men who rarely call back and typically do not wish to (and cannot) be traced. Given that; (a) young men per se are in a very high risk category for completed suicide in Australia (de Looper & Bhatia, 2001) and elsewhere (Clark & Fawcett, 1992); (b) the physically ill, in general,

are at greater risk of suicide (Peruzzi & Bongar, 1999); (c) the baseline risk of experiencing depression appears to be specifically increased in CD (see Hallert, 1984, 1997); and (d) depression is possibly the single greatest indicator or predictor of suicide (Isometsä, Aro, Henriksson, Heikkinen, & Lönnqvist, 1994), early psychological assessment, and intervention if required, might be especially indicated in some newly identified CD subgroups. These include patients expressing suicidal ideation, those exhibiting questionable self-care behaviours or simply low motivation, due to accompanying depression, or patients with reduced support and lower socio-economic status, who presumably also comprise a significant proportion of those least inclined to either make contact with their local CD support group or able to comply with the GFD.

In people with a history of depression, the lifetime risk of suicide in untreated mood disorder may reach 19% (Montano, 1994). The lifetime risk in the general population for developing various mood disorders range from 10-25% for women and 5-10% for men (for Major Depressive Disorder; APA, 1994) and about 6% overall for Dysthymic Disorder (APA, 1994). As noted, there is an increased prevalence of both Major Depressive and Dysthymic Disorder in CD (Carta et al., 2002), with subclinical thyroid disease touted as "a significant risk factor" in the possibility of their development (p. 789). A major differential diagnosis for these two mood disorders is Mood Disorder Due to a General Medical Condition (APA, 1994), an entity which, intuitively, may be highly applicable in CD and requires closer inquiry.

An overlap between various categories of psychiatric diagnoses is not uncommon, nor is an increased prevalence of other mental disorders if a mood disorder already exists (APA, 1994; Fawcett & Kravitz, 1983). Certainly, the issues involved in assisting people with CD to recognise, accept and/ or embrace their illness, and managing the emotional, technical, practical and social implications of the GFD, are of direct relevance to health professionals involved in their care. The extent of compliance with the GFD may also be pivotal upon the recognition, by gastroenterologists, general practitioners and dietitians, that patients require encouragement and validation of their experiences of the GFD, as well as factual information, clear advice and medical follow-up and monitoring.

Gluten-Free Dietary Treatment and Compliance

Anderson (1960) proved that the mucosal damage in CD is reversible by adopting a GFD, without which "a regression of intestinal damage...is a very rare event" (Carroccio et al., 2001, p. 1105). Strict, lifelong GFD adherence, although challenging, is indeed the only recognised and effective treatment for people diagnosed with CD (Howdle, 1994). Described as "easy to prescribe but hard to follow" (Lohiniemi, 2001, s14), the exclusion of gluten "induces remission but not cure" (Ryan, 2000, p. 835). Nutritional deficiency correction, management of decreased bone density, ongoing assessment for related disorders and annual follow-up (by a gastroenterologist) are other "mainstays of treatment" (Ryan, 2000, p. 838; see also Ciclitira, 2001). Membership of a coeliac association or support group is also highly recommended (Selby & Faulkner-Hogg, 1998; Fasano & Catassi, 2001; Ryan, 2000), since supported patients cope better and adhere more consistently with the dietary and lifestyle adjustments (Lohiniemi, 2001).

The intestinal damage in CD is caused by the alcohol-soluble prolamin fraction of gluten; that is, gliadin in wheat, secalin in rye and hordein in barley (Wieser, 1998), with "potency proportional to their nitrogen content" (wheat > rye > barley; Duggan, 1997, p. 312) and the effects probably dose-dependant (McNeish, 1980). Besides being widespread in bread, pasta and pastry products, gluten is undisclosed or hidden in many food additives, modified starches, stocks, thickeners, malt extracts, sauces and alcoholic beverages (Price, 1997; Selby & Faulkner-Hogg, 1998). Gluten may also be an inactive excipient in medications (Fasano & Catassi, 2001; Pham & Barr, 1996). At the lower end of the consumption continuum, "the relationship between the quantity of gluten ingested and the severity of the histological and clinical abnormalities in CD patients is still unclear" (Catassi et al., 1998, p. 97). The effect of trace amounts of gluten on CD patients is subject to ongoing research (Selby & Faulkner-Hogg, 1998).

In Italy, where the cost of gluten-free food for CD patients is partially covered by the national health care system, unintentional gluten ingestion was reported in correspondence by Ciacci and Mazzacca (1998). These authors noted that a single dose of 100 mg of gliadin, or even smaller

amounts ingested continually over a prolonged period, may damage the intestinal mucosa. They analysed the gliadin content of common, putatively gluten-free foods in key food groups, finding that 6.4% of "gluten-free" foods could be potentially toxic, exceeding 30 mg of gliadin per 100 grams. Gluten-free flours were found to be the most suspect.

Oats have been determined to be relatively safe for adolescents and adults with CD in the preceding decade (Hallert, Kilander, et al., 1999; Janatuinen et al., 2002; Lohiniemi, Mäki, Kaukinen, Laippala, & Collin, 2000). Studies in children are lacking, but Holm, Vuolteenaho, and Mäki (2000) reported an absence of antibody responses in 10 out of 14 children aged over seven years during a 24 month challenge. Two children had symptoms of vomiting and diarrhoea within hours of oat ingestion, albeit without gut inflammation.

Størsrud and Lenner (2000) showed that the addition of oats to the GFD increased nutritional status over two years in another small, adult Swedish series, members of whom subjectively experienced a "tastier and more varied diet" (S19) and also improved symptomatically. However, cross-contamination with gluten between the harvesting and final production stage is believed to be a principal reason apparent sensitivities are often reported (Fasano & Catassi, 2001; Hallert, Kilander, et al., 1999). Unfortunately, unadulterated sources of oats are not yet available in Australia (Ryan, 2000), and have therefore been explicitly excluded from the local GFD by leading dietitians (Selby & Faulkner-Hogg, 1998). Contamination, as well as secondary food intolerances, may account for the adverse effects CD patients sometimes report in relation to other gluten-free grains, such as quinoa and amaranth, which, if sourced and produced unadulterated by gliadin, are otherwise suitable, nutrient-dense options.

Other alternatives to gluten containing grains include rice, maize (i.e., corn, or as polenta), soy, millet, sorghum and soba (buckwheat), chickpea, lentil (e.g., dhal), faba (or fava) bean; popular in the Mediterranean/ Middle and Near East, arrowroot (tapioca/ cassava), breadfruit (Artocarpus incisa), sago or taro flours (used throughout Oceania), and potato, almond meal, lupin, psyllium, and rapeseed (see also Selby & Faulkner-Hogg, 1998). Indeed, there are plentiful leguminous plants, pulses, starchy vegetable or tubers and grass varieties in the plant kingdom available to, or

potentially suitable for, people with CD. Several of the latter, lesser known choices, which are dietary staples in some Asian and Pacific regions, are gradually becoming more accessible to people with CD, as commercial food manufacturers worldwide recognize the specific dietary needs in CD. A gluten-free "grainaissance", lead by Italy and the Nordic countries (see Lohiniemi, 2001) is increasingly palpable in Australia, where a prodigious increase in the importation and local production of suitable grains has been witnessed, coeliac-friendly corner store merchants are no longer a rarity and commercially viable gluten-free bakeries now exist. From a health perspective, many of the abovementioned foods offer the advantage of being relatively unprocessed compared to the more widely available gluten-containing products, an additional consideration in the event of CD-associated illness (e.g., diabetes mellitus).

Furthermore, notwithstanding the inconvenience, substitutions required and restrictions involved, "homemade gluten-free pasta is as well or better digested than gluten-containing pasta" (Clemente et al. 2001, p. 110). Certainly, the GFD has generally been believed to be at least adequate nutritionally. However, the latter assumption has been questioned, especially in relation to the B-group vitamins (Thompson, 1999), which occur naturally in unrefined grains. Homocysteine, a metabolic marker of vitamin B_6, folic acid and B_{12} status, was elevated in 41% of a Swedish cohort of biopsy-normalised CD patients treated for ten years, indicating the likelihood of inadequate vitamin intake (Hallert, Lilliecreutz, et al., 1999; see also Hallert, Grant, Grehn, et al., 2002).

Raised homocysteine, like LDL cholesterol, appears to be a significant risk factor associated with cardiovascular disease mortality (Alfthan, Aro, & Gey, 1997), although the level of risk remains unresolved (Wilson, 2002). However, since many treated CD patients also consume higher levels of dietary fat than untreated patients and controls (Capristo et al., 1997), and homocysteine is carried by LDL cholesterol (McCully, 1999), raised homocysteine in two out five CD patients warrants further analysis of the GFD, as formulated by CD patients with and without dietetic advice.

Neurotoxicity has also been linked to increased homocysteine levels (Lipton et al., 1997). Homocysteinemia is associated with neurological and psychiatric disorders, including Alzheimer's

disease (Clarke et al., 1998) and schizophrenia (Regland, Johansson, Grenfeldt, Hjelmgren, & Medhus, 1995). Vitamin B_6, B_{12} and folic acid (the latter being reduced in 85% of new CD patients in one series; Hallert, Tobiasson, & Walan, 1981) each have an integral protective role in reducing homocysteine levels (McCully, 1999), as well as their direct involvement in neurotransmitter production (Sauberlich, 1991). Unrefined grains, whole meal bread, fortified breakfast cereals, wheat germ and malt – among the items most difficult to replace in a GFD – are major sources of vitamin B_6 and folic acid.

The modern way of life makes it awkward to maintain a diet free from gluten, let alone a nutritionally complete and balanced one, with compliance waning over time (see McCrae, Eastwood, Martin, & Sircus, 1975). More than one third of Quebecers with CD recently reported difficulty in adhering to the GFD (Lamontagne, West, & Galibois, 2001). Travelling, dining out, fast food and convenience eating are particular challenges. Apart from the scarcity of gluten-free items in certain settings (e.g., sandwich bars), additional problems include undeclared ingredients, incomplete, unclear or inaccurate food labelling and cross-contamination in the process of cooking (e.g., the use of cooking surfaces or implements exposed to gluten). Undoubtedly, "more stringent regulations and more precise identification of ingredients in processed foods would make it easier for those affected to obtain a safe and varied diet in our culture of heavily processed food" (Murray, 2002, p. 362). Unsurprisingly, lack of awareness about CD among health care professionals extends throughout the hospitality industry, where a waiter's failure to communicate a gluten-free requirement request or a chef's inadvertent use of gluten, oversight or misunderstanding may result in days of acute GI distress for a CD patient.

Moreover, accidental gluten exposure entails more than a short-term, painful or uncomfortable experience. Delayed reactions involving significant histological damage, with villi taking weeks to normalise, may occur following a single gluten challenge. Those experiencing severe reactions upon exposure may decide eating out is simply not an option. Giving, receiving and sharing food, attending work luncheons and dining with family or friends is a normal part of most people's lives, but constant uncertainty about whether a given meal is gluten-free accompanies every outing for someone with CD.

Since radically compromising one's way of life by entirely avoiding eating in public is hardly appealing, many people with CD get into the habit of pre-preparing their own food. Although the alternatives to wheat flour are relatively limited in variety, less palatable and more expensive (Barr et al. 1993) than their gluten-containing counterparts, CD patients are often sufficiently amazed at the improvement in their general health and well-being to at least attempt to follow the prescribed diet. For the long-suffering, newly identified person with CD, feeling healthy is frequently a novel experience. This was portrayed by Greco (1997), in recounting the words of an apparently oligosymptomatic CD sufferer, who was struck by the sheer "pleasant[ness]" of his existence on the GFD, having previously been "convinced life required tolerance, hardship, patience, sometimes misery..." (p. 13). This newfound vitality and exuberant outlook following dietary change encapsulates the experience of many people first detected with CD in middle or later life. In a large scale survey in the United States, improved quality of life after diagnosis was reported by 77% of respondents (Green et al., 2001).

Despite the relief of diagnosis and experience of radically improved health, rigorous compliance with the specified diet is difficult to sustain. For a range of practical, social, cultural and psychological reasons (Becker, Maiman, Kirscht, Haefner, & Drachman, 1977; Buckfield, 1997) this is especially the case for children and adolescents (Booth, 1991; Cinquetti, Micelli, & Zoppi, 1997; Cinquetti et al., 1999; Della Morte et al., 1992; Ljungman & Mydral, 1993; McNeish, 1980), people diagnosed late in life (Hankey & Holmes, 1994), people with intellectual limitations (e.g., Down's syndrome), symptomless patients (Catassi, Rätsch, Fabiani, D'Angelo et al., 1998), patients from minority groups (Butterworth, Banfield, Iqbal, & Cooper, 2002) and adolescent males compared to females with CD (Greco, Mayer, Ciccarelli, Troncone, & Auricchio, 1997).

In contrast to the findings regarding dietary compliance, women prepare the family meal more often than men, possibly influencing observations of reduced female, compared to male, life quality (Hallert et al., 1998) and increased perceptions of burden of illness among women with CD (Hallert et al., 2002). Reviews of follow-up studies indicate that only 17-65% of adolescent and adult CD

patients sustain a strict GFD (Kaukinen et al., 1999) and 30-50% of patients have dietary transgressions later in life (Mäki & Collin, 1997). Poor compliance is the main reason for an unsatisfactory response to the GFD and health complications.

Buckfield (1997), at the Centre of Applied Psychology, University of Canberra, investigated whether a wide range of biomedical and attitudinal factors influenced GFD compliance. She surveyed one hundred Australian Capital Territory members of the Coeliac Society of New South Wales. A multiple linear regression analysis showed that the perceived utility of the GFD by patients and, to a lesser degree, time on the GFD, accounted for the greatest amount of variance in dietary compliance. Greater non-compliance was associated with low perceived benefits, high perceived costs, low self-efficacy and a longer time on the GFD. There also appeared to be a lack of knowledge about the long-term consequences of non-compliance among people with CD and of the presence of gluten in certain ingredients and food products. Interestingly, health belief models predicting that many of the factors examined by Buckfield would underpin significant variance in dietary adherence (e.g., Becker et al., 1977) were not verified, with 80% of variance in compliance unexplained.

Poor compliance in children with CD was "correlated with poor knowledge of the disease" among their parents, which was "in turn related to the family's social status (Jackson, Glasgow & Thorn, 1985, p. 672). The level of knowledge about CD has also been assessed by Ciacci, et al. (1998) in their study of depressive symptoms in adult CD. An inverse "trend towards correlation" (p. 249) was found between depressive symptomatology and CD knowledge. The latter entity was in turn significantly correlated with higher socioeconomic levels (itself based on educational attainment and work status). No interactions with compliance were reported.

Buckfield (1997) suggested the strong need for interventions involving education programmes and greater assistance for people who do not join support groups. However, at the present time, broader-based health campaigns are unlikely to be inclusive of coeliac content, or sensitive to the specific needs of people with CD, who are therefore strongly "encouraged to join their state Coeliac Society" (Ryan, 2000, p. 835) by Australian gastroenterologists. Recent evidence found membership of a Coeliac

Society correlated most strongly with self-rated compliance with the GFD in English CD patients of Caucasian extraction (Butterworth et al, 2002). Other factors correlating with GFD compliance in Butterworth et al.'s study, in descending order of strength of significance, were a detailed explanation of CD by a physician, regular dietetic follow-up and the affordability of gluten-free products, understanding food labelling, getting sufficient prescription gluten-free products, having a follow-up small-bowel biopsy, and obtaining gluten-free products on prescription. Compared to Caucasians, compliance was poor among South Asian CD patients, who reported feeling relatively dissatisfied with information provided by doctors and dietitians, and "were less likely to attend dietetic clinics... or be members of the Coeliac Society" (A18).

Certainly, membership with a local coeliac association enables personal contact with other CD sufferers, invaluable both after initial diagnosis and following the honeymoon period of improved health described by many CD patients (e.g., Lohiniemi, 2001), after which medical follow-up, ongoing interpersonal support and sustained dietary compliance, are essential to health maintenance, but incumbent on the patient. The GFD remains the cornerstone of treatment, notwithstanding the wish expressed by many CD patients that "one day a pill, vaccine, or preventative measure might perhaps be available to save them from a lifelong restricted diet (Lohiniemi, 2001, s14).

In relation to this hope, double blind clinical trials are underway in Melbourne, Australia, to assess the effectiveness of an enzyme supplement protective against gluten challenge in diagnosed adult patients (Macrae, Cornell, Stelmasiak, & Bhatal, 2002). This enzyme is capable of digesting (in vitro) the proteins of wheat, barley, rye and other cereals that damage the small bowel in CD. Its preliminary usefulness in human CD patients, if proven, may be limited to reducing health risks associated with inadvertent ingestion of small amounts of gluten in people with relatively mild enteropathy. A "possible enzyme therapy strategy" has also been proposed by others, stemming from independent research simultaneously underway at Stanford University (Hausch, Shan, Santiago, Gray, & Khosla, 2002, p. G996; see also Shan et al., 2002).

Macro-level Issues and Food Labelling

Australia's national coeliac society recommends a strict GFD treatment regimen and only endorses food products that are 100% gluten-free. This absolute standard of no detectable gluten ("in practice, less than 0.003% gluten"; Ryan, 2000, p. 836) is also favoured in New Zealand, whose food authority is aligned with Australia's, Canada, the United States, Italy, Spain and Austria. It is more stringent than the contentious international protocol currently approved by most government bodies or dietetic associations elsewhere throughout Europe, which permit 10 mg of gliadin per day for CD patients, generally in the form of wheat starch based gluten-free products (Ryan, 2000; Selby & Faulkner-Hogg, 1998). This was also the case in Australia prior to 1994.

In accordance with the Codex Alimentarius Commission of the Food and Agricultural Organization of the United Nations and the World Health Organization, this more permissive protocol translates as a definition of gluten-free food that permits up to 0.02% gluten (Ryan, 2000), or 0.3% protein from gluten-containing grains in foods labelled gluten-free (Faulkner-Hogg, Selby, & Loblay, 1999). Such products are more economically viable and readily available than the totally gluten-free alternatives, and appear to be well tolerated by many people with CD (Lohiniemi et al., 2000). On the other hand, "the consumption of trace amounts of gluten, traditionally allowed in a Codex-GFD, could be responsible for the continuing symptoms seen in some patients with CD" (Faulkner-Hogg et al., 1999, p. 784; see also Chartrand, Russo, Duhaime, & Seidman, 1997). Zarkadas and Molloy (1996) reported that Italian doctors have declared it "...unethical for medical doctors to prescribe foods containing any amount of gluten in diets for CD, when they know that even small amounts of gluten can increase the risk of osteoporosis, malignancies and other complications" (p. 3). Pre-diagnosis, though, many patients' daily life will have revolved around the convenience of readily available, commercially made, processed foods (i.e., cereal, sandwiches and pasta).

Not infrequently, lactase deficiency coexists with untreated CD. If associated with the intestinal damage preceding CD diagnosis, lactase activity recommences in many Caucasian patients following adherence to the GFD. Since a continuation of diarrhoea after gluten withdrawal may be secondary to

a lactase insufficiency that is associated with GI infections or imbalances predating CD diagnosis (e.g., bacterial overgrowth; Hallert, 1984), or is co-dependant with or exacerbated by CD, a lactose-free, as well as GFD may be necessary "until there is substantial histological improvement" (Barr et al., 1993, p. 9), or indefinitely if a lactase-deficiency is substantive to CD. Fortunately, it appears that "lactose intolerance does not affect the severity of osteopenia" in CD (Lanzarotto et al., 2000, p. S22), with 26 out of 42 lactose intolerant patients in an Italian series osteopaenic or osteoporotic, compared to 13 out of 30 who were lactose tolerant, a statistically insignificant result. Furthermore, many dairy products, such as yoghurt, cottage and hard cheeses, in which lactose is pre-digested, absent or minimal, are well tolerated by people who are lactose intolerant. The lactobacilli in fermented products may supplant, support or even stimulate the body's capacity or ability to produce its own lactase, aiding the synthesis and absorption of many micronutrients, including calcium (Lee, 1988). Importantly, these foods, combined with gradual and/ or limited increments in lactose ingestion, may therefore have a dietary role in the treatment of osteoporosis (Lee & Krasinski, 1998; Tamm, 1994), so prevalent in CD pre- and post-diagnosis (McFarlane et al., 1995). Concern about the development of osteopathy, and prevention of other long-term complications of CD, as well as the sensitivity of many patients to marginal or even trace amounts of gluten, have contributed to the formal adoption zero tolerance to gluten by the medical establishment and dietetic fraternities in Australia.

Following intense lobbying by CD sufferers, the Coeliac Society, the Dietitians Association of Australia, general practitioners, paediatricians and gastroenterologists, changes to the Australian Food Standards Code were foreshadowed in 1994. From March, 1995, the Australian National Food Authority required that foods labelled as gluten-free cannot contain any detectable gluten, while low gluten products must not have more than 0.02% gluten (Faulkner-Hogg et al., 1999). A clearly displayed panel providing nutritional information is now required if a food is described as being either gluten-free or low gluten. The accuracy and reliability of detecting gluten in food diminishes at very low levels (Price, 1997) and was a major impetus behind the adoption of no detectable gluten as the local GFD standard. These changes put Australians and New Zealanders with CD in the position

of being able to make highly informed choices when formulating their GFD. A counter argument is that this unconditional benchmark is not proven to be absolutely necessary in the majority of people with CD. It has also been regarded as excessively restrictive from a patient's standpoint and a deterrent to the provision of gluten-free foods, from a cost and convenience viewpoint, and even the legal perspective. The latter issue has been observed in the case of a major Australian airline, whose temporary response to a complaint about the addition of a bread roll to an otherwise gluten-free meal was to remove the gluten-free option from the menu.

Whilst evidence exists that very small amounts of daily gluten (as contained in thickeners or even wheat starch) may not adversely affect health in many CD cases, an essentially zero default setting regarding gluten intake nevertheless confers several advantages at an individual and population level. A flow on effect subsequent to rigorous food labelling in Australia has been the accelerated emergence of exclusively gluten-free products, available in supermarkets, and menu items in restaurants, that are indeed far more likely to be genuinely gluten-free. In addition to increased safety for CD patients who are highly gluten-sensitive, all CD patients may enjoy greater peace of mind, as well as enhanced choice, when shopping or dining out. Another benefit of strict, medically endorsed GFD restrictions and highly regulated food labelling laws is a reduction of confusion about the GFD among medical staff and key allied health care professionals, including dietitians, who may only see a small number of CD patients annually, among CD patients themselves about what is permissible in the GFD, and among food industry personnel who are responsible for manufacturing, preparing and distributing gluten-free food, or relaying information regarding the GFD requirements.

At a population level, the mere principle of zero tolerance towards gliadin is also more likely to raise thresholds regarding the degree of reduction, if not elimination, of both obvious and hidden sources of gluten by CD patients (and food providers). At this time, a source of oats guaranteed to be free from contamination with gluten is becoming commercially available in Australia, as a direct result of sustained demand by local CD patients based on expectations of zero gluten content (and increased awareness of CD). The vast majority of local patients who previously avoided oats –

perhaps unnecessarily – may be more likely to add this nutritious food to their diet, also improving variety, as aforementioned (Størsrud & Lenner, 2000).

Worldwide, different nations may be assisted or disadvantaged by idiosyncratic conditions that impact on endeavours to meet local GFD standards. In the United States, for example, maize – compared with wheat in Australia – is a predominant grain, so thickeners, starch and flour mixes, sauces and additives in many foods are more likely to be gluten-free. On the other hand, the development of, agreement to, and enforcement of food regulations becomes even more challenging in a much larger comparative population, with a higher number of regulatory authorities and greater dissemination of powers across many more states and sub-jurisdictions.

Although Australian food labelling laws have been found to be contravened in the case of many new and pre-existing food products, the various state Coeliac Societies, which are well coordinated nationally, keep a close watch on all edible commodities marked "gluten-free" and are in a position to provide regularly updated information to Society members, including those newly and distantly diagnosed. The compilation of a commercial gluten-free food directory is no longer undertaken, given that information may be "out of date even before printing" (Price, 1997, p. 5), but the national society endorses foods that are tested and found to have no detectable gluten via the use of a gluten-free logo. Australian CD patients and their families benefit considerably – in many other ways – from membership of their state Coeliac Society and local support groups. "Dietary support and information is critically important for the maintenance of diet restrictions in coeliac disease" (Ryan, 2000, p. 838) and local websites are increasingly helpful (e.g., www.coeliac.org.au – the Australian Coeliac Society). Practical aids include the national Coeliac Society's extensive, annually updated, ingredient list, which can be used in conjunction with current information on the gluten-content of most commercial foods (available from each state office), and identity-information cards, designed to assist in conveying clear, specific information when dining out (see Appendix A). These cards declare "I have been medically diagnosed a 'coeliac'" and are available in many European and Asian languages.

Overview of Coeliac Disease

Coeliac disease is an autoimmune enteropathy with multifactorial genetic underpinnings. It is caused by gluten ingestion, in up to approximately 1% of ethnically Caucasian populations, fewer than 20% of whom are clinically diagnosed, even where high CD awareness exists. Prior to universal treatment with the GFD, provoked by Dicke's (1950) World War II observations, the outlook for people with acute CD was bleak. Today, though, sound health is attainable via the meticulous, sustained exclusion of dietary gluten and the spryly identification and decisive management of concomitant sequelae. Complying with the GFD is very challenging from a practical and psychological viewpoint. Gluten is ubiquitous in processed foodstuffs, food labelling cannot be taken fore granted as exacting, and an element of risk always accompanies assumptions that foods prepared by others are gluten-free. Confidence in accepting and embracing, rather than concealing one's illness, including communicating one's needs assertively, is indispensable when eating out socially. These personal qualities often take time to develop, especially in younger patients.

Extra attention is also imperative to ensure the GFD is nutritionally complete (Hallert, Lilliecreutz et al., 1999). On a positive note, "its emphasis on fresh fruits and vegetables" (Ryan, 2000, p. 838) and the necessity of querying or avoiding almost all processed foods, may motivate and facilitate the adoption of exceptionally healthy dietary habits. The opposite consequence – of substituting high fat foods to compensate for lowered caloric intake (due to a diminished choice of carbohydrates in the GFD) – has been observed after diagnosis (Capristo et al., 1997) and may be detrimental to health.

There is a great breadth of clinical presentations in CD (Fasano, Guandalini, & Kagnoff, 2000). These range from acute illness in infancy, following weaning, to asymptomatic screening-detected cases in adulthood. In some high-risk groups (e.g., relatives of people with CD) the proportion of symptomatic to asymptomatic cases may be surprisingly greater in adulthood (e.g., Berti et al., 2000), in contrast to an increasingly higher ratio of atypical to typical symptoms at diagnosis at many centres (e.g., Sanders et al., 2002). Although clinically apparent loss of vitality is often precipitous just before diagnosis, the erosion of health is frequently insidious, even in childhood-

detected cases (Anderson, 1969), and, eight decades on from Still's (1918) observations, it remains "by no means easy to be sure of the date of onset" (p. 163). In spite of doughty resistance in the face of long-term, unexplained loss of well-being pre-diagnosis, a dramatic dénouement of health in untreated sufferers classically precedes – and unfortunately remains crucial in ultimately ensuring, let alone expediting – clinical diagnosis, in many people found to have CD (e.g., Lohiniemi, 2001).

Seemingly mild presentations, in which CD has been previously unsuspected, make up a proportionately greater percentage of total diagnoses, if, when and where CD awareness is increased. In most diagnoses designated as silent or oligosymtomatic, there is actually a history of chronic or recurrent ill-health, typically dating back years or decades. At least one serious, and not uncommonly inveterate, health complication (e.g., skeleton pathology) usually accompanies diagnosis, with an increased duration of gluten exposure pre-diagnosis possibly heightening the risk of developing other autoimmune disorders (Ventura et al., 1999).

Clinical depression, a common observation prior to treatment, may antedate CD diagnosis by many years (Goldberg, 1970; Hallert & Åström, 1982). Although salient psychological amelioration is evident upon intervention with the GFD in numerous cases, and many of the physical markers of illness improve, above-average depressive symptomatology is still witnessed post-diagnosis in a significant proportion of patients (e.g., Addolorato et al., 2001.). These authors, like Hallert, Åström, and Walan (1983), observed that lowered mood may initially be intractable post-treatment, at least without intervention additional to the GFD (Hallert, Åström, et al., 1983). Conversely, "psychological issues [whilst a legitimate consequence of CD] can often divert diagnosis" (Marziani & Pianaroli, 2000, S14), and, if GI symptoms coexist, may "simulate a functional [10] abdominal pain". This is a serious issue previously noted by Hallert (1984) that may lead to incorrect diagnoses and prolonged, unnecessary suffering. In younger CD patients, irritability, restlessness, hyperkinesis or inattention

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[10] "Functional gastrointestinal disorders (FGD) are the result of disordered GI function in the absence of known pathology of structure. FGD are among the commonest medical conditions" (Jones et al., 2000 p. ii2)

may be misinterpreted pre-CD diagnosis as having a behavioural aetiology. In adult patients, apathy and lassitude parallel the lack of concentration, distractibility and peevishness described in coeliac children, or irascibility seen in adolescents with CD, but may also "mimic psychiatric disturbance" (Hallert, et al., 1998, p. 936), notwithstanding the existence of genuine depressive illness or symptomatology at higher than expected levels (Goldberg, 1970; Hallert, & Åström, 1982).

Tentative impressions of a constellation of symptoms resembling DSM-IV dysthymic disorder or ICD-10 neurasthenia (WHO, 1993) may be titrated from the literature. In a modified version of the Zung Self-Rating Depression Scale, "psychologic" and "biologic" items made equivalent contributions to increased depressive symptoms in a large, Italian CD group (Ciacci et al., 1998), and "a tendency for greater impairment to occur in the mental domains of the SF-36 than the physical ones" (p. 936) was noted by Hallert et al. (1998) among treated female CD patients.

The hypothesis that somatic-affective (rather than cognitive) elements – which may represent the somatic features of mental or physical illness, or both – preponderate among a substantial number of mildly depressed or apparently dysthymic CD patients, will be investigated in the current thesis. Anger is a clinical dimension in psychiatry that often overlaps with depression (Fava & Rosenbaum, 1999; Glenmullen, 2000), but anger levels are a relatively unknown quantity in CD and will be investigated in the cross-sectional and longitudinal studies of this thesis. Elevated anxiety in CD recedes after diagnosis (Addolorato et al., 2001) and the quality of life subsequently improves (Mustalahti et al., 2000), but does not quite reach usual community levels, particularly in women (Hallert et al., 1998).

Results ostensibly suggesting otherwise (Lohiniemi, Mustalahti, Collin, & Mäki, 1998) have been partly interpreted by those authors in terms of a sense of relief upon diagnosis "at getting an answer to unexplained complaints", that was conceded to be an overly optimistic "impression of perfect health" (p. 76). General psychological well-being may indeed noticeably improve after implementation of the GFD in relation to a CD patient's former emotional state and general expectations, but – abstrusely – ebb after many years of following the GFD, compared to the general

population (Lohiniemi et al., 1998; see also Hallert et al., 1998).

Intellectual ability remains intact in adults with longstanding CD, even prior to GFD treatment (Hallert & Åström, 1983), but the question of fine gradations in cognitive functioning after dietary treatment has not been the subject of large, case control studies (Collin, Eerola, & Pirttilä, 1997), in spite of the not infrequent finding of neurologic complications in CD, especially in men, despite the greater female incidence of CD (Hadjivassiliou et al., 1998), also noted by Ciclitira (2001). Neuropsychological status, quality of life and mood/ affective state are three key, interconnected, but somewhat neglected, areas of coeliac research addressed in the cross-sectional and longitudinal studies comprising this thesis. The next chapter will review previous biopsychosocial, physiological and neuropsychiatric research in CD, framing the current project.

Chapter 2: Psychophysiology of Coeliac Disease

The physical effects of CD, by encroaching upon multiple metabolic processes (Howdle, 1997), not infrequently involving the endocrine and nervous system (Gobbi et al., 1997), influence the psychological functioning of those affected. Numerous underlying mechanisms are proposed (Hallert, Åström, & Sedval, 1982; Holmes, 1997; Luostarinen, Collin, Peräaho, Mäki, & Pirttilä, 2001; Wills, 2000), with depression the predominant psychiatric problem encountered (Addolorato et al., 2001; Goldberg, 1970; Hallert & Åström, 1982; Carta et al., 2002). Secondary psychological reactions in CD also originate from several sources. These include the realisation that CD is a complex, lifelong health issue involving permanent dietary and lifestyle restrictions (Cinquetti et al., 1999; Gasbarrini & Addolorato, 1997). The sense of self may be affected. Perceptions of inferiority and vulnerability in response to delayed, interrupted or less than optimal physical development were noted by Hallert (1987). A disruption in early relationships and family dynamics has also been observed (Gardiner, Porteous, & Walker-Smith, 1971; Marziani & Pianaroli, 2000; Prugh, 1951). Adolescence, a key period of identity formation, may be especially challenging in CD (Fabiani et al., 2000).

Quality of life in CD is significantly affected in children (Kolsterman et al., 2001) and adults (Grech et al., 2000; Lohiniemi et al., 1988), with the GFD failing to restore life quality to healthy community levels (Hallert et al., 1998). This issue is pronounced in women (Hallert et al., 1998), who perceive the burden of their illness as greater than their male counterparts (Hallert et al., 2002). Based on those authors' inferences, an underlying reason may be the greater responsibility placed on women, compared with men, to prepare their own gluten-free meals, which is consistent with local Australian observations of the preponderance of female attendees at regular cooking demonstrations provided by the Coeliac Society. Conversely, "an overview of neurologic complications [in CD] reveals a mainly male predominance" (Ciclitira, 2001, p. 1536; see also Hadjivassiliou et al., 1998) – an observation mirrored in neuropsychological findings of male cognitive processing speed inferiority in CD (Grech et al., 2000) – despite a higher incidence of CD in women.

Mood state, cognitive functioning and perceived quality of life in CD are inter-related entities, each partly a function of having a chronic illness per se (Wells, Golding, & Burnam, 1988) and many CD-specific variables (Hallert, 1987; see also Hallert et al., 2002). These include the severity of CD, ranging from quiescent to debilitating, and one indication of which is the magnitude of steatorrhoea (i.e., fat malabsorption) at diagnosis. This key symptom significantly correlated pre-treatment with the level of depression in CD (Hallert & Åström, 1983). Other hypothetical variables include the symptomatic period (pre- and post diagnosis), duration of gluten exposure (see Ventura et al., 1999), degree of dietary compliance in CD (see Buckfield, 1997; Mayer et al., 1991), and interaction of various other inherent and exogenous psychosocial factors, such as spousal or family support. Direct research primarily focussing on these interactions is lacking.

Prior studies have generally failed to find clear-cut associations between GI symptomatology and mental state in CD (Goldberg, 1970; Hallert, Åström, 1982) or, for that matter, other physical and psychological factors, except for the correlation between fat malabsorption and depression mentioned and a cause/ effect relationship linking nutritional (vitamin B_6) status and depression (see Hallert, 1997), to be discussed shortly. In the present thesis, such considerations were of interest, with key measurable health-related indices documented in all participants.

Historical References to Neuropsychiatric Disorders in CD

Although evidence of neurological, psychiatric and psychological complications of CD have accumulated during the preceding century, the exact prevalence and nature of these sequelae are difficult to catalogue accurately for numerous reasons. Firstly, different researchers have included (or omitted) various conditions under many umbrellas such as *neuropathy*, *neurological disturbances* and *psychiatric disorders*. In some studies, only severe or diagnosed psychiatric disorders were considered, whereas others included subtle signs of disorders, mild or transient affective symptomatology, or a prior history of psychiatric disturbance in their prevalence estimates. Secondly, information from referral centres such as coeliac societies or gastroenterology clinics may be unreliable because patients are

drawn from selected groups. Although the most severely ill patients in the clinical spectrum are often observed in a consecutive series of hospital-based clinical diagnoses, the opposite may be true in other circumstances (e.g., screening studies). Thirdly, the duration of undetected CD and stage of GFD treatment profoundly influences both prevalence estimates and the apparent severity of complications. A succession of CD patients assessed at diagnosis or in the early stage of treatment with the GFD may display higher levels of psychological disturbance than long-term patients compliant with the GFD.

The literature abounds with adjectives pertaining to the breadth of psychological sequelae encountered in CD. Affected children have been portrayed as "irritable, fretful, capricious or peevish" (Gibbons, 1889; cited in Gardiner et al., 1971, p. 39) and "characteristically unhappy" prior to gluten restriction (Challacombe & Wheeler, 1987, p. 145). Daynes (1956) reported "naughtiness, depression and fits due to wheat sensitivity" in the context of a "pre-cœliac syndrome" in young children, marked by "irritable, negativistic and spiteful" behaviour and disturbed sleep remitting upon gluten exclusion (p. 391). Reference was made to a "headache/ insomnia/ depression (H.I.D.) syndrome" in adults with CD (p. 392). The demeanour of gluten-intolerant people has also been described as "turned inward", "rigid" and "schizoid" (Hunter, 1987, p. 13), which relate to supposed associations of CD with schizophrenia and autism (Dohan, 1970, 1980, 1983; Rudin, 1981; see also Bersani, De Palma, Sandri, & di Pietralata, 1997; Coleman, 1997; and Marson, Michetti, & Volterra, 1997; in Gobbi et al, 1997).

Purported connections between CD and schizophrenia stemmed from an improvement and earlier hospital discharge in psychotic patients on cereal and milk-free diets (Dohan, 1973), positive worldwide correlations between major mental illness diagnoses and gluten consumption, histories of CD in the childhood of some schizophrenia patients and isolated case studies (see Dohan, 1983; Pfeiffer, 1984), not all of which found an improvement on the GFD (e.g., Storms, Clopton, Wright, 1982). Suggestive reports still appear (e.g., De Santis, 1997), but no cases of schizophrenia were found in a large Swedish epidemiological CD study (Hallert, 1982). Also, "no evidence was found to link schizophrenia with CD" in an MMPI profile of CD patients compared to surgical controls (Hallert, 1987, p. 129), nor was CD detected in two separate groups of autistic children displaying GI symptoms

(McCarthy & Coleman, 1979; Walker-Smith, 1973). Table 1 provides an overview of the current status of a selection of neuropsychiatric and neurological entities with CD, with the strength of association denoted by the number of plus (+) signs, on the balance of empirical evidence.

Table 1

Current Status of Association of a Selection of Neuropsychiatric and Neurological Entities with CD; Entities under Direct Investigation in Present Thesis are Underlined

Entity	Status	*Association*
ADHD	6.8% of GFD treated CD patients had ADHD characteritiscs[1]	–
Anger	No prior studies; state/ trait anger assessed in present thesis	?
Asperger's syndrome	Reported by Asperger[2] 40 years ago; unsubstantiated	–
Ataxia	Atypical symptom reported as part of cerebellar syndrome[3]	+++
Anxiety	State-anxiety elevated pre-GFD[4]; normal levels post-GFD[4]	++
Autism	Isolated case reports; Unconfirmed[5]	–
Cerebellar syndrome	Many case reports[6]	++
Cognition (specific skills)	Visual discrimination and short-term memory reduction[7]	+
Dementia	Uncommon[8]; refractory where identified[9]	– / +
Depression	Common at diagnosis[10]; significant incidence post-GFD[11, 12]	+++
Depressive symptomatology: [MMPI]	Elevated pre-/ post-diagnosis[12] (psycho-vegetative and subjective depression components prominent)[13]	+++
[Zung SRDS]	About half of CD patients affected pre-/ 1 year post GFD[14]	
Dysthymia	Very common; 23% of small Italian CD series[15]	+++
Down's syndrome	Definite association[16]; gluten-independent	+++
Epilepsy/ seizures	Association in two geographic areas (e.g., Italy[17]; Ireland[18])	+++
Intellectual capacity (overall)	No consistent signs of impairment in Swedish series[19]	–
Migraine	Often reported anecdotally; some evidence[20]	+
Neurological disorders [of unknown cause]	CD not uncommon[21]; screening recommended[22]	++
Peripheral neuropathy	Case reports in middle-aged coeliac men[23]; otherwise rare[24]	– / +
Quality of life	Slightly but significantly reduced, especially in women[25]	++
Schizophrenia	Popular theory in 1970s[26]; epidemiologic evidence lacking[27]	–
Spinal cord degeneration	Several case reports[28]; infrequent finding	– / +
Substance-related disorders	Unknown; reduced incidence of cigarette smoking[29]	–

Strength of Association Key: +++ (strong); ++ (moderate); + (weak or inconsistently replicated) – / + (ambiguous/ unknown) – (Doubtful)

Note: References in Table 1 (1-29) are listed in numerical order in Appendix B.

Wills, Turner, Lock, Johnston, Unsworth and Fry (2002) recently noted that "neuropsychiatric complications have been reported in up to 26% of [CD] patients" (p. 259). Indeed, it is not uncommon in the CD literature to find high rates of reported neuropsychiatric symptomatology (e.g., Kozlowska, 1991) or disorders (e.g., Carta et al., 2002) among CD patient groups, but negligible increases above expected levels of the prevalence of CD if screening is undertaken in psychiatric patient groups. Admittedly, the latter effect is susceptible to the unreliability of identifying relatively low incidence entities (i.e., CD) in already highly selected groups. For instance, Pynnönen, Isometsä, Aalberg, Verkasalo, and Savilahti (2002) found only one case of CD in a screen of 140 new adolescent psychiatric outpatients, but clearly the absence of this sole CD patient, or addition of just one or two extra CD patients (by chance selection), would have dramatically altered this result.

It may be further argued that, due to high CD awareness in Finland, potential CD patients would be relatively likely to be identified prior to the development of neuropsychiatric complications attributable to or associated with CD. Conversely, Kozlowska (1991), in an "evaluation of mental status of [41] children with malabsorption syndrome after long-term [GFD] treatment" (p. 130) found "various psychiatric symptoms...in 48.8%, and EEG abnormalities in 70.7%" (p. 130).

Proposed associations between CD and psychiatric disorders other than depression, and neurologic conditions except for Down's syndrome, epilepsy, cerebellar syndrome and perhaps migraine, have generally been unsustained. Nevertheless, "tangential references" (Prugh, 1951, p. 220), "impressionistic" portrayals (Hallert, 1987, p. 128) and pejorative sounding connotations and extrapolations attached to the descriptions of psychological sequelae in CD are historically widespread.

Prugh noted that the "secondary nature" of reactions arising "from the stresses imposed by protracted illness and difficult management" (p. 220) had traditionally been acknowledged in children with CD, as well as their mothers, and within the mother-child relationship. That author's observations of a series of 14 children with CD indicated to him the evolution "of a consistent though non-specific personality" structure (p. 226), via psychodynamic mechanisms, stemming from the onset and aggravations of illness. According to Prugh, his group of children appeared "to be passive, often

withdrawn, definitely inhibited personalities, commonly exhibiting certain aspects of the obsessive-compulsive trends seen in their mothers" (p. 227). He also observed "intensification" of "irritability and constant crying...during episodes of illness in infants". The "expression of aggressive or angry feelings" in periods of "freedom from exacerbations" (p. 227) was evident in older children. More recently, Carlsson et al. (2001) listed "proneness to nightmares" (p. 45) with two GI symptoms as characterising the symptomatic, screening detected 2.5 year old infants with CD in a Swedish series.

Personality was evaluated in CD from a clinical perspective (see Hallert and Åström, 1982), with only depressive features prominent. Therefore, from the viewpoint of Hippocrates' conceptualisation of four fundamental personality dimensions (see Davison & Neale, 1990) – as represented by essential bodily fluids (blood, yellow bile, black bile and phlegm) – surfeit black bile, producing a pessimistic persona or "melancholic" temperament, may be conjured to depict a "coeliac personality". Abundance of blood results in an optimistic attitude and extraverted behaviour, with the converse – introversion – not infrequently seen in CD, although an inhibited, withdrawn or gloomy outlook may also reasonably reflect the reality of poor ongoing health, or indeed clinical depression, rather than true personality traits. Moreover, the relative optimism, calmness and relief observed in patients after diagnosis (e.g., Lohiniemi et al., 1998) is preferentially suggestive of Hippocrates' "sanguine" dimension.

In his view, excess lymph resulted in a stoic and apathetic (or "phlegmatic") disposition – evocative of Greco's portrayal of the long-suffering, but indomitable adult sufferer who soldiers on in the face of wretched health prior to CD diagnosis. Finally, anger and irritability, pointing towards the "choleric" disposition, was represented by the yellow bile; vividly reflected in Prugh's younger coeliac patients, who are perhaps less equipped to cope emotionally and socially with fluctuating ill-health preceding identification of CD, and who may also suffer from the effects of clinical depression, albeit expressed differently. The irascibility and turmoil observed in children often recedes post-diagnosis, further supporting the likelihood that peculiarities of affective functioning observed may be ascribed to depressed mood directly attributable to biological mechanisms stemming from untreated illness (Hallert & Sedvall, 1983; Hernanz and Polanco, 1991), and reflecting a "reactive condition",

as opposed to enduring "personality traits" or typologies (Gasbarrini & Addolorato, 1997, p. 350).

Described behaviours and suggested underlying dynamics in Prugh's series of coeliac children (and their mothers) were presumably potentiated by many uncertainties owing to a lack of awareness of the primary cause CD at that time, with universal dissemination of Dicke's findings imminent but not yet embraced by paediatricians in the United States (Allen, 1996). Nevertheless, Prugh's detailed observations, including those of largely repressed, but at times increased, "resentment, hostility and anger" (p. 227), have contemporary implications. Since present day CD diagnoses are often delayed until adulthood in a substantial proportion of cases, aspects of the psychodynamic processes and perturbations inferred by Prugh, if considered valid, are still likely to operate. After diagnosis, adolescent patients may also be "angry at society for pitying them" (Ashkenzai & Barash, 1992, 240).

Glenmullen (2000) has noted that core psychological symptoms of depression (i.e., feeling helpless, hopeless and worthless) "represent...stifled anger and sadness turned against oneself" (p. 271). In undetected CD, uncertainty about the cause of feeling physically and emotionally unwell may fuel resentment against others (e.g., health care practitioners), but ultimately revert to anger at oneself and consequently depression. After diagnosis, the rigours of a restricted lifestyle, including the ubiquitous infiltration of gluten into everyday foods, can also lead to futile bitterness towards the external world that is eventually turned inward, sustaining depression in some cases.

Behavioural Disturbance Prior to Diagnosis: Case Reports

Hernanz and Polanco (1991) noted that nine out of fifteen children exhibited signs of behavioural disturbance pre-CD diagnosis that improved after GFD institution. They reported that untreated, symptomatic children "can be irritable, querulous, depressive, apathetic, or negate, and they also may present with stereotyped movements" (p. 1480). Contained within patients' perspectives of CD compiled by Bennet (1998), diagnosed herself in 1995, are the poignant personal stories of 7 men and 14 women who grappled with elusive symptoms, often underlying troubled behaviours, throughout various life stages. One elderly patient frequently admonished and spanked for eating dirt and stealing

food from garbage cans recalled that "her father had mistakenly thought she was just being a naughty child. She reflects, 'This was very cruel as I was getting no nutrients from my food and that was reason I was always starving'" (p. 9). Another patient reported "constant nightmares" in childhood (p. 61), concentration problems throughout life and losing track of conversations midstream, but managed to graduate from college late in life, muddling "through with sheer determination and persistence" (p. 63).

Recently, Pynnönen, Isometsä, Verkasalo, Savilahti and Aalberg (2002) retrospectively detailed the effect of untreated CD on the "development of mental disorders in children and adolescents" (p. 331). In two compelling case studies, those authors described how one patient "had serious problems controlling her temper and problems with explosive anger" (p. 332), while another met the criteria for "intermittent explosive disorder" (p. 333) pre-CD diagnosis. In each case, clinical levels of depression and aggression, as measured by the Beck Depression Inventory (BDI) and Child Behavior Checklist (CBCL) receded significantly post-CD diagnosis, "without psychiatric treatment or known psychosocial factors to explain the remission" (p. 333).

In the subject of the first case study "anorexia nervosa was suspected" and criteria for "eating disorder not otherwise specified" were met "on the basis of an interview with the Schedule for Affective disorders and Schizophrenia for School-Age Children – Present and Lifetime Version" (p. 332). In hindsight (post CD-diagnosis), this diagnosis appeared inappropriate. The latter case report noted "autistic-like" behaviours, "disruptive restlessness", "difficulties concentrating and studying" and "obsessive aggression" for years prior to the identification of CD and "severe and increasing tiredness" (p. 332-333) leading up to the diagnosis. That young patient had also been "shunned by his schoolmates" (p. 332) as a result of his behaviour, compromising his self-esteem to such an extent that he remained withdrawn after CD diagnosis, but was able to successfully return to his studies at the age of 17 and was apparently "coping better with his chronic loneliness" (p. 333).

As reported in Chapter One, behavioural reactions emanating from these early, secondary psychological processes may also deflect investigations of true underlying aetiology (i.e., the existence of CD; Marziani & Pianaroli, 2000). The restlessness, inattention and unruliness of undiagnosed children

(later responding favourably to the GFD) may mimic many of the symptoms of unrelated disorders such as ADHD. As part of a doctorate thesis at the University of Madrid, Martínez-Bermejo (1998) found that 6.8% of GFD treated CD patients had characteristics of ADHD, using DSM-IV criteria. This figure did not differ greatly from rates reported in the general population, ranging from 2.2% to 10.1%, depending on studies cited by Martínez-Bermejo and Polanco (2002). Those authors recently summarised the neuropsychological changes in coeliac disease, in a detailed overview translated from Spanish by a colleague of the author (M. Alvarenga, personal communication, Jan. 2003).

Certain components of the psychological sequelae, even in known CD, remain largely unexplored psychometrically. The true levels of state and trait anger in CD are good examples, and subject to inquiry in adult patients in this thesis. In one of the few reviews even alluding to anger (Goldberg, 1970), that author found "most" idiopathic steatorrhea (i.e., probable CD) patients "can show anger (74%)", in stark contrast to Paulley's (1949) sample, whose personality profile was summarised by Goldberg ("in the interests of brevity", p. 463) as, conversely, being unable to "show anger" (see Table VIII, p.462). Such contrasting results may be interpreted as cancelling each other regarding overall levels of anger in CD. Alternatively, they could point to either normal or elevated – but repressed – angry feelings, either when chronically unwell pre-diagnosis, during perturbations of CD, or as part of a passive/ aggressive mechanism of anger expression, shaped by fluctuating ill-health and related factors from an early age. More recently, Ashkenzai and Barash (1992) noted that in Jewish teenagers with CD, anger may be directed "at society for pitying them and considering them as having a disease" (p. 240).

Subjective feelings, tendencies towards or objective manifestations of irritability, "contrariness" (as noted by Sheldon, 1959, p. 137) or overt anger may be connected in several ways to the development of individuality and temperament in relation to coping with having a chronic, but in Paulley's time, undefined illness (still relevant today), and, in the GFD era (from the decade post-WWII), managing a restricted diet, disease exacerbations related to deviations from the GFD and primary CD-related psychological processes akin to the aetiologies proposed in relation to depression.

Recently, Ciacci, Iavarone, Siniscalchi, Romano and De Rosa (2002) noted that "anger was the

predominant emotion that induced patients to transgress" from the GFD, being "inversely correlated with actual compliance" (p. 2082). People with CD, especially those moderately to severely affected or noncompliant with the GFD, may also be less resilient to extraneous stressors, and more susceptible to developing psychiatric disorders or clusters of symptoms across the mood and affective spectrum.

In his review of previous surveys, Goldberg (1970) concurred with findings of an above-average existence of depressive and obsessional traits, emotional reactivity and sensitivity, and introspection/ introversion in relation to his sample, with the depressive aspects most pronounced. Against the backdrop of Dohan's and others' hypotheses of links with psychotic and developmental disorders (discounted by Hallert, 1984), other researchers have further pondered the existence of a distinct coeliac personality, most often associated with depression and anxiety in CD. These include Gasbarrini and Addolorato (1997), who found no evidence for trait anxiety in CD, but indications of reactive (state) anxiety and depression in a small CD group, compared to healthy controls.

More recently, Carta et al. (2002) reported that "compared to controls, a significantly higher number of CD patients met criteria for lifetime and 6-month major depressive disorder (MDD) and lifetime panic disorder" (p. 789). Addolorato et al. (2001) noted a significant elevation of state anxiety at diagnosis compared to healthy controls, which decreased one-year post-GFD to control levels, but above-average depressive symptomatology that did not remit.

Previously, Hallert and Åström (1982) reported that the Minnesota Multiphasic Personality Inventory (MMPI; Hathaway & McKinley, 1951) depression subscale was the only scale clinically elevated in 12 consecutive adult CD patients (mean [M] T score = 70.3, SD = 12.5) compared to 12 matched surgical controls (M = 59.2, SD = 9.3), selected from patients awaiting elective cholecystectomy. Further delineation using the Harris subscales revealed that subjective depression (D1), psychomotor retardation (D2) and Physical Malfunctioning (D3) were significant elements in the elevation observed by Hallert and Åström (1982) in Scale 2 (compared to controls), which remained clinically significant after institution of the GFD and folate supplementation, but normalised following additional treatment with pyridoxine (i.e., vitamin B_6; Hallert, Åström, & Walan, 1983).

Neurological Complications in CD: Underlying Mechanisms

Relationships between enteric diseases, GI and neurological functioning have been well described a propos possible gut-brain effects (e.g., malabsorption) and vice versa (e.g., defects of gut innervation) in detailed reviews (Perkin & Murray-Lyon, 1998; Willis & Hovell, 1996). The preceding chapter demonstrated that as CD awareness increases and screening programs expand, the subclinical part of the coeliac iceberg is exposed. In turn, the proportion of minimal-symptomatic cases increases. It may be expected that "the complications of malabsorption will become rare" (Collin, Eerola, & Pirtillä, 1997, p. 285), but more subtle signs of long-term ill health, including neurological manifestations, such as dementia, will be detected. The apparent prevalence of psychopathologic processes in CD populations at any time is probably balanced by the marriage of both truths, in that a diminishing frequency of severe CD-related malnutrition as a primary cause of psychopathology is being counterpoised by an increased identification of cases involving neuropathy stemming from circuitous and protracted immune-mediated pathogenic mechanisms, either operating concurrently and independently of CD (e.g., common genetic linkage; Luostarinen et al., 2001) or indirectly (e.g., extra-intestinal immunologic pathways; Gobbi et al., 1992), via gliadin-related or auto-antigen activation due to CD (Howdle, 1997). The multiple genetic underpinnings involved in susceptibility to CD, combined with great individual variation in vulnerability to the neuropathic changes potentially associated with CD, make the task of pinpointing related pathways very challenging.

In a significant number of cases, CD is being diagnosed after the detection of neurological disorders (Luostarinen et al., 1999). A re-emerging recognition and interest in cerebral dysfunction and the clinico-neuroradiological aspects of CD has been precipitated by new structural and functional imaging technologies (see Gobbi, Andermann, Naccarato, & Banchini, 1997), further influencing the apparent strength of association between CD and various neuropathologies (Wills, 2000).

Where detected, brain atrophy in CD is most often found in the cerebellar regions, the deep grey and brain stem nuclei, and the spinal cord tracts (see Collin, Eerola, & Pirtillä, 1997 for a review). The cerebellar damage is marked by Purkinje cell loss and the "deep grey matter structures affected include

the thalamus, caudate nucleus, globus pallidus, putamen, amygdala, anterior hypothalamic nuclei, periaqueductal grey matter, corpora quadrigemina, the substantia nigra, and the red nuclei" (Perkin & Murray-Lyon, 1998, p. 296). These structures are involved in mood attenuation, memory and fine motor function (Kolb & Whishaw, 1990). The resultant clinical syndrome – typically ataxia and peripheral neuropathy in adult cases – is frequently resistant to the effects of GFD intervention and/ or supplementary nutrition (e.g., folic acid, B_{12} and/ or vitamin E therapy). However, Pellecchia et al. (1999) reported "a clear improvement of clinical and electrophysiologic abnormalities and resolution of villous atrophy" (p. 1607) after two years of the GFD in 34-year-old man with a seven year history of slowly progressive ataxia. White-matter lesions have also been found in one in five GFD treated children with CD (Kieslich, Errázuriz, Posselt, Moeller-Hartmann, Zanella, & Boehles, 2001).

A proliferation of case studies emerging in the preceding decade (Collin et al., 1997) has illustrated a significant incidence of neuropathy in newly diagnosed CD patients (Luostarinen et al., 1999) and, conversely, a greater than expected prevalence of CD in people with occult or cryptic neurological dysfunction (Hadjivassiliou et al., 1996), which is often identified prior to CD (Cooke & Thomas-Smith, 1966; Hadjivassiliou et al., 1998). In cases of "gluten ataxia", about 80% of patients have the same HLA DQ2 (=70%) or DQ8 (=10%) genetic profile ordinarily observed in CD, but "20% have the HLA DQ1...not yet reported in association with CD" (Hadjivassiliou et al., 2002, p. 1226).

A modest but significant association between epilepsy and CD, with or without evidence of concomitant cerebral calcification, has also been reported worldwide, in Ireland (Cronin et al., 1998), Finland (Luostarinen et al., 2001) and Italy, where the combination of CD, epilepsy and intracranial posterior calcification is widely reported (see Gobbi et al., 1997). Immunological mechanisms, probably independent of malabsorption in CD (Fasano & Catassi, 2001), may underlie this correlation, but the aetiology remains speculative. Although some case reports have demonstrated improvements in intractable epilepsy following CD diagnosis and adherence to the GFD (see Cronin et al., 1998), the consequences of untreated CD in concomitant cases are yet to be fully elaborated.

The Down's syndrome/ CD association is gluten-independent (Fasano & Catassi, 2001). Specific

genetic underpinnings are possible (Salur et al., 2000), but, with the exception of Down's syndrome, "the mechanism of links between neurological diseases and CD... cannot be simple, because a substantive number of factors (nutritional, immunological, neuroendocrine, etc.) may be involved" (p. 709). Salur et al. (2000) ruled out the "induction of cross-reactive immunological reactions against brain tissue" (p. 710) in the development of neurological diseases in their study, which found a "high frequency of CD among children with neurological disorders" (p. 707). Kieslich et al (2001) found brain white-matter lesions in 15 (20%) of 75 young, diet-treated CD patients ranging in age from 2.8 to 24.2 years (mean of 11.6 years). They held the view abnormalities "may be ischemic in origin as a result of a vasculitis or caused by inflammatory demyelination" (p. e21). Salur et al.'s (2000) and Kieslich et al.'s (2001) results indicate "CD should be suggested as a differential diagnosis in children with unclear white-matter lesions" (Salur et al., p. e21), or in any neurological irregularities of uncertain aetiology.

Luostarinen et al. (2001) reported a 16.7% CD frequency in patients with ataxia of unknown origin when cases of alcohol abuse were omitted, suggesting the possibility of a "shared and immunologically mediated mechanism contributing to the mucosal and neural tissue damage" (p. 447). Pratesi et al. (1998) observed that "sera from patients with active CD contain IgA antibodies that react with human brain vessel structures" (p. 817), while Alaedini et al. (2002) identified serum anti-ganglioside antibodies "reactive against brain gangliosides" in 6/ 27 CD patients (p. 145), proposing that "the neuropathy of celiac disease may be autoimmune and associated with anti-ganglioside antibodies" (p. 145).

In a review of neurology and neuropathy in CD, Wills (2000) noted the predominance of "case reports...small, uncontrolled studies" and "idiosyncratic definitions of gluten sensitivity" (p. 445), upon which several etiological theories are speculated, commenting that "separating the wheat from the chaff" in the neurology of gluten sensitivity is not straightforward (Wills & Unsworth, 2002, p. 519). Wills (2000) isolated immunological dysfunction, citing potential pathogenic mechanisms, and "disordered metabolism secondary to trace vitamin deficiency" (p. 445) as likely causes of neurological complications in CD. For other useful contributions in this area, see Piattella et al. (1997), Pengiran Tengah, Wills and Holmes (2002) and Hadjivassiliou et al. (2003).

Orthomolecular Psychiatry: Nutritional Deficiency in CD

Collin, Eerola, and Pirtillä (1997) have noted that "in earlier [CD] series, many neurological symptoms have been the consequence of severe malabsorption" (p. 285). The existence of sustained nutritional deficiencies during the untreated phase of illness may indeed contribute to, or specifically underpin, several of the mental abnormalities observed in CD, especially changes in mood state (Hallert, Åström, & Sedval, 1982; Hallert & Åström, 1983; Holmes, 1997; Morris, Ajdukiewicz, & Read, 1970; see also Hallert, Mårtensson, & Allgén, 1982), some aspects of which may improve on the GFD (Hallert & Sedvall, 1983), or additional supplementation with pyridoxine (Hallert, Åström, & Walan, 1983).

In the case of pyridoxine, Morris et al. (1970) "confirmed that pyridoxine deficiency occurs in adult celiac disease and that the restriction of gluten from the diet appeared to affect pyridoxal levels favourably" (p. 549). Those authors noted that CD patients in another series (Cooke & Smith, 1966) had previously "appeared to respond to parenteral pyridoxine therapy", as well as the "similarity between the neurological disorder of adult celiac disease and that seen in mood states of disturbed pyridoxine metabolism" (p. 549) observed by Cooke and Smith (1966). Delayed and reduced uptake has also been noticed upon oral loading in the untreated phase of CD in young children, compatible with a shifting of the site of absorption away from damaged areas, as well as reduced overall absorption (Reinken & Zieglauer, 1978). These results were in agreement with earlier data (Reinken, Zieglauer, & Berger, 1976).

Tryptophan metabolism and serotonin production are certainly dependent on pyridoxine and other micronutrients (which function as coenzymes in key steps; Hallert, 1987), with a disruption in these processes related to mood disorder in children with CD (Challacombe & Wheeler, 1987; Hernanz & Polanco, 1991), even after GFD treatment, and in adults (Hallert, Åström, & Sedval, 1982). As noted earlier, clinically significant depression observed in the MMPI profiles of newly detected CD patients was refractory to GFD treatment and concomitant folate supplementation, but remitted in response to vitamin B_6, supplied over a six-month period prior to re-assessment

(Hallert, Åström, & Walan, 1983). A dose of 80mg, at least forty times above the Australian recommended daily intake (of 1-2mg, depending on age, gender and other factors; Truswell, 1990), was used in this study. Hallert (1987) subsequently concluded that "there is good evidence to implicate metabolic effects from vitamin B_6 deficiency in the pathogenesis of depression in adult celiacs" (p.133).

It could also be surmised that the body's own production of niacin (partly supplied in the diet), which is dependent on adequate tryptophan and vitamins B_1, B_2 and B_6, may also be compromised in CD, increasing the risk of marginal or deficient status, a known factor in the depressive aspects of pellagra. Interestingly, dementia is part of the "classic triad of pellagra: dermatitis, diarrhea, and dementia" (Baron, 2002, p. 1282), the latter beginning "with insomnia, irritability, and apathy", progressing to "confusion, memory loss, hallucinations, and psychosis. The diarrhea can be severe and may result in malabsorption due to atrophy of the intestinal villi" (p. 1282). Although non-specific, these universally documented effects of niacin deficiency are remarkably inclusive and descriptive of those observed in undiagnosed CD, and possibly not incidental in some cases.

Holmes (1997) also noted that pathological lesions located in the brains of some CD patients may be reminiscent of particular deficiency states, including pellagra, the classic niacin (B_3) deficiency disease (also inclusive of pyridoxine and tryptophan insufficiencies; Pfeifer, 1975), Wernicke's encephalopathy, which is primarily caused by a vitamin B_1 deficit in alcoholics (Kolb & Whishaw, 1990), and the generalised avitaminosis status of malnourished prisoners of war.

Folic acid deficiency has been found in CD (e.g., Hallert, Tobiasson, & Walan, 1981). Although low folate has been separately linked to psychiatric disorders, especially depression (Young, 1989, 1991) and neurological disease (Reynolds, Rothfeld, & Pincus, 1973), it is possibly less crucial in the potential development of neural atrophy than other nutritional inadequacies in CD (Collin, Eerola, & Pirttilä, 1997; Hallert, 1987). The aforementioned finding of raised homocysteine in treated CD cases (Hallert et al., 1999) may be symptomatic of decrements in the intake, absorption or metabolism of vitamin B_6 and B_{12}, as well as folic acid, in CD, as indicated by those authors. Cyanocobalamin (B_{12})

status has generally been found to be adequate in the majority of CD patients, or only marginally reduced (Holmes, 1997), but was deficient in four out of ten newly diagnosed patients in a recent Scottish series (Dahele & Ghosh, 2001), with levels normalising on the GFD.

Reduced absorption of iron is usually involved in any of a range of anaemic conditions in CD, which together account for one of the most common observations at – and principal reasons leading to – initial diagnosis. Iron deficiency, also "the most common nutritional deficiency worldwide, has negative effects on...motor and mental development in infants, children and adolescents" (Looker, Cogswell, & Gunter, 2002, p. 2114) and has been implicated in behavioural lability (Lozoff, 1989). Its role in mental health in CD requires further investigation.

Deficiencies of vitamin E have been implicated in neurologic degeneration associated with a range of diseases involving chronic fat malabsorption. These include abetalipoproteinaemia (Muller, Lloyd, & Wolff, 1983), small bowel resection (see Federico, Battisti, & Dotti, 1997) and cystic fibrosis (Sung, Park, Mastri, & Warwick, 1980). Low serum concentrations of vitamin E, secondary to impaired fat absorption (which also impacts on vitamin A, D, K and essential fatty acid assimilation), have also been found in CD patients, including those with neurological disorders (Harding, Muller, Thomas, & Willison, 1982; Muller et al., 1983; see also Holmes, 1997) and may be significantly involved aetiologically (Ackerman, 1989; Trabert et al., 1992). In addition, vitamin E functions synergistically, as an antioxidant, with the trace mineral selenium (Mindell, 1982).

Selenium is of considerable importance to human health (Rayman, 2000). Its deficient or marginal status has been implicated in lowered mood state during a double-blind crossover trial on the standard Profile of Mood States (POMS) inventory (Benton & Cook, 1991) and in a double-blind study using the POMS Bipolar form (Hawkes & Hornbostel, 1996), while supplementation has reduced intractable seizures in children (Ramaekers, Calomme, Vanden Berghe, & Makropoulos, 1994; Weber, Maertens, Meng, & Pippenger, 1991). Selenium has also been found to be deficient in patients noncompliant with the GFD or in the early stages of GFD therapy (Kalita et al., 2002). It was even suppressed in clinically well people on the GFD, compared to healthy controls (Hinks, Inwards,

Lloyd, & Clayton, 1984), and in treated Scottish children with CD, in relation to the standard reference range for whole blood selenium content (Ward, Arthur, Russell, & Aggett, 1984).

The fact that lower levels of selenium have been found in CD patients on both a gluten-free and unrestricted diet, compared to healthy controls (Cortigiani, Nutini, Caiulo, Ughi, & Ceccarelli, 1989), suggests that the GFD itself, as well as primary malabsorption, may play a role in reduced levels in some patients. Selenium's additional roles in immunocompetence, thyroid functioning (which may impact on mood, behaviour and cognitive function; Sher, 2001) and cancer mortality (reviewed by Rayman, 2000) underline the range of potential implications of malabsorption, deficiencies and under-nutrition in CD on physical and mental health.

In the case of many micronutrients that may be reduced in CD, such as selenium and vitamin D, there is often a narrow range between a marginal or overt deficiency, adequate dietary levels, therapeutic doses and potential toxicity, as well as intricate interrelationships and synergy between different nutritional co-factors, so any supplementation addition to the GFD needs to be carefully medically assessed and monitored.

Multiple nutritional deficiencies associated with CD pre-diagnosis, especially of the B vitamins (including, but unlikely to be limited to, B_3, B_6, B_{12}, folic acid and B_{12}) and tocopherols (vitamin E), major electrolytes (e.g., magnesium and potassium) and other less-studied micronutrients such as selenium, may presumably aggravate or even instigate neuropsychiatric problems in some CD patients. It is also plausible that the effects may resemble, either clinically or at a neuro-imaging level, processes in other types of nutrient malabsorption (e.g., cystic fibrosis), depletion (e.g., alcoholism) and deficiency states (e.g., starvation), that lead to protracted avitaminosis.

The current consensus is that any sustained orthomolecular insufficiencies in CD appear more likely to be involved in neurotransmitter dysregulation, in turn associated with decrements in mood state (Hallert, 1997), than overt "cell degeneration in brain tissues" (p. 213). In addition to reduced uptake or assimilation of vitamin B_6, these nutritional shortfalls include "enhanced enteric protein loss" pre-diagnosis (Hallert, 1987, p. 131), expressly involving degradation of tryptophan – a

marginally available, essential amino acid even under optimal physiological conditions (Chaitow, 1991) – by gut bacteria (Cluysenaer & Van Tongeren, cited in Hallert, 1987), probable mineral deficiencies other than selenium and iron and the likelihood of marginal status in relation to many vitamins. Use of therapies additional to the GFD, including supplementary dietary regimes, were noted in the interviews of all CD participants and their healthy and disease control counterparts in the present thesis, in view of their potential effect on health and mood state and the previously identified therapeutic role of pyridoxine in CD (Hallert, Åström, & Walan, 1983).

In the preceding decade in Australia, it was estimated from community samples that 25.8% of Australians (30.3% of women and 21.3% of men) used vitamin or mineral supplements in the fortnight prior to interview (National Health Survey, 1995), compared to about 40% of United States citizens in similar surveys (Ervin, Wright, & Kennedy-Stephenson, 1999). In another representative survey of South Australian residents in 1993 (MacLennan, Wilson, & Taylor, 1996), 48.5% of respondents reported using at least one non-medically prescribed alternative medicine in the preceding year, with non-prescribed vitamin use most commonly reported (41.2% of females and 33.8% of males). Given moderately and possibly increasing use of vitamin use in Australia (Australian Institute of Health and Welfare, 2000) and potential roles for vitamin supplementation as an adjunct to GFD treatment in CD patients with refractory depression, the incidental level of supplement use among local CD patients, compared to healthy controls, was considered especially noteworthy, and was monitored in the present thesis.

It should be noted that not all CD researchers perceive nutritional deficiencies to be a key factor in observed neuropsychiatric complications. For example, Magauddu et al. (1997) remarked that "no correlation between the neurologic disorder and a nutritional deficiency could be established" (p. 127) in a number of reports and studies (e.g., Cook, 1976; Collin et al., 1991). These authors favoured "the hypothesis of a common genetic origin for CD" (p. 128) and neurological disorders, ahead of nutritional and other causes. However, aetiological models and evidence for other pathways leading to neural dysfunction in CD are relatively scarce at present.

Federico, Battista, and Dotti (1997) made reference to a multi-faceted model of neuroaxonal degeneration in psuedoglutaric aciduria II, inclusive of concepts of nutrient malabsorption, as well as immunological abnormalities, toxins, environmental stress and genetic background, which may have some utility in discerning the range of potential pathologic mechanism in CD-related neurological impairment, where this occurs. It is possible that each of these mechanisms may play a role in isolation or in coalition, with the emphasis of one or several accentuated in individual cases.

Depressive Symptomatology, Mood and Anxiety Spectrum Disorders

Four decades ago, Sheldon (1959) noted that there was "little to add to [Gee's 1888] clinical account" (p. 132) in the diagnosis of CD over the "passage of 70 years", except greater awareness "of the psychologic disturbances that may accompany physical disease; certainly the unhappiness of the celiac child is a very typical feature of the fully developed disease" (p. 132). Most recently, and two decades after confirmation of Goldberg's (1970) observation of depression as the key psychological complaint in CD (Hallert & Åström, 1982), Hallert et al. (2002) concluded that "depressiveness appears to be by far the most common neuropsychiatric complication among treated adults" (p. 42), in line with Holmes' (1997) and Carta et al.'s (2002) findings.

Nevertheless, unravelling genuine causality and underlying associations between mood or mental state, potential neuro-radiological or -functional (e.g., neurotransmitter level) correlates, nutritional status, GI symptomatology and other possible indices of pathogenesis or physical markers of CD, remains a complex task. As noted by Goldberg (1970), in the case of diarrhoea – which is common in CD pre-diagnosis – a "well-known psychophysiological relationship" with mood exists, but "what causes what" (p. 462) is unclear. A finer grained analysis by that author in 46 patients with idiopathic steatorrhoea, 23 patients with Crohn's disease and 11 patients with alactasia demonstrated that "diarrhoea is neither sufficient nor necessary for psychiatric illness" (p. 462).

Furthermore, Hallert and Åström (1982) found "no distinct relationship between abdominal complaints – mostly diarrhoea...and pain..." (p. 23) and depression in their aforementioned study of

12 newly diagnosed CD patients (8 women and 4 men), although a positive correlation was found between the degree of steatorrhoea and depression, as noted. Significantly, "early signs of mental depression" have also been observed in malabsorption syndromes other than CD, including those involving fructose (Ledochowski, Sperner-Unterweger, Widner, & Fuchs, 1998) and lactose in females (Ledochowski, Sperner-Unterweger, & Fuchs, 1998). Regarding fructose malabsorption, Ledochowski, Widner, Bair, Probst, and Fuchs (2000) reported that depression scores (using Beck's Depression Inventory; BDI) decreased by 65.2% on a fructose- and sorbitol-reduced diet after four weeks, with the majority of 53 adults showing mild to moderate mood disturbance (BDI score $\geq$ 11) prior to dietary intervention, which those authors associated with decreased serum tryptophan concentrations. Their results highlight both the possible impact on mood of malabsorption of nutrients concomitant with disordered digestion in a general sense and the considerable potential difference in mood pre- and post-dietary intervention.

During the preceding decade, the existence of depression in CD was corroborated, irrespective of aetiology, as a significant issue at several centres throughout Europe, including Germany, the United Kingdom and Italy. In a large scale Italian project specifically investigating neuropsychiatric symptoms in the clinical pattern of CD (Bottaro et al., 1997), data from 550 children with CD (age range 7 months to 17 years) were collected. These authors found that behavioural disturbances frequently presented as an associated symptom at diagnosis. Children less than two years of age often presented with irritability and muscular hypotonia, simulating a peripheral neuropathy, while obsessional neuroses, apathy, epileptic seizures and cerebral calcifications occurred in older children at levels greater than chance.

Vaitl and Stouthamer-Geisel (1992; cited in Hallert, 1997) posted the Hopkins Symptom Check List (SCL-90R) to 182 adult members (mean age 45 years) of the German Coeliac Society. Hallert reported that in the experience of one in two members of that series, their pre-existing CD symptoms (before diagnosis) had been attributed to psychological causes, leading to pharmacological treatment in 32% of the sample and psychotherapy in 14%. These observations are clearly acutely relevant to

clinical and health psychologists, mental health care professionals in psychiatry, and general medical practitioners, who are all likely to come into contact with undiagnosed CD cases in hospital settings, community outpatient settings, and general or private practice. Hallert reported Vaitl and Stouthamer-Geisel's (1992) précis that "coeliacs are apt to show a distinct "psychovegetative" state of exhaustion featuring a depressive component", and "found that patients who had gone unrecognized" as having CD "for many years, or were unable to maintain a strict GFD" once identified, "were particularly at risk of showing symptoms of mental ill-health and to report more pronounced psychological complaints" (p. 212).

Holmes (1997) noted that, in the United Kingdom, depression (at 10.1%), epilepsy (3.6%), migraine (3.1%), anxiety (2.3%), self-poisoning and carpal tunnel syndrome (each 2.1%) were the six most common psychiatric or neurological disturbances among 388 patients with CD attending the Derbyshire Royal Infirmary. In recent Italian research, 92 consecutive adult CD patients ($\underline{M}$ age = 29 years, 76% female) on the GFD for an average of 7.9 years and 48 Hepatitis C patients (serving as "chronic condition controls") were compared with each other, and 100 normal subjects, on a modified version of the Zung Self-Rating Depression Scale (Ciacci et al., 1998). Three items "evaluating gastroenteric symptoms of depression" (p. 247; i.e., decreased appetite, weight loss and constipation) on the Zung were omitted to avoid bias due to CD. Results indicated a strong group effect on depression, with mean scores differentiating CD patients ($\underline{M}$ = 31.81, $\underline{SD}$ = 7.84) from normal controls ($\underline{M}$ = 27.14, $\underline{SD}$ = 5.26) upon post hoc analysis ($\underline{p} < .0001$), and CD scores also significantly lower ($\underline{p} = .038$) than those of Hepatitis C patients ($\underline{M}$ = 28.73, $\underline{SD}$ = 7.09).

Notwithstanding these statistical differences, it is evident that the greatest mean group score difference of 4.67 (between the CD and normal control groups) represents an average item score difference of 0.27 (i.e., 4.67 divided by 17 items), in relation to possible item scores of 1 to 4 for each item, with a higher score corresponding to a greater experience of the particular symptom of depression described by each item. From a clinical perspective, it is arguable that the differences identified by Ciacci et al. are relatively small (with the mean normal control score equal to 85% of

the CD score). Differences in the proportions of CD patients above a certain threshold of depressive symptomatology (compared to the control groups) are perhaps more meaningful. Indeed, while cut scores using the Zung were not provided by Ciacci et al., they reported that depression affected "at different levels, about one-third of coeliacs, in contrast to 1 in 10 [Hepatitis C] patients", suggesting "that depressive symptoms are better related to the characteristics of CD than to a general chronic disease condition" (p. 249). Age at diagnosis, duration of and compliance with the GFD did not correlate with depression in the CD patients. A trend towards an inverse correlation was reported between depression and the CD patients' level of knowledge about CD, prompting those authors to tentatively remark that "depressive symptoms may prevent patients from reaching a high level of knowledge of the disease or, conversely, that a good level of knowledge about the disease could play a role in reducing the depression level" (p. 249-250).

Ciacci et al. reported that "both 'psychologic' and 'biologic' scores were able to distinguish CD patients well" (p. 249) from normal controls ($p < .00001$ and $p < 0.0002$ respectively), but "within the CD group the analysis failed to show a significant difference [between psychologic and biologic scores]" (p. 249). Ciacci et al.'s conclusion that the psychologic – compared to the co-occurring biologic – mechanisms underlying depressive symptomatology were "probably...in our sample, predominant" (p. 250) appeared to be an over-interpretation of the results in relation to the evidence provided. However, their depth of analysis drew attention to the important question of the degree to which either somatic/ affective or cognitive factors, or an equal combination of both, underlie the increased prevalence of depression and heightened intensity of depressive symptomatology frequently reported in CD.

As noted earlier, Hallert and Åström (1982) had previously reported a slight relative increase in the Harris subscales D1 to D3 (i.e., Psychomotor Retardation, Physical Functioning and to a lesser degree Subjective Depression), more so than Mental Dullness or Brooding, compared to controls and Psychomotor Retardation over Subjective Depression within the CD group, using the MMPI. It appeared that somatic, rather than cognitive, indications of depression were possibly of slightly

greater clinical significance in that sample, although neither the Harris subscales nor the MMPI was designed to make these distinctions.

In a smaller study, Gasbarrini and Addolorato (1998) compared anxiety and depression in ten CD patients with the same number of inflammatory bowel disease (IBD) patients and healthy volunteers. The tests used were the State-Trait Anxiety Inventory and IPAT Depression Scale Questionnaire and chi-square analyses were undertaken. A large number of physiological functions were also measured (e.g., serum electrolyte levels). Unfortunately, it was not reported for how long the CD or IBD patients had been treated. Gasbarrini and Addolorato (1998) noted a trend, although not a statistically significant difference in anxiety levels across groups. Participants in the CD group were significantly more depressed than healthy controls but not statistically more depressed than IBD patients, notwithstanding another reported trend.

Gasbarrini and Addolorato (1998) concluded that "the anxiety and depression found in coeliac patients could be secondary to a reduced neuronal production of monoaminergic substances, a mechanism currently implicated in the pathogenesis of behavioural disturbances, and to the emotional reaction to the symptoms of disease which often determine a reduction in the quality of life...It would therefore always be advisable to evaluate not only clinical, laboratory and biopsy parameters in these patients but also carry out a psychometric evaluation to determine the level of anxiety and depression and to distinguish between 'reactive' and 'trait' forms" (p.352-353). In a study reported earlier (Addolorato et al., 1996), using the same measures but a higher number of participants from the same three groups of patients (n = 16), state but not trait anxiety was more common in CD and IBD patients compared to healthy controls and depression was present in a greater percentage of CD patients, compared to healthy controls.

Recent, longitudinal findings at the same centre showed that almost half of a newly diagnosed Italian adult CD group (14 males, 21 females; M age = 29.8 years, SD = 7.4) remained depressed after one year on the GFD, compared to only one in ten healthy controls (Addolorato et al., 2001). Those authors used a cut-score of 37 on a modified version of the Zung Self-Rating Depression Scale

(used by Ciacci et al., 1998, as mentioned above), which corresponded to a point score of 49 on the full Zung Scale, considered high and conferring a positive predictive value of a diagnosis of depression in about nine out of ten people (Magruder, Norquist, Feil, Kopans, & Jacobs, 1995).

Addolorato et al.'s findings suggest that depression may, like anaemia, be very common in CD pre-diagnosis but, analogous to the aforementioned finding of refractory osteopenia in a significant percentage of cases (Kalayci et al., 2001), resistant to early GFD treatment in the absence of additional dietetic, psychiatric or psychological therapies. In contrast to results pertaining to depression, the percentage of CD patients with high levels of state anxiety (71.4%) decreased significantly, compared to controls, after one year on the GFD (to 25.7%), with a cut score of 40 on Spielberger's State-Trait Anxiety Inventory used to designate high or low anxiety. No difference between CD patients and controls was observed in trait anxiety, and the percentage of CD patients displaying high trait anxiety was essentially unchanged after one year of the GFD (25.7% versus 17.1%).

Finally, the most recent research (Carta et al., 2002) has found an increased prevalence of several psychiatric disorders in 36 adult CD patients compared to healthy controls, notably Major Depressive Disorder, Dysthymic Disorder, Panic Disorder and Adjustment Disorder, using DSM-IV criteria and the Italian version of the composite international diagnostic interview (Robins, Wing, & Wittchen, 1989). Carta et al. (2002) implicated subclinical thyroid disease as a "significant risk factor" (p. 789) for psychiatric disorders in CD, in addition to the role of autoimmunity in general, "severe dietary deficits", age of onset of CD and "environmental stress" (p. 791).

In summary, there are many possible causes of depression in CD. These include general biological susceptibilities and endogenous mechanisms related to nutritional deficiencies and/ or immunological factors, primary psychiatric symptomatology associated with aspects of concomitant physical illness specific to CD and secondary psychological reactions connected with uncertainty about the cause of physical illness pre-diagnosis and the ramifications of CD, including the personal and social implications associated with sustaining the GFD post-diagnosis.

Substance Use in Coeliac Disease

Vaitl and Stouthamer-Geisel (1992; cited in Hallert, 1997) found that in half of a large series of 182 adult German Coeliac Society members, symptoms of ill-health prior to CD diagnosis were assessed as having a psychological cause, leading to pharmacological treatment in one in three of these respondents. Since depression is generally more common in CD and antidepressant medication is typically the treatment of choice by general practitioners (Harris & Penrose-Wall, 2001), the German findings may be pertinent to CD populations locally in Australia and elsewhere.

Among 388 patients attending a clinic in the U.K., Holmes (1997) noted eight cases (i.e., 2.1%) of self-poisoning, a finding congruent with greater medication misuse among most populations in which the rate of prescriptions for drugs are increased due to an increased diagnosis of mood disorders (Andrews, Hall, Teesson, & Henderson, 1999; Tippett, Elvy, Hardy, & Raphael, 1994). Indications in the CD literature that people with CD have an increased likelihood of use or abuse of prescribed, or for that matter illicit drugs, or alcohol, are lacking and may be unlikely, outside of the context of pharmacological treatment for mood disorders.

An interesting recent finding in Argentine CD patients was "a positive linear correlation between the age at diagnosis and the estimated daily cigarette consumption in active smokers" (Vazquez, Mauriño, & Bai, 2002, p. 1258). Most of the few studies undertaken indicate a lower prevalence of smokers among CD patients compared to age- and sex-matched controls or community levels (e.g., Snook et al., 1996; Vazquez et al., 2001, West et al, 2002). Perhaps this is related to the fact people with CD struggle enough with their health pre-diagnosis without compounding their ill-health by smoking, and following diagnosis are more health conscious. In any event, a large scale Australian community survey indicates that cigarette smoking – in addition to its relationship with physical ill-health (AIHW, 1996) – is associated with poorer mental health, including depression (Jorm et al., 1999), even after controlling for other well known mediating correlates. Therefore, a reduced incidence of the habit in CD patients is a positive finding. Cigarette, alcohol, prescribed and illicit drug use, based on self-report, were recorded in the histories of all participants in the present thesis.

Neuropsychological Observations

Given that neurological complications have been reported in as many as one third of CD patients (Banerji & Hurvitz, 1971), there have been few studies investigating the neuropsychological impact of CD. Pavone, Mazzone, Incorpora, Drago, and Bottaro (1997) investigated a wide range of cognitive abilities in children with CD. They retrospectively compared two groups, one on a strict GFD (69 children) and another "not completely compliant" (p. 291) group (51 children). Compliance was assessed via blood testing for markers of gluten ingestion. A control group of age-matched children without clinical signs of GI, nutritional or metabolic disease was also included. These authors failed to find evidence in the CD group of neurological or psychiatric problems, but found significant *relative* impairment in the non-compliant CD group in visual discrimination ability and short-term memory. There were not significant differences in mean WISC-R intelligence quotients between the groups. Given the cross-sectional design, it was not possible to determine whether the non-compliant CD group's specific identified deficits were attributable to, or preceded, non-compliant dietary behaviour.

Using the revised Wechsler Intelligence Scale for Children and the Rey-test, Pavone, Mazzone, Incorpa, Drago and Bottaro (1997) found visual discrimination and short-term memory deficits using the latter instrument in a small subgroup of children with CD, compared to healthy controls, "with a slightly more significant occurrence of impairment of these abilities in patients not compliant with the [GFD]" (p. 292). Other cognitive skills were unaffected.

Pavone et al.'s (1997) results were noteworthy, but the significant results pertained to a sample of just nine CD patients, compared to twenty control participants. Therefore, the possibility of a chance finding is increased. Dementia is uncommonly associated with CD (Holmes, 1997) and, accordingly, there was an absence of distinctive signs of intellectual dysfunction in a detailed study of untreated Swedish CD patients (Hallert & Åström, 1983) and in 25 out of 26 Italian CD patients (De Maria, Gorno, Cappa, Guarneri, & Antonini, 1997).

Hallert and Åström (1983) studied a consecutive series of 19 untreated, middle-aged Swedish

patients (M = 48 years, SD = 11; 12 females and 7 males), who were under investigation and later found to have confirmed CD, with a comprehensive psychometric test battery sensitive to neurological illness. That study's results were not suggestive of organic brain disease in CD, at either a group or individual level, notwithstanding that 4 out of 19 patients (i.e., 21%) had an overall pattern of scores falling in the borderline range. The mean scores for all tests fell within one standard deviation of the general population range, based in most cases on the conversion of scores to a stanine scale. In summary, those authors found "no consistent signs of cognitive impairment" (p. 87) and "unaffected intellectual ability" (p. 88). The performance of the 8 patients "with overt illness in their childhood" (p. 88) was indistinguishable from the remaining 11 patients in that series.

De Maria et al. (1997) used tests geared to the detection of posterior impairment, including Benton's Judgment of Line Orientation test and the Rey-Osterrieth Complex Figure (see Spreen & Strauss, 1991) in their assessment of 26 Italian CD patients. All except one patient performed at a level within expected margins. However, those authors also found that all five of another group of patients – having both CD and epilepsy – returned scores in the abnormal range in Benton's test and three out of five scored below normal on the Rey. These two tests have previously been found to best discriminate between patients with early to mid-stage Huntington's disease, in which posterior impairment has emerged, and healthy controls (Grech, 1993).

In a review of dementia, cognitive impairment and brain atrophy in CD, Collin, Eerola, and Pirtillä (1997) published a list of 17 CD patients with known dementia or brain atrophy, noting the degree of cognitive impairment (i.e., mild to severe and/ or progressive) associated with each case. They noted that peripheral neuropathy was the "most frequent" neurological symptom (p. 285), while brain atrophy was often localised in the "cerebellum, deep grey and brain stem nuclei, and spinal cord tracts" (p. 286), with "progressive cerebellar disease" also referred to in relation to other small series.

In bilateral cerebellar-damaged patients without CD, various indices of speed of information processing, movement time and reaction time have been lowered in several studies (see Botez, Botez,

Elie, & Attig, 1989; Botez-Marquard, Botez, Cardu, & Léveillé, 1989; Ivry & Keele, 1989), with "the role of subcortical structures in speed of information processing" well recognised (Beaumont, Kenealy, & Rogers, 1996, p. 202) and higher cortical associations likely (Schahmann, 1991).

Memory impairment was reported by Luostarinen, Pirttilä, and Collin (1999) in their series of CD patients with neurological symptoms, while Bürk et al. (2001) found "moderate verbal memory and executive dysfunction" (p. 1013) in the subset of sporadic cerebellar ataxia patients with gluten sensitivity. In summary, given that "cerebellar damage is commonly reflected in problems of fine motor control, coordination, and postural regulation...some aspects of sensory processing, perceptual discrimination, motor learning and emotionally toned responses" (Lezak, 1983, p. 46; see also Watson, 1978), links appear to emerge regarding the abovementioned psychometric findings of decreased visual discrimination ability and short-term memory, and general observations of increased depression in CD. Additional effects of damage to the cerebellum include "weakness and a tendency to fatigue" (Kolb & Whishaw, 1990) – symptoms often observed post-diagnosis in CD – which may also be elements of otherwise unaddressed depressive illness in CD (Hallert, 1997). Teasing apart respective contributions of neurological damage and clinical depression in the neuropsychological sequelae of CD is therefore problematic.

Considered together, the neuro-imaging, psychiatric, orthomolecular, psychological and case study perspectives lead to the conceivable notion of a continuum regarding the potential neuropsychological performance or status of CD patients. It appears that global functioning remains relatively intact in the majority of patients, but dysfunction ranging from subtle to severe may emerge in the event of untreated or more severe cases of CD, with some of the changes reflected in functional pathology, cerebral atrophy or other structural changes. Collin, Eerola, and Pirtillä (1997) acknowledged the likelihood of "multifactorial" aetiologies underlying any "neurological complications in CD" (p. 288), further remarking that "a cross-sectional study of the intellectual ability of new and earlier diagnosed CD patients is needed" and "the impact of the GFD on intellectual ability must be evaluated" (p. 288).

The evaluation of fine gradations in neuropsychological functioning, including abilities in distinct areas such as verbal comprehension, perceptual organisation, working memory and processing speed, was indeed undertaken in a large adult CD sample, compared to two comparison groups, in Study 1 of the present thesis. Preliminary results using healthy controls have been previously presented (Grech et al., 2000). One year follow-up assessment of a smaller subgroup, newly diagnosed with CD at entry into Study 1, is discussed in Study 2.

Health Status and Quality of Life in Coeliac Disease

Perceived health status and quality of life (QOL) in chronic illness became the subject of increasing research in the preceding decade (Walker & Rosser, 1990), with GI illnesses, including inflammatory bowel disease (ulcerative colitis and Crohn's) the subject of considerable interest (Künsebeck, Körber, & Freyberger, 1990). In Danish inflammatory bowel disease patients, perceptions of diminished life quality were reported in relation to disease exacerbation, but not everyday life, compared to controls with acute short-term illness (Sorenson, Olson, & Binder, 1987). In treated CD patients, subjective health has been found to be slightly decreased, although only in females (Hallert et al., 1998), perceived disease burden was increased, albeit again exclusively in females (Hallert et al., 2002) and female adolescent CD patients report more physical complaints (Kolsterman, Koopman, Schalekamp, & Mearin, 2001). Psychological general well-being was reduced in CD patients, regardless of gender, before and well beyond one year after adoption the GFD, but not at precisely one year post-diagnosis in Finnish patients (Lohiniemi et al., 1998).

In their study of QOL in CD, Lohiniemi et al. (1998) stated that "the life of a coeliac disease patient may be full of contradictions between the difficulty of following the diet and the possibility of complications following an incomplete diet" (p.72). They approached the task of generating a QOL measure relevant to CD by dividing the concept into two aspects: "objectively measurable welfare" (with the concept of health or a disease appearing as signs), and "subjective well-being" (symptoms). Specifically, Lohiniemi and colleagues assessed psychological general well-being (via

a standardized schedule), GI complaints (via the Gastrointestinal Symptom Rating Scale), self-expressed quality of life and self-expressed general health in two groups of CD patients, one assessed cross-sectionally and the other followed longitudinally for one year. These were 188 adults coded as CD patients in the membership register of the Finnish Coeliac Society who had followed the GFD for 7.6 years on average, and 39 newly diagnosed CD patients at the Department of Medicine in Tampere University Hospital. A third, control group consisted of 108 randomly selected, non-coeliac Finnish adults.

The cross-sectional study showed that GI complaints remained common for CD patients on a GFD, while the longitudinal subjects initially reported a marked reduction in GI symptoms, with the symptoms almost reappearing to pre-diagnosis levels over time. Similarly, psychological well-being improved significantly following diagnosis and adoption of the GFD (rising from well below to above normal levels), but diminished over time (to well below normal levels). One could conclude that while the GFD is critical in treating CD, it may not quite be the total cure hoped for. Indications are that the psychological outcomes of CD are complex and separating reactive versus intrinsic factors is not straightforward.

In a not unfamiliar tale in Bennett's compilation of patient perspectives touched on earlier, an adult patient reported that pre-diagnosis "no one understands that when you are hanging on to your life by your fingertips, you either give up or try everything you can to find an answer" (p. 65). Although angst, signs of depression, and eroded life quality evident in many of Bennett's narrative case histories were accompanied by resilience and spirit in the face of relentless ill health, relief and newfound hope just after diagnosis may wane as new realities dawn. These include maintaining a strict diet, managing CD-related complications (e.g., osteoporosis) and other fresh challenges (e.g., weight gain), as well as the normal everyday pressures of life. Although prevailing in the battle with CD may assist some patients to cope better psychologically after the honeymoon period of improved health, the possible effects of CD on physical systems (e.g., thyroid and adrenal function) and psychological state (e.g., reduced self-worth) may leave a legacy, increasing vulnerability to stress and reducing life quality.

In a further study examining psychological general well-being using the Psychological General Well-being questionnaire and the Gastrointestinal Symptom Rating Scale, Mustalahti, Lohiniemi, Collin, and Mäki (2000) found that psychological general well-being improved in 20 silent CD patients ($\underline{M}$ = 105.4 to 115.6; possible score range of 22-132) and in 20 clinically diagnosed patients ($\underline{M}$= 93.3 to 112) after one year on the GFD, compared to just before GFD intervention. The extent of GI symptoms also decreased in both groups in that time. Those authors proposed that screening for CD in healthy family members was therefore warranted on the basis of improvements in QOL.

Hallert et al. (1998) assessed subjective health status in 89 adult CD patients (61% female), treated with the GFD for 10 years and in clinical remission, using the Short Form 36 Health survey (SF-36; Swedish version). Those authors found that CD patients, as a group, scored significantly lower than 5277 age-matched, gender-balanced Swedish adults comprising a normative group in only two of the eight scales, General Health and Vitality, each of which "measure both physical and mental aspects of health" (p. 934). Three each of the remaining six scales (none of which significantly differentiated the CD group from normative scores) were indices of either physical or mental health.

Neither age nor GFD compliance impacted on the results. However, upon gender breakdown, the difference between CD patients' and normative scores was actually confined to female CD patients, who scored significantly lower within the General Health, Vitality and Role Emotional domains, "suggesting poor subjective health and excessive tiredness that tend to interfere with daily activities" (p. 934) and most pronounced in middle-aged women. Among male CD patients, the picture was reversed across most scales, with scores for Bodily Pain and Social Functioning actually lower and higher respectively compared to population norms.

Although no differences were reported in the mean SF-36 scale scores between CD patients in histologic remission compared to those with ongoing, gluten-related mucosal abnormalities, a negative correlation was found, regardless of gender, between subjective well-being and GI symptoms, using the Gastrointestinal Symptoms Rating Scale.

The salient finding of reduced subjective health among female, in contrast to male, CD patients

was tentatively attributed, at least in part, to contextual social factors, such as the greater likelihood of males having "their meals cooked by someone else" (p. 937). Notwithstanding the tendency towards equalisation of domestic duties across gender worldwide in western cultures, at least among younger age groups, this possibility is intuitively appealing in light of the present author's anecdotal observations of Australian CD patients. Local patients' eating habits certainly also parallel the broader societal mores, in which the responsibility regarding food preparation is typically assumed by women, at least in older age groups. This reality is pertinent to the spouses of middle-aged or older men with CD and the mothers, in-laws and relatives of younger men with CD, with the men perhaps perceiving their coeliac needs as readily accommodated and catered for by others, while female patients assume an inordinate responsibility which may be more easily felt as a burden.

With wider, superorder issues in mind, Hallert et al. (2002) further investigated whether women's lower level of subjective health "could be explained by differences in the perceived disease burden" (p. 39), comparing 34 men with CD and the same number of age-matched women, all diagnosed 8-12 years earlier, treated with the GDD and in clinical remission. Those authors also used a matched group of type-2 DM patients as controls, also treated for 10 years. The Burden of Illness protocol utilised is detailed in their paper, with the 9 items "constructed in order to assess relevant non-cost aspects of the perceived burden of illness" (p. 40). Hallert et al. found that CD patients were "convinced to a similar degree that keeping to the gluten-free diet was the key to health" (p. 41), regardless of gender, and there were no significant differences between people with CD or type-2 DM, despite Hallert et al.'s reasonable assertion that "in clinical terms, diabetes is a more serious condition than being coeliac" (p. 41). However, with the CD group, female patients were significantly "less satisfied with the outcome at 10 years" (p. 39) than males. This was reflected in their significantly higher Burden of Illness sum scores, suggesting "that the subjective poor health in otherwise well-treated coeliac women is closely associated with the perceived disease burden" (p. 41). Notable aspects of reduced satisfaction among women were related to "the need to gain more knowledge about the disorder, the interference with socialising with friends at work and at leisure,

the demand to have to abstain from important things in life and the possibility that their children could get the disorder" (p. 41).

Specific explanations of disease burden proposed by Hallert et al. to explain the evident "perception of restriction" (p. 41) included "an intense feeling of being diverse, this being particularly true for coeliac women" (p. 41) and "bitterness at not being diagnosed earlier in life" (p. 41), expressed by both male and female CD patients, and partially interpreted by those authors as possibly being connected with the likelihood that "early diagnosis implies better outcome" (p. 41) in CD, as is true in the case in many medical conditions. The experience of greater GI symptomatology among treated female CD patients (Hallert et al., 1998) was also regarded as a key underlying reason for higher levels of female dissatisfaction and distress. No gender differences were noted among the type-2 DM patients.

Health status and quality of life, knowledge of CD (clearly regarded by Ciacci et al., 1998, and Hallert et al., 2002 as related to QOL) and multidimensional health locus of control were all investigated in CD patients in the present thesis, as detailed in Chapter 5 – Study 1. The chapter which immediately follows provides an overview of the psychological sequelae (cognitive functioning, affect and QOL) previously observed in DM patients, selected to provide a chronic illness comparison group in relation to the range of assessment undertaken in the cross-sectional and longitudinal CD groups (Study 1 and 2).

Synopsis of Psychological Factors in CD

Reviewing previous studies relevant to the psychology of CD, depression stands out as the most prominent psychiatric disorder associated with the illness. Swedish, Italian and British research all converge upon this seemingly universal conclusion. The slight to moderately increased prevalence of generalised depressive symptomatology, compared to expected community levels, is heightened prior or close to diagnosis, and tends to increase in association with correlates of more overt or severe GI illness, but not in any consistent way. Given the relationship and overlap

between depression and anxiety, it not surprising that psychometric evidence of the reactive form of the latter may also accompany depression at the time of diagnosis. State anxiety normalised after sustained implementation of the GFD and regression of physical symptoms of CD, while

Finnish researchers reported an increase in psychological general well-being – to above-average community levels – one year after GFD therapy. This was partly attributed to a sense of relief at receiving medical confirmation of the genesis of physical ill-health (see also Ciacci et al., 2002), which may have temporarily accentuated the level of subjective mental health in a positive direction. Indeed, the cross-sectional picture was less positive, with psychological general well-being found to be reduced after many years on the GFD. In a broader sense, "the medical characteristics of a disease may show only a modest correlation with those perceived by patients" (Hallert et al., 1998, p. 41-42, in reference to Maes, Leventhal, & DeRidder, 1996), with the inconsistent associations between the physical and psychological features of CD perhaps more easily understood in this context.

Evidence has been presented in this chapter that disabling clinical depression may predate the diagnosis of CD by many years (Hallert, 1984; Vaitl and Stouthamer-Geisel, 1992) and two studies (Addolorato et al, 2001; Hallert, Åström, & Walan, 1983) are in agreement that signs of depression are, to a significant degree, refractory following diagnosis, at least without additional nutritional therapy, over and above the passage of time.

The question of whether somatic, cognitive or multifactorial dimensions of depression underlie the lowered affect in CD remains open. Ciacci et al.'s (1998) study was inconclusive in this regard, while Hallert and Åström's (1982) findings, although not geared to shed light on this issue, provided an indication that somatic factors may be somewhat more prominent. This hypothesis is subject to systematic investigation in the present thesis, via the use of psychometric analysis equipped to answer this question.

Empirical support for the hypothesis of a "distinct depressive mood [in CD] that is separated from reactions to being medically ill" (Hallert, 1987, p. 129) has been presented using physiological evidence (Hallert, Åström, & Sedval, 1982) indicating reduced central monoamine metabolism in

CD in relation to nutrient malabsorption, and by means of studies utilising chronic illness control groups (e.g., Ciacci et al., 1998; Gasbarrini and Addolorato, 1998; Hallert & Åström, 1982). These results support suggestions that "depressive symptoms are better related to the characteristics of CD that to a consequence of being affected by a chronic disease condition" (p. 505).

Quality of life, while not studied as extensively as depression in CD, has been observed to be slightly lowered among treated patients, compared to community levels, but only amongst females (Hallert et al., 1998). The perceived burden of illness was not higher compared to type-2 DM patients, but, within the CD group, women were less satisfied with the outcome following sustained GFD adherence than males (Hallert et al., 2002).

A breakdown and verification of the specific factors involved in the reduced QOL reported in CD is required, in addition to "a cross-sectional study of the intellectual ability of new and earlier diagnosed CD patients" (Collin, Eerola, and Pirtillä, 1997, p. 288), notwithstanding relatively intact intellectual functioning in a small group of untreated CD patients with evidence of lifelong intestinal malabsorption (Hallert & Åström, 1982). Isolated findings of visual discrimination and short-term memory deficits (Pavone et al., 1997) suggest the need for further research. Furthermore, the "the impact of the GFD on intellectual ability" (p. 288) has not been evaluated, but is one of the key undertakings of this thesis. The relatively newly diagnosed CD patients assessed in Study 1 (Chapter 4) formed the cross-sectional sub-group re-evaluated in Study 2 (Chapter 5), using standard protocols to be outlined.

Other aspects of psychological functioning in CD, such as health locus of control and anger, have not previously been investigated and form part of the assessment of CD patients in Studies 1 and 2. The predominance of "case reports and small, uncontrolled studies" in this area has been noted recently (Wills, 2000) and so the use of two comparison groups, including people with, and without, another distinct chronic illness was considered essential in building upon the body of CD research reported thus far. The next chapter outlines prior psychological research pertaining to the chronic illness comparison group selected for use in the present thesis.

Chapter 3: Psychological Aspects of Diabetes Mellitus

Selection of a Disease Comparison Group

Several studies examining health-related perceptions and behaviours in CD have used chronic illness comparison groups. These include a 10-year follow-up study of the burden of illness in CD, which compared 68 people with CD and the same sized sample of people with age- and sex-matched type-2 diabetes (Hallert et al., 2002), as discussed in the preceding chapter. Another study investigated the relationship between cigarette smoking and CD in 87 CD patients, using 174 age- and sex-matched individuals diagnosed with functional GI disorder (Snook et al., 1996). However, "the difficulty in finding a proper control group sharing key features with CD" has been conceded (Hallert et al., 2002, p. 42)

Only a minority of studies investigating psychological functioning in CD have in fact used either chronic illness or healthy control groups, and very few have used both. Two reported in the literature are a large scale study (Ciacci et al., 1998) which compared the extent of depressive symptomatology in people with CD ($\underline{n}$ = 100), people without a chronic illness ($\underline{n}$ = 100) and Hepatitis C patients ($\underline{n}$ = 48). A smaller study of anxiety and depression in CD utilised ten inflammatory bowel disease subjects (Gasbarrini & Addolorato, 1997).

In addition to developing a sizeable comparison group of healthy volunteers in this thesis, an appropriate chronic illness comparison group was sought to assist in determining whether any group differences that may emerge were due to the CD condition, or partly or wholly attributable to simply having a chronic illness. Selecting a suitable chronic illness comparison group involved the consideration of a number of factors. Medical conditions without predominantly GI symptomatology were preferred, since processes related to the disruption of nutrient uptake, implicated in the psychological sequelae of CD, also occur in other gut-related disorders. The decision to rule out other GI illnesses (e.g., inflammatory bowel disease) – with which CD patients may be misdiagnosed – also reduced the need for systematic medical screening for

undiagnosed CD in the chronic illness comparison group.

As CD is a chronic, lifelong but treatable condition, with dietary self-management of paramount importance, many diseases with fundamentally dissimilar characteristics were overlooked in selecting a comparison group. These included disorders with terminal courses (e.g., HIV or Hepatitis C infection and cancer), those requiring entirely pharmacological interventions, typically acute, but remitting, or degenerative diseases, and illnesses with mainly neurological or psychiatric symptoms (e.g., Alzheimer's, epilepsy, Huntington's disease and schizophrenia).

Other classes of chronic illness not considered ideal candidates for inclusion as a chronic illness comparison group were those generally perceived to be significantly less or more severe, in general, than CD (e.g., cystic fibrosis). Illnesses of fluctuating or seasonal intensity, such as eczema and hay fever, were regarded as being somewhat less severe, or restrictive, than CD overall. Additionally, both are very common illnesses in Australia and were therefore also expected to be widespread in the CD sample. Finally, practical restraints dictated that the chronic illness comparison participants chosen should be recruited readily within a two year time frame, limiting the diseases contemplated to those affecting sufficiently large numbers of people.

Presently incurable but treatable diseases were preferred, with management leading to relatively pain-free living, in accordance with the general parameters of CD. Asthma warranted serious thought, having been the subject of a pre-thesis review by the author, but emotional factors were considered to precipitate or ameliorate symptomatology in a significant percentage of sufferers (Rietveld & Prins, 1998), potentially confounding results. Like eczema and hay fever, asthma is another very common illness in Australia, with a significant number of CD patients expected to have asthmatic conditions, so a less prevalent disease was sought.

One class of chronic illness survived the application of all exclusionary criteria and, in addition, stood out as sharing many similarities with CD. Diabetes mellitus (DM) is a very common "group of metabolic diseases" (American Diabetes Association, 2000, p. 69) partly or chiefly subject to dietary control, with cumulative long-term physical complications in untreated

or poorly managed cases, not unlike the situation – albeit generally to a less severe degree – in CD. Disease onset and development is often insidious in non-autoimmune or type-2 DM (the most prevalent form), as in CD, and a "long subclinical prodromal phase" (Serrano-Rios, Goday, & Larrard, 1999) is also observed in type-1 DM. Although type-1 and -2 DM arise as a result of distinct causes, the symptoms are often comparable. Ongoing self-regulation is a key to health maintenance in the case of both major types of DM, which is a major similarity to CD.

Overview of Diabetes Mellitus

Characterised by a "dysregulation of glucose homeostasis" (Todd & Farrall, 1997, p. 284), resulting in hyperglycaemia (high blood glucose), DM affects about 6% of the general population. The illness was officially ranked as the seventh highest direct cause of mortality in the United States in 1998 (64,751 deaths or 24 per 100,000 of the population that year; United States Department of Health, 1999). Diseases of the heart were the leading cause of mortality, with DM estimated to be an underlying factor in a significant proportion of these deaths (Brunner, 2001). The illness is associated with an insufficient production, or an inability to utilise, the hormone insulin, which is responsible for keeping blood glucose levels within tight parameters. Insulin transports the sugar out of the blood and into the body's muscles, where it is used to provide energy for the body.

Type-1, immune-mediated, or insulin-dependent DM, previously called "juvenile diabetes", is a "clinically and etiologically heterogenous...genetically determined chronic autoimmune disorder" (Serrano-Rios et al., 1999, p. 113). It occurs most commonly in children and young adults and develops when the immune system attacks the insulin-producing beta (β) cells of the pancreas, destroying them. As a result, the pancreas does not produce adequate insulin, with insulin injections needed to replace the deficit. Typically, insulin deficiency "manifests only after 80-90% of endocrine β-cells have been destroyed" (Schloot, Pozzilla, & Mandrup-Poulsen, 1999, p. 141). The "β cell destruction is irreversible, and despite insulin replacement by injection, patients suffer early mortality, kidney failure and blindness" (Todd & Farrall, 1997, p. 284). As in

CD, both genetic and environmental factors are involved in the multifactorial aetiology of type-1 DM (Buzzetti, Quattrocchio, & Nistico, 1998). Environmental influences may include viral infection, psychological stress and early exposure after weaning to cow's milk proteins (Akerblom & Knip, 1998). Human leukocyte antigen associated genes at the DR and DQ loci contribute more than 40% of the inherited susceptibility, but an increasing number of non-HLA genes are being recognized (Buzzetti, Quattrocchio, Nistico, 1998; Serrano-Rìos et al., 1999). A 30-70% concordance for DM is reported in identical twins (Todd & Farrall, 1997). The peak age of onset ranges between 10 to 14 years and a male to female ratio approaching unity is observed in most areas (Muntoni & Muntoni, 1997). The greatest incidence of DM occurs in the Nordic countries, with the rate highest in Finland (Tuomilehto et al., 1992) and some high-incidence areas situated in Mediterranean regions (e.g., Sardinia; Muntoni, Stabilini, Stabilini, Mancousa, & Muntoni, 1995). The risk of type-1 DM is comparatively low in Negroid populations and the illness is rare in Asian and Pacific Islander groups. Slightly fewer than one in ten people with DM are initially diagnosed with the insulin-dependent form, which affects about 0.4 to 1% of the population, or up to 200,000 Australians (ABS, 2001).

Type-2, insulin-resistant, or non-insulin-dependent DM, was previously called "adult onset diabetes" and classically occurs in older adults. However, it is becoming increasingly common in younger age groups, where it is accounting for a growing proportion of new diagnoses, due to the rise in obesity (Hansen, Fulop, & Hunter, 2000). Type-2 DM stems "from insulin-resistance, mainly caused by visceral obesity, with a defect in compensatory insulin secretion" (Masharani & Karam, 2002, p. 1203). Typically, sufficient insulin is produced, but the body of type-2 DM patients gradually becomes insensitive to its effects, resulting in hyperglycaemia. Most patients are overweight, having a body mass index (BMI) greater than 25, with the majority designated as obese (BMI > 30). By creating an insulin-resistant state, obesity "abets the development of diabetes and, once diabetes manifests itself, accelerates its deterioration" (Pi-Sunyer, 2000, 1451). Oral agents or intravenous insulin are often necessary to treat this form of diabetes, which affects

more than nine out of ten DM patients (Zimmet, 1995). This equates to more than one million Australians, around half of whom are undiagnosed (ABS, 2001).

Other forms of diabetes exist. For example, diabetes insipidus is a pituitary disease with symptoms of excessive thirst and urination, but is caused by an entirely different mechanism to diabetes mellitus. Another example is gestational diabetes, which may occur during pregnancy. However, it was not planned to include any participants with diabetes insipidus or gestational diabetes in the chronic illness comparison sample of the present thesis.

Short-term dangers and complications of diabetes, especially pertinent to type-1 patients, include hypoglycaemia (low blood sugar), which is typically of swift onset and may lead to shock and unconsciousness if untreated (via repletion of blood glucose). The other main short-term danger is of the opposite type; ketoacidosis or diabetic coma, which develops slowly and results from extremely high levels of blood sugar (Cooke, 2002). Early signs of ketoacidosis include flushed dry skin, blurry vision, a dry mouth, excessive thirst and urination, abdominal pain and deep, rapid breathing or difficulty breathing, followed by drowsiness and coma (American Diabetes Association, 2002). Immediate medical attention is required.

In both major types of DM, the treatment goal is to achieve euglycaemia, or stable blood glucose levels, as consistently as possible. This process involves a sustained combination of pharmacological therapy (usually including insulin), dietary and lifestyle modifications (i.e., aerobic exercise and weight loss). The first two factors, medication and diet, are of primary significance in the case of type-1 DM and the latter two, diet and lifestyle changes, are most important in type-2 DM, especially in the earlier stages of treatment. Long-term complications and cumulative effects of DM involve multiple organ systems. Various degrees of vascular and neurological damage are common (Phillips et al., 1998), including kidney failure, stroke, blindness, impotence, peripheral neuropathy and circulatory problems, which may eventually lead to amputation of extremities or limbs. There is also an increased prevalence of GI symptoms in each major form of DM (Locke, 1995). These are reported more frequently by female patients and

have been attributed to diabetic complications, especially peripheral neuropathy, and the effects of poor glycaemic control (Bytzer et al., 2002).

Hyperglycaemia leads to most of the specific long-term complications in DM, with all three aforementioned treatment factors geared towards reducing glucose levels to or below the non-diabetic range. However, excessive reductions result in hypoglycaemia (i.e., low blood sugar), "the limiting factor in the management of diabetes" (Cryer, 1999, p. 42). Initial symptoms usually develop rapidly and include light-headedness, dizziness, weakness, nausea and hunger (Tierney et al., 2002) and confused, nervous, excitable or irritable behaviour, shallow breathing and pale, moist skin (Cooke, 2002). Shock, convulsions and unconsciousness may ensue if sugar is not provided and intravenous glucose is then required. Neural damage and cognitive impairment is associated with recurrent, severe episodes (Langan, Deary, Hepburn, & Frier, 19991). From a psychological perspective, fear of hypoglycaemic episodes, with consequent weight gain as a result of compensatory overeating (coupled with increased insulin use), represent major, but under-recognised, problems for many DM patients (Cypress, 1999).

Of the chronic illnesses considered in relation to developing a disease comparison group, DM, like CD, was one of the most affected by the patient's self-management of his or her condition. A DM patient's medical regime compliance, diet, exercise, personal habits, weight control, emotional state and self-care behaviours collectively determine his or her immediate, medium and long-term physical and psychological health. In view of the primary subject matter of the thesis – psychological sequelae in CD – a review of affective and neuropsychological functioning and life quality in the chosen chronic illness comparison group was undertaken.

Review of Mood, Anxiety and Other Psychiatric Disorders in DM

Moderate-severe levels of depressive and anxiety-related symptomatology are common in both major types of DM (Lloyd, Dyer, & Barnett, 2000). Clinical depression is two to three times more prevalent in DM than in the general population (Lustman, Clouse, Alrakawi, Rubin, & Gelenberg,

1997), with at least one out of every five DM patients experiencing a major episode (Gavard, Lustman, & Clouse, 1993). A clinical and epidemiologic review noted that life-time prevalence rates of depression in DM "vary between 24% and 29%" in type-1 patients, with "the symptom rofile...similar to that in non diabetic psychiatric patients" (Eiber, Berlin, Grimaldi & Bisserbe, 1997, p. 351). As well as occurring more frequently in DM, depressive episodes also tend to persist for longer than in psychiatric patients (Lustman et al., 1997) and recur earlier (Kovacs, Obrosky, Goldston, & Drash, 1997; Lustman, Griffith, & Clouse, 1988; Lustman, Griffith, Freedland, & Clouse, 1997). A meta-analysis of 27 studies (from 1975-1999) also found "a significant and consistent association of diabetes complications and depressive symptoms" (de Groot, Anderson, Freedland, Clouse, & Lustman, 2001, p. 620), with effect sizes ranging from small to moderate (r = .17 to .32).

There are two major, inter-related hypotheses proposed to account for all of these findings (see Talbot & Nouwen, 2000). One proposes that depression in DM is a result of biochemical factors directly related to the illness or its treatment. The DSM-IV criteria for Mood Disorder Due to a General Medical Condition are relevant to this theory. The second hypothesis suggests that depression in DM is a secondary consequence of incapacity, stress and psychosocial demands emanating from and associated with managing a chronic illness per se.

In their detailed review, Talbot and Nouwen (2000) found limited exclusive support for either hypothesis, instead concluding that major depressive disorder in DM "represents a multidimensional phenomenon resulting from interactions between biologic and psychosocial factors" (p. 1556). Those authors also questioned the assumed direction of causality (that DM leads to depression), by presenting evidence that depression typically precedes the diagnosis of DM by many years, at least in type-2 patients (Lustman et al., 1988), and increases the risk of developing complications after diagnosis. An exception was noted in the cases of late-onset depressive illness, which has been found to be associated with the micro- and macro-vascular changes in DM (Alexopoulos et al., 1997; Robinson, Morris, & Fedoroff, 1990).

Finally, it should not necessarily be assumed that the level of depression is always elevated in

groups of DM patients. A case-control Finnish study of people with type-2 DM of ten years duration, using the Zung Self-rating Depression Scale, showed no difference in the level of depression compared with non-DM controls (Viinamaki, Niskanen, & Uusitupa, 1995). Also, in Dutch research using the Beck Depression Inventory (BDI), newly diagnosed DM patients did not differ from healthy controls (Palinkas, Barrett-Connor, & Wingard, 1991). In that study, more distantly diagnosed DM patients had higher age-adjusted BDI scores, and affective and somatic BDI subscales, than newly diagnosed patients or healthy controls. However, age and number of chronic conditions were independent predictors of depressive symptomatology, with the latter perhaps better projected by the "presence or severity of complications and comorbid conditions" in DM (Luscombe, 2000, p. 21), rather than the existence of diabetes of itself, except where depression precedes the development of diabetes.

Studies assessing aspects of mood in DM other than depression have investigated the levels of state and trait anxiety and anger. These have been found to be higher in diabetes patients than in a comparison group of people suffering from "somatic disease", but "clearly below those with psychological disturbances" (Laederach-Hofmann, Mussgay, Schill, & Ruddel, 2000, p. 169) in a large scale German study. McCrimmon, Ewing, Frier, & Deary (1999) noted a "significant increase in feelings of anger" (p. 35) during experimentally induced hypoglycaemic episodes in people with both DM and non-diabetic subjects, while Sato et al. (2002) reported increased anxiety in female, compared to male, DM patients. In a systematic review of 18 studies, Grisby, Anderson, Freedland, Clouse and Lustman (2002) determined that elevated symptoms of anxiety were present in about 40% of patients with DM (males: 33%; females 55%), whether type-1 or -2, and 14% of DM patients have Generalised Anxiety Disorder.

With regard to other clinical disorders in DM, "disturbed eating behaviour" is more prevalent in DM patients than in matched, healthy controls (Engstrom et al., 1999, p. 117), with an eating disorder (ED) diagnosis able to "be made in up to 10% of young women" with type-1 diabetes, according to an Italian review (Verotti, Catino, De Luca, Morgese, & Chiarellia, 1999, p. 21). Those authors attributed weight gain, dietary restraint and food preoccupation as predisposing features of DM in the

development of EDs. In a large German multicenter study, "the overall prevalence range of current EDs was 5.9 - 8.0% (lifetime prevalence 10.3 - 14%)" (Herpertz et al., 1998, p. 1110), with no differences in relation to gender, or between type-1 and -2 DM. Those authors reported "intentional insulin undertreatment or omission" (p. 1110) – sometimes referred to as "insulin purging" – in 4.1% of their sample. Hoffman's (2001) belief that "the weight gain associated with good glycemic control likely increase [female adolescent DM patients'] susceptibility to abnormal eating" (p. 73) has a parallel in the tendency towards weight gain following GFD institution in CD, which is perhaps also worthy of investigation in relation to EDs. As in CD, "there is no specific personality pattern in diabetic patients" (Eiber et al., p. 351).

Neuropsychological Functioning

Decrements in neuropsychological functioning are widely reported in both type-1 and type-2 DM (Ryan, Williams, Finegold, & Orchard, 1993; Worrall, Moulton, & Briffett, 1993). These appear to be more pervasive in older type-2 patients (Croxson & Jagger, 1995; Scott, Kritz, Barrett, & Wiederholt, 1998) and those with DM-related health complications (Knopman et al., 2001). However, a number of studies have failed to find evidence of cognitive decline in either type-1 (Deary & Frier, 1996; Kramer et al., 1996) or type-2 patients, especially in cases "uncomplicated" by other medical disorders (Cosway, Strachan, Dougall, Frier, & Deary, 2001). Evidence against the presence of cognitive changes in type-2 DM includes both case-control studies (Kail, Wolters, Yu, & Hagen, 2000; Stewart & Liotitsa, 1999; Strachan, Deary, Ewing, & Frier, 1997) and population-based research (Scott, Kritz-Silverstein, Barrett-Connor, & Wiederholt, 1998). In tests sensitive to neuropsychological dysfunction (e.g., the Wechsler scale's Digit Symbol test; Crowe et al., 1999) the findings in DM are certainly mixed, with the majority of studies not showing substantial impairment (see Asimakopoulou, Hampson, & Morrish, 2002, for a review).

Support for the existence of affected neuropsychological performance in DM includes associations between reduced cognitive functioning and each of; glucose intolerance (Kalmijn, Feskens, Launer,

Stijnen, & Kromhout, 1995), hyperinsulinaemia (Kalmijn et al., 1995), various cardiovascular risk factors related to DM (e.g., hypertension; Knopman et al., 2001), recurrent severe hypoglycaemic episodes (Langan, Deary, Hepburn, & Frier, 1991), chronic hyperglycaemia (Northam, Anderson, Werther, Warne, & Andrewes, 1999; Reaven, Thompson, Nahum, & Haskins, 1990; Ryan & Geckle, 2000) and each of type-1 and type-2 diabetes per se (Ott et al., 1996; Worrall, Moulton, & Briffett, 1993). These associations are observed in type-2 patients in both middle-aged adults (Knopman et al., 2001) and elderly populations, in which the risk and prevalence of dementia is also increased (Ott et al., 1996). In older people with type-2 diabetes, "minimal cognitive impairment" was detected after controlling for confounding factors (Asimakopoulou et al., 2002, p. 311), including alcohol intake, hypertension and cardio/ cerebrovascular conditions. In type-1 DM patients, multiple occurrences of serious hypoglycaemic events are believed to substantially contribute towards the cognitive dysfunction reported, with "permanent neuropsychological impairment" documented (Wredling, Lavender, Adamson, & Lins, 1990, p. 152).

There is general consensus that the neuropsychological changes associated with DM are due to cumulative processes that correlate with the duration of illness (Cosway et al., 2001). Typically, the magnitude of intellectual decline is attributed primarily to the total number of – and susceptibility towards – acute hypoglycaemic events in type-1 patients (Langan et al., 1991), and to gradual, subclinical accretion of the effects of discrete events (e.g., ischaemic mini-strokes) resulting in diffuse cerebral infarction and other aspects of arteriosclerotic disease, vascular degeneration and malfunction (e.g. hypertension) in type-2 patients (Knopman et al., 2001). Since glycaemic control in older type-2 patients has lead to improved cognitive functioning (Gradman, Laws, Thompson, & Reaven, 1993), it appears that the declines in performance are not necessarily entirely irreversible.

Almost all major indexes of neuropsychological performance have been implicated somewhere in the body of research involving cognitive deficits in DM. The most frequently reported, in descending order, are speed of information processing (psychomotor slowing) – in both type-1 (Deary et al., 1992) and type-2 patients (Ryan & Geckle, 2000), memorial functioning, especially

short-term verbal memory in type-2 DM (Asimakopoulou et al., 2002; Helkala, Niskanen, Vinamaki, Partanen, & Uusitupa, 1995) and attention (U'Ren, Riddle, Lezak, & Bennington-Davis,1990).

There is neurophysiological evidence "indicative of abnormal brain function" (Ryan & Geckle, 2000, p. 1486) in the form of longer P300 latencies in middle aged, type-2 patients (Dey, Mistra, Desai, Mahapatra, & Padma, 1997; Kurita, Katayama, & Mochio, 1996). Central nervous system involvement is likely (Biessels, 1999; Cerizza et al., 1999), with signs of autonomic neuropathy (Zaslavsky, Gross, Chaves, & Machado, 1995) and brain atrophy observed (Pirttilä, Järvenpää, Laippala, & Frey, 1992; Soininen, Puranen, Helkala, Laasko, & Reikkinen, 1992), "consistent with subtle compromise of anterior and medial temporal brain regions" (Northey et al., 2001, p. p1541). Focal damage of hippocampal structures, as a result of severe, recurrent hypoglycaemic events, has been specifically implicated in the memorial deficits documented (Hershey, Craft, Bhargava, & White, 1997). Mild impairment of executive functioning reflective of frontal lobe involvement has also been documented in elderly type-2 Finish patients (Vanhanen et al., 1999). In general, though, abstract reasoning, problem-solving, non-declarative memory functioning and learning skills appear to be relatively spared in type-2 DM (Ryan & Geckle, 2000).

Although cognitive dysfunction in DM is mainly found in older type-2 patients, significant psychomotor slowing, but preserved accuracy, has been described in children and adolescents with type-1 DM in a large scale U.S. case-control study (Deichmann, 1998) and also in adult patients (Hill, 1995). In the latter study, "a verbal IQ decrement was found relative to performance IQ" (p. 1700). Processing speed, attention, long-term memory and executive skills were all lowered compared to community controls in a separate Australian study of children with type-1 DM, six years after disease onset (Northam et al., 2001). These deficits were accentuated in children with early-onset DM, confirming independent Norwegian findings of reduced psychomotor efficiency and attention in a sub-group of young patients also diagnosed early in life (Bjorgaas, Gimse, Vik, & Sand, 1997).

Overall, the results reviewed suggest that higher cortical functions may remain relatively intact, regardless of diabetes type. Conversely, abilities in the areas of processing speed, short-

term memory and attention/ concentration may be quite susceptible to subtle disruption from early in the disease, with greater physical degeneration associated with more pronounced neuropsychological dysfunction.

Quality of Life

Since DM is an illness with wide-ranging biopsychosocial perturbations and its "management depends almost entirely on behavioural self-regulation" (Gonder-Redenick, Cox, & Ritterband, 2002, p. 611), the quality of life (QOL) of patients is invariably affected at some level or stage of the illness. In a review, Luscombe (2000) noted "decrements in virtually all aspects of health-related QOL due to the disease or its complications" (p. 21). The major emergent themes in a pilot study of younger DM patients were "restrictions" (in relation to dietary regimentation/ scheduling and social ramifications), "differentness", "negative emotion" and "adaptation", with the latter two "expressed most often by participants who had had diabetes for a longer period of time" (Faro, 1999, p. 247). All four themes were reminiscent of secondary reactions to CD.

Type-2 DM patients without complications had only slightly lower health-related QOL than healthy age-matched people in the general community in a recent, large-scale Dutch study, with insulin therapy, obesity, and complications all significant determinants of lower life quality (Redekop et al., 2002). Comparable results were reported by Glascow, Ruggiero, Eakin, Dryfoos, and Chobanian (1997), with lower QOL also associated with femaleness and lower levels of physical activity. Self-reported higher QOL by male DM patients and a lower sense of disease burden has been reported elsewhere (Rubin & Peyrot, 1999), but is by no means a universal finding (Hallert et al., 2002; Wredling et al., 1995). Health-related QOL in newly identified DM patients was found to be equivalent to people who did not have DM upon the systematic screening of Veterans in a U.S. study (Edelman, Olsen, Dudley, Harris, & Oddone, 2002). Interestingly, impaired memory and concentration were cited as the most salient aspects of reduced QOL in Chinese DM patients (Fan, Huang, & Li, 1996), confirming that these commonly reported

neuropsychological problems may significantly affect daily living.

According to Watkins et al. (2000), positive QOL outcomes in both type-1 and -2 DM are most strongly related to patients' perceptions of control over their illness, as well as their understanding of diabetes. However, as in CD, the "health behaviours that comprise up to 99% of disease treatment [in DM] are difficult to maintain over time" (Watkins et al., 2000, p. 1511). This was yet another likeness between the two illnesses that augured in favour of the selection of DM patients as a suitable disease control group.

The Envisaged Chronic Illness Comparison Group – A Summary

Having made the decision to use DM as the chronic illness comparison group in this thesis, a fundamental question was whether to use type-1 or type-2 patients, or a combination of both. Hallert et al. (2002) recently reported the use of type-2 DM patients, in their CD case-control burden of illness study, as representing "another group...in whom the medical treatment is largely regulated by the patients themselves by adhering to a diet" (p. 39), two key features shared by CD. Another similarity between CD and DM included the fundamental chronicity of illness, as distinct from the abrupt or acute pattern of exacerbations and remissions, intermittent symptoms, or seasonal variation characterising many other illnesses after diagnosis. Unlike the gradual health gains in CD following strict GFD compliance, there is often an eventual marked degeneration in health in DM. However, this contrast in outlook was deemed to be more relevant to longitudinal considerations than the cross-sectional assessment comprising study 1 of the present thesis, in which the duration of illness and stage of diabetes in each patient could be monitored during recruitment in developing a matched comparison group.

Nevertheless, a major concession expressed by Hallert et al. (2000) in using DM as a comparison group was that, "in clinical terms, diabetes is a more serious condition than being coeliac" (Hallert et al., 2002, p. 41). Presumptions of greater disease severity in DM, compared to CD, were initially imagined by the writer to especially apply to type-1 patients, but this assumption

was not necessarily supported in the DM literature, with "more pronounced psychopathology" not infrequently reported in type-2 patients (Herpertz et al., 2000, p. 161; see also Karlsen, Bru, & Hanestad, 2002). Differences between various indexes of disease severity in type-1 and -2 DM, whether in the physical or psychological domains, are more likely to be attributable to the heterogeneity of samples, disease stage and duration, treatment compliance and extent of concomitant medical problems, than diabetes type per se.

Therefore, notwithstanding the etiological distinctions between both major forms of DM, the lack of consistent differences in the degree of neuropsychiatric symptomatology between type-1 and -2 patients paved the way for potential consideration of either or both forms of DM prior to the development of the chronic illness comparison group. This policy also had the practical benefit of reducing restrictions on the potential pool of DM participants considered for recruitment into Study 1. The impending task of matching groups across demographic variables was consequently made easier, given envisaged practical difficulties such as the relative ages of type-1 and -2 patients, which were expected to be, respectively, considerably above and below the median age of the general and adult CD population at the time of (or relatively close to) diagnosis with DM.

As reviewed in this chapter, the prevalence of Axis I clinical disorders appears to be elevated in DM compared to people without a chronic illness, but only to a limited degree in diabetes groups uncomplicated by other medical disorders. An increased frequency of subtle to modest neuropsychological impairment and somewhat reduced life quality has also been consistently reported. For those reasons, DM was regarded as constituting a fair disease comparison group for use in the present thesis, in establishing the existence or strength of any differences in the psychological functioning of patients with CD, compared to people without a chronic illness and against the backdrop of the expected effects of a chronic illness in itself, with analogous issues to CD. The next chapter outlines the hypotheses proposed in the cross-sectional study of this thesis, the methodology used in the selection of CD, DM and healthy participants and the results of extensive psychological assessment, followed by a discussion of the key findings.

Chapter 4 – Study 1:
Cross-Sectional Analysis of Psychological Sequelae in CD

A review of the CD literature in reference to psychological sequelae has revealed a scarcity of research throughout most decades of the preceding century, punctuated by brief, intense periods of interest in discrete areas. Purported associations between CD and schizophrenia (Dohan, 1973, 1983) were not supported by epidemiological evidence (Hallert, 1982), while evidence for neurological complications in CD (see Morris, Ajdukiewicz, & Read, 1970), and vice versa (Hadjivassiliou et al., 1996) accumulated (see Cooke & Holmes; Gobbi et al., 1997).

Goldberg's (1970) observations of an increased prevalence of depression in CD patients have also been substantiated (Hallert & Åström, 1982). Depression may rank with many of the more extensively researched physical repercussions of CD (e.g., osteoporosis), as a common and debilitating health problem preceding the detection of CD (Hallert & Derefeldt, 1982). For many CD patients, depression remains post-diagnosis without specialised treatment (Hallert, Åström, & Walan, 1983), thwarting a timely and complete recovery, despite compliance with the GFD (Hallert, 1997). These observations of depression as the predominant psychiatric disorder in CD have been corroborated by others (e.g., Addolorato et al., 2001).

The Beck Depression Inventory – Second Edition (BDI-II; Beck, Steer, & Brown, 1996; described in this chapter on pp. 130-132) was selected by the author ahead of the Zung SDS, due to the correspondence of BDI-II items with the criteria used for diagnosing depressive disorders in the DSM-IV and the opportunity to ascertain the relative contributions of somatic/ affective and cognitive dimensions of self-reported depression in CD. These dimensions were based on two mutually exclusive sets of BDI-II items identified by Beck et al. (1996) as loading onto two such-named factors in a sample of psychiatric outpatients following factor analysis. Exploration of these dimensions in CD was considered potentially important in view of the prominence of elements of psychomotor retardation previously identified in the MMPI profiles of depressed CD patients (Hallert & Åström,

1982), plus discrete (although perhaps additive) aetiological explanations for depression in CD, including disruption of monoamine synthesis (Hallert, Åström, & Sedval, 1982a) and unspecific secondary reactions to the implications of having a physical illness.

Although not a primary focus of previous CD research, many symptoms of anxiety (e.g., restlessness and insomnia) often feature in depressive illness (Fawcett & Kravitz, 1983). Anxiety disorders also frequently coexist with mood disorders such as major depressive disorder and dysthymia (APA, 1994). Reactive (i.e., state, as opposed to trait) anxiety has been identified in CD (Gasbarrini & Addolorato, 1997), but the sample size was insufficient to draw definitive conclusions.

Lowered frustration tolerance also commonly occurs in conjunction with mood disorders (APA, 1994) and extreme examples have long been recognised in children with CD (Gibbons, 1889). In adults the period antedating recognition of CD may be onerous and exasperating, and reflections about the cumulative health effects associated with undetected CD, due to a belated diagnosis later in life, may invoke resentment. As the symptoms of irritability and agitation found in depression – in addition to any build up of resentment – are also commonly associated with anger (Spielberger, 1988), it was decided to investigate anger, a relatively unknown entity in CD, but not uncommon in other chronic illnesses (Grech, 1993). Therefore, both anxiety and anger were independently assessed cross-sectionally (Study 1) and longitudinally (Study 2) in the current thesis, using the State-Trait Anxiety and Anger Expression inventories (Spielberger et al., 1983; Spielberger, 1988; see this chapter's description of these measures on pp. 138-140 and 140-142).

Although changes or decrements in neuropsychological functioning frequently have neurological substrates (Kolb & Whishaw, 1990; Lezak, 1983), and these have received increased attention in CD (e.g., Gobbi et al., 1997), intellectual ability has been found to be relatively intact in CD patients (Hallert & Åström, 1983), with no deficits peculiar to CD consistently found. However, notwithstanding a sparing of global cognitive capacity, the specific "cognitive functions of CD patients have not been extensively studied and large cross-sectional studies are lacking" (Collin, Eerola, & Pirttilä, 1997, p. 285). This was a principal motivation for systematically assessing the neuropsychological status and

indexes of performance in a large group of Australian CD patients. Since there may be a "pernicious interplay" (Lezak, p. 127) between any combination of particular neuropsychological functions (e.g., memory), depression and brain damage and both of the latter have been a cause for concern in CD, the concurrent evaluation of mood state and core areas of neuropsychological aptitude in each CD participant was also regarded as important.

Finally, perceived health status and quality of life (QOL) in chronic illness have been increasingly researched in the preceding two decades. Reduced life quality during active irritable bowel disease was found compared to transient illness controls (Sorenson, Olson, & Binder, 1987) and slightly decreased life quality was identified in treated CD patients, especially in females (Hallert et al., 1998; Lohiniemi et al., 1998). In view of the comprehensive investigation of mood state and cognitive functioning in Study 1, an assessment of QOL underpinned by a self-evaluation of behaviours and actions, as opposed to affective and cognitive perceptions, was sought. Therefore, the Quality of Life Questionnaire (QLQ: Evans & Cope, 1989; see this chapter pp. 145-149), a generic measure based on self-reported behaviours as representations of QOL, was selected. The previous findings of mild, overall reductions of life quality in CD, rather than a gross impairment in daily living, was another factor that influenced the choice of the QLQ ahead of disease-specific or illness-related measures. A self-rating of general health status, adapted from a scale used in comprehensive Australian health surveys (McLennan, 1998), was also administered to the CD, healthy control and diabetes mellitus groups, to assist in establishing a reference point of perceived general health measurable against local norms.

Mood in CD: Primary Hypotheses

The first goal of Study 1 was to examine the prevalence and nature of depressive symptomatology in an Australian CD group of one-hundred patients, compared to demographically matched healthy controls and people with diabetes mellitus, a chronic illness in which the prevalence of symptoms of depression, has also been found to be elevated (Lustman et al., 1997). Evaluation of the symptoms of anxiety and anger, which often overlap with depression and other psychiatric diagnoses (APA, 1994),

were also measured. Selection of the test measures used to assess these areas of functioning were based on their specificity, sound psychometric characteristics and, in the case of the Beck Depression Inventory – II, excellent predictive power (see pp. 126-128). Although the composition of each of the two disease groups (CD and DM) vis-à-vis respective disease severity, duration of illness or compliance with treatment was unknown at the outset of Study 1, six hypotheses were made regarding depression, anxiety and anger, in CD participants in relation to two demographically matched comparison groups, DM and healthy participants, based on limited prior research:

1. Levels of depressive symptomatology would be higher in the CD group than the NC group, but not the DM group.

2. Levels of depression would be higher in CD patients who were multisymptomatic, compared to oligosymptomatic at diagnosis.

3. There would be no difference in the prevalence of Cognitive versus Somatic/ Affective depression within the CD group, or compared to either comparison group.

4. State, but not trait, anxiety would be higher in the CD group than the NC group and also higher in newly diagnosed, compared to distantly diagnosed, CD patients.

5. Anxiety levels would be increased in CD patients who were multisymptomatic, compared to oligosymptomatic at diagnosis.

6. State, but not trait anger, would be higher in the CD group relative to the NC, but not DM, group.

Cognitive Hypotheses

A second aim of the thesis was to assess specific indices of performance in neuropsychological functioning in CD. This was achieved by selection of the Wechsler Adult Intelligence Scale-III (Wechsler, 1997), enabling the calculation of standard scores across the three experimental groups in the areas of verbal comprehension (VC), perceptual organisation (PO), working memory (WM) and

processing speed (PS), as well as the full scale intelligence quotient (IQ). Given evidence in support of intact overall intellectual ability in CD (De Maria et al., 1997; Hallert & Åström, 1983) and a lack of consistent findings of specific decrements in cognitive functioning, it was hypothesised that:

7. General intellectual ability (IQ) would not be significantly different in the CD group, compared to either the NC or DM group, provided that these groups were matched for age, years of education and socioeconomic status (SES).

It was envisaged that the total mean IQ scores across groups, which were expected to converge on comparable figure during the simultaneous development of each of the three experimental groups, may also be used to assist in matching the groups against a baseline level of functioning, or, as a minimum, help define the CD group relative to normative expectations. It was further anticipated that the assessment of a large group cross-sectionally would maximise the likelihood of detecting any subtle systematic strengths or deficits in performance in the CD group, should they exist. On the balance of limited previous research in CD (Hallert & Åström, 1983; Pavone et al., 1997) and the larger body of DM literature (Hershey et al., 1997; Ryan et al., 1993; Worrall et al., 1993) reviewed in the preceding chapter, it was hypothesised that:

8. The DM group would perform at a significantly lower level than the NC but not the CD group in the area of Working Memory.

It was also expected that, depending on the makeup of the eventual CD sample, the influence of other factors on intellectual performance (e.g., disease intensity and GFD compliance; eg. Pavone et al., 1997) may also be able to be determined. A dual hypothesis was made regarding these factors on neuropsychological performance, in a direct test of Pavone et al.'s (1997) findings, based on a small sample size:

9. CD participants non-compliant with the GFD would perform at a significantly lower level than participants following the GFD in the Perceptual Organisation and Working Memory Indexes of the WAIS-III.

Quality of Life and Health Status Hypotheses

The third general aim of Study 1 was to undertake a fine grained analysis of self-reported QOL in CD patients, compared to healthy controls and people with DM. On the basis of previous research (Hallert et al., 1998; Hallert et al., 2002, Lohiniemi et al., 1998) two directional hypotheses were made regarding the hypothesised quality of life in CD patients in relation to the comparison groups:

10. Female, but not male, CD participants would report a significantly lower overall quality of life than NC but not DM participants.
11. General well-being, a major domain of the Quality of Life Questionnaire, would be significantly lower in participants with CD compared to NC, but not DM, participants.
12. Physical well-being, as subdomain of the Quality of Life Questionnaire, would be significantly lower in participants with CD compared to NC, but not DM, participants.

Two hypotheses were made regarding retrospectively self-reported general health status pre- and post-CD diagnosis/ GFD implementation, as measured by a modified version of an Australian scale used in national community surveys:

13. Health status would be significantly higher post-diagnosis/ GFD implementation, compared to pre-diagnosis, within the CD group.
14. Patients with CD who were multisymptomatic at CD diagnosis would retrospectively report lower health status pre-diagnosis than oligosymptomatic patients.

CD Awareness and Multidimensional Health Locus of Control Hypotheses

Three hypotheses were generated in relation to CD awareness/ knowledge, regarded by Ciacci et al., 1998 and Hallert et al., 2002 as being connected to QOL, and multidimensional health locus of control (MHLC), not previously investigated in CD research, but widely used in health-related fields (Wallston & Wallston, 1978), including DM (e.g., Wright, 1997).

15. Increased CD awareness/ knowledge in CD patients, as measured by a new scale developed the author, would be positively correlated with greater compliance with the GFD and higher QOL.

16. Internal MHLC would be positively correlated with greater compliance with the GFD, self-reported health status and quality of life in CD participants and negatively correlated with depression in participants from all three groups.

17. Internal MHLC would be lower and Chance MHLC higher in CD and DM patients, compared to NC participants.

Development of a Theoretical CD-Specific Damage Quotient

Of the calculable non-demographic factors associated with CD which may influence psychological functioning, two static symptom-related and two dynamic dietary variables were selected by the author to form a logical quartet of factors comprising a hypothetical risk scale referred to in this thesis as a "damage quotient" (DQ). Selection and refinement of the four factors was based on previous research pertaining to measurable correlates, or perceptions, of physical illness in CD in relation to psychological outcomes (e.g., Hallert & Åström, 1982; Lohiniemi et al., 1998).

It was hypothesised that each of these factors may have a directional impact on mood state or affective functioning, and possibly cognition and life quality in a significant proportion of people with CD. Considered simultaneously, these factors were also hypothesised to potentially comprise a DQ scale that could explain a large proportion of variance in decrements (or relative improvement) in mood, affect, quality of life and cognitive functioning.

Increases in magnitude of the two symptom-related DQ variables were theorised to increase the likelihood or severity of decrements in mood, and possibly cognitive functioning or quality of life. Conversely, increases in the two dietary-related variables were presumed to decrease the likelihood or severity of decrements in mood or affect, and perhaps decrements in cognitive functioning, should these exist. These four factors and their possible impacts on affective and cognitive functioning, or life quality, are outlined below.

Table 2

Symptom and Dietary-Related Factors Comprising a Hypothetical Damage Quotient (DQ)

Factor/ Variable	Possible Impact
Number of Symptoms at CD Diagnosis (termed "severity of CD")	Increased risk of affective disorder/ cognitive impairment; decreased life quality
Total Duration of Symptomatic Period Pre-diagnosis	Increased risk of affective disorder/ cognitive impairment; decreased life quality
Compliance with GFD (two measures used)	Decreased risk of affective disorder or cognitive impairment, should latter exist
Time Since Diagnosis *and* Being on GFD	Decreased risk of affective disorder or cognitive impairment, should latter exist

These hypothetical effects were partly based on previous findings of increased GFD compliance being associated with reduced health complications over time (see Club del Tenue Study Group, 2001) and an assumption that the observed amelioration or normalisation of health risks following GFD treatment may extend to improvements in mental or psycho-social health. Given the lack of association between the duration of the GFD and quality of life in a previous study (Lohiniemi et al., 1998) there were no specific predictions made in relation to life quality. Instead, the hypotheses made were limited to considerations of the predictive power of DQ variables on depression in CD. It was considered inappropriate to use the DM group in any comparisons pertaining to the damage quotient factors outlined, as these were tailored from the outset to reflect unique aspects of monitoring disease severity and progression in CD, with the possibility of better anticipating psychological sequelae in this illness.

In summary, there were four unidirectional hypotheses:

18.a) An increased number of CD-specific symptoms at CD diagnosis (termed "CD severity", and assessed retrospectively) were expected to increase depression at assessment in Study 1.

b) Increased total symptomatic duration pre-diagnosis (also retrospectively assessed) was expected to increase the level of depressive symptomatology.

c) Increased time since diagnosis (*assuming* GFD compliance) would be negatively correlated with depressive symptomatology.

d) Increased compliance with the GFD would be negatively correlated with depression.

If significant correlations were found in any of the expected directions, it was planned to construct an additive model as a basis for discriminating between depressed and non-depressed CD patients post-diagnosis (i.e., as assessed at the point of study entry in Study 1). A DQ model could be based of any combination of the four damage quotient factors. The first two static, symptom-related, variables were expected to operate in the opposite direction to the two dynamic dietary variables.

Due to the heterogeneity of symptom severity in CD, ranging from severe illness to an increasing proportion of asymptomatic cases indistinguishable clinically from normal health, it was anticipated that inclusion of the relatively asymptomatic or oligosymptomatic cases in the full CD group may potentially mask any significant differences between the CD group and comparison groups. Therefore, as well as defining the first factor for use in the hypothetical DQ, the partitioning process underlying subdivision of the CD sample – according to number of symptoms at diagnosis – was also undertaken to compare CD patients who were symptomatic pre-diagnosis with the other two experimental groups.

Known or quantifiable disease indices (e.g., symptomatology at diagnosis), compliance with the GFD, and second tier parameters (e.g., body mass index) were also systematically recorded. Gauging their relevance or potential influence on psychological symptoms in CD, in relation to readily identifiable static and dynamic variables such as age at study entry, age and severity of CD at diagnosis, time since diagnosis, and compliance with the GFD, were considered important in delineating risk

profiles able to discriminate between CD patients with minimal or mild-severe depressive symptomatology post-diagnosis, given the greater prevalence of depression in CD. Noting these correlates also aided in carefully defining an intensively researched sample, in order to assist in ruling in or out the impact of CD-specific and general illness-related factors on psychological functioning.

A diverse cohort of one-hundred and ten Australians with CD, four out of five with British or Irish ancestry and typically of middle-high socio-economic status, was interviewed and clinically evaluated. They were demographically representative of the adult Australian population in many respects, except that about 8% of Australians are of Asian ancestry (ABS, 2001) and there were no participants of Asian background in the CD sample. Half of the CD participants were in the third or fourth decade of life at study entry and when diagnosed with CD, which, on average, was four years earlier. All volunteered without payment to be involved in the study. They were recruited primarily via advertisements in the Victorian supplement of the national Coeliac Society magazine (Appendix D) and in response to direct marketing of the project at local coeliac meetings, conferences and functions.

Each CD participant was individually interviewed and completed an extensive battery of psychological questionnaires and tests during a three-four hour assessment session and received a one hour feedback meeting with the author. All sessions in the cross-sectional study occurred during an 18 month period between June, 1999 and February, 2001, and twenty-seven CD patients (one quarter of the cross-sectional sample), who were relatively newly diagnosed, were re-assessed 12 months later (see Chapter 5 – Study 2: Longitudinal).

Two well-matched comparison samples were simultaneously developed, one consisting of fifty-three people with a chronic illness (type-1 or -2 diabetes mellitus) and another comprising sixty-nine healthy volunteers, ten of whom participated in Study 2. The final non-CD participants entered the Study 1 in January, 2002. The present chapter reviews the methodology, test instruments and procedures used in psychologically evaluating the three study groups in Study 1, outlines the statistical design utilised and reports the experimental findings. A discussion of the key results of Study 1 completes this chapter.

Method

Coeliac Disease (CD) Participants

One-hundred and ten people with biopsy-confirmed CD (66 female; 44 male), with a mean age of 41.0 years (SD = 14.4; range = 16 to 84) living in the state of Victoria, Australia (80% in metropolitan Melbourne or Geelong; population 3.8 and 0.2 million respectively), were recruited for the study. Half of the remaining 20% of participants were living in the rural city of Ballarat (population: 84,000), within proximity to the local university, at which the author was enrolled in clinical psychology doctoral studies. Proportions of urban/ rural dwellers in the CD group were equivalent across gender (χ^2 with continuity correction = 1.21; $p = 0.27$).

The full sample had a mean educational level of 12.4 years (SD = 2.6), with the seventh year of education corresponding to the first year of high school, twelve years equating to the last year of high school and fifteen signifying completion of an undergraduate degree at university. Independent samples t-test indicated no significant gender differences ($\alpha = .05$) across age, educational level or the mean age at diagnosis with CD, which was 36.9 years (SD = 15.4; range = 1 to 84). A breakdown of age at diagnosis (with number and gender of participants) is displayed in Table 3.

Table 3

Diagnosis with CD: Number and Gender of Participants in each Age Group

Age Range at Diagnosis	Number (and gender) of Participants
Infancy (0-2 years)	4 (Male = 2; Female = 2)
Childhood (3 -12 years)	2 (M = 1; F = 1)
Adolescence (13-19)	8 (M = 5; F = 3)
Adulthood; Young (20-34)	33 (F = 23; M = 10)
Middle (35-49)	44 (F = 26; M = 18)
Mature (50-64)	15 (F = 9; M = 6)
Senior (65+)	2 (M = 2)

In the great majority of cases the diagnosis of CD had been made in adulthood (20+ years; 87%); in eight cases in adolescence (age 13-19 inclusive), and in the remaining six cases in infancy or childhood (defined as less than 13 years). In the one age category with sufficient numbers to permit meaningful comparisons (young adulthood: age 20-34), there were more than twice as many females (23 compared to 10 males) represented. For one quarter of these females (6 out of 23), anaemia identified during pregnancy was the principal reason for investigation leading to diagnosis.

All participants (98% prior to enrolment in study) had received a definitive, biopsy-confirmed diagnosis of CD, according to European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) criteria (Walker-Smith et al., 1990), based on clinical, immunological and bioptical features and proven histologic improvement on the GFD. Just under half of all CD participants (48%) had received a single upper GI endoscopy in establishing a CD diagnosis, 37% had received two, and three or more biopsies had been performed on the remaining 15% in their lifetime at the time of study inclusion. People with dermatitis herpetiformis in the absence of villous atrophy or inflammatory changes in the small bowel and pregnant or lactating women were not invited to participate. All participants, except two people awaiting an appointment with a dietician, had started on the gluten-free diet (GFD), with 92% demonstrating a positive clinical response prior to recruitment (or, in the case of those newly diagnosed, within 12 months of inclusion). In a further 4% of participants the clinical response was partial or ambiguous, while in the remaining four participants (three of whom were asymptomatic at diagnosis and compliant with the GFD) there was no apparent improvement.

Adherence to GFD

Duration of dietetic restriction for CD participants ranged from one day to 40 years ($\underline{M}$ = 4.2 years; $\underline{SD}$ = 7.9 years). Using two different self-report measures of compliance (frequency of gluten consumption in one year and beliefs/ intentions; see pp. 134-135) there was not a significant gender difference in adherence to the GFD using independent samples $\underline{t}$-test (at .05 confidence level). A strict GFD was defined as including no detectable gluten, as opposed to one allowing up to 0.03% protein

derived from gluten-containing grains, as determined by the Codex Alimentarius Commission of the World Health Organization and Food and Agricultural Organization (Selby & Faulkner-Hogg, 1998).

Consistent maintenance of a strict GFD for a year (preceding inclusion or subsequently, in those newly diagnosed) was reported in 68% of the sample, as determined at interview, and a further 24% of participants were moderately compliant, with their diet most closely – and consistently – following the Codex standard, with occasional transgressions. Various degrees of flagrant non-compliance were noted in 8% of the sample, with seven people keeping to a partial GFD and one highly symptomatic participant reporting the inclusion of gluten-containing foods several days per week, including the fortnight prior to interview and assessment. No CD participants included in the study typically followed, or intended to follow, a regular (non-gluten-free) diet post-diagnosis.

CD Symptomatology

Major circumstances and symptomatology retrospective and relevant to the diagnosis of CD were recorded in the *Questionnaire for Diagnosed Adult Coeliacs* designed by the author (see Appendix C). Estimated duration of CD symptoms before diagnosis averaged 56 months (SD = 78), with no significant gender differences. At interview, each participant nominated the primary reason for referral leading to diagnosis. Although a constellation of related symptoms were frequently encountered the key reason for each person was categorised (see Table 4, overleaf). Where combinations of apparently equally troubling pre-diagnostic symptoms were recorded, the most intense and/ or frequent of these just prior to the final referral leading to diagnosis was determined where possible.

From Table 4, it may be observed that in 50 out of 110 CD participants (45% of cases) GI symptoms (most often diarrhoea) were the dominant clinical feature immediately preceding diagnosis. In a slight majority of cases, however (60/ 110, or 55%), the investigation resulting in a diagnosis of CD was precipitated primarily by non-GI symptoms, most frequently iron-deficiency anaemia. Although psychiatric symptoms were not uncommon prior to CD diagnosis, they were rarely the primary reason prompting the identification of CD.

Table 4

Primary Reason for Referral Leading to a Diagnosis of Coeliac Disease: Subcategories Indented

Gastrointestinal (GI) symptoms:	
Diarrhoea	27 %
Nausea; vomiting; abdominal pain[1]	11 %
Constipation	3 %
Mild steatorrhoea; flatulence	2 %
Equal combination of GI symptoms	2 %
	45 % (subtotal)
Abnormal blood test results:	
Iron-deficiency anaemia (and/ or low folate/ B_{12})	19 %
Other	3 %
	22 % (subtotal)
Screening (blood relatives with CD)	8 %
Dermatitis herpetiformis	8 %
Weight loss; unable to gain weight (in absence of diarrhoea)	5 %
Lethargy/ fatigue (severe and persistent)	5 %
Psychiatric/ psychological condition:	
One case of major depression; another of dysthymia	2 %
Anxiety (with GI symptoms very minor)	1 %
	3 % (subtotal)
Migraine (intractable, with mild/ transient GI symptomatology)	2 %
Other extra-intestinal symptoms (fainting episodes; angina attack)	2 %
	100 % (Grand total)

[1] includes other persistent or recurrent upper abdominal (dyspeptic) symptoms (e.g., abdominal bloating, heartburn, early satiety, postprandial fullness, belching and regurgitation).

In most cases, the nominated key reason leading to referral and ultimate diagnosis with CD did not preclude a history of other key symptoms of CD of less prominent intensity, frequency or recency. For instance, lethargy of varying degrees was cited by the majority of participants as a concomitant symptom, but only occurred in the absence of a more significant reason leading directly to referral for diagnosis in five people, each of whom had a prior history of other (presumably CD-related) GI symptoms.

The majority of the total CD sample (81%) reported an unequivocal lifetime history of recurrent GI symptoms, typically a combination of diarrhoea, nausea, abdominal pain or cramping (with one symptom slightly more frequent) and not uncommonly constipation alternating with diarrhoea. Only 19% had an anamnesis without GI symptoms. The history or otherwise of GI (and extra-intestinal) symptoms noted above needed to be recurrent, persistent and personally troubling to be recorded formally for use in statistical analysis in this study, as population studies have shown that more than 50% of the general population experience significant upper GI symptoms (excluding diarrhoea) in their lifetime (Heading, 1999).

Diarrhoea was nominated by 27% of CD participants as the principal reason for referral leading to diagnosis, although 59% of the sample reported a persistent history of diarrhoea or loose bowels. However, for half of these people, another symptom was more prominent and the precursor to referral. Overall, the most common health conditions reported in the CD sample (as having been diagnosed during their lifetime) were iron-deficiency anaemia (72%); hay fever[2] (47%), migraine[2] (37% current or previous sufferers), asthma[2] (34%), reduced bone mineral density (BMD), typically

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[2] Hay fever and asthma are highly prevalent in Australia (Australian Institute of Health & Welfare, 2000), which has the highest child mortality rate for asthma in relation to other developed nations (Peat et al., 1994). Self-reported asthma prevalence was 113 per 1,000 people in 1995 (ABS, 1997), peaking in 5-14 year olds (192 per 1,000 persons). In the 1995 National Health Survey, 14% of Australians reported that hay fever was a long-term health condition (experienced for $\geq$ 6 months, compared to 11% for asthma); 13% reported that headache constituted a recent illness (experienced in fortnight preceding survey).

identified via DEXA[3] scanning (32% of total sample, but 58% of those actually tested) and dental enamel hypoplasia (28%). Other health related and second tier demographic variables were recorded in the CD and control groups (see Appendix C).

For each participant a full socio-demographic, bio-medical and psychiatric anamnesis was obtained utilizing a general questionnaire (Appendix C) and clinical interview (description on p. 153). The majority of the CD sample was married or living in a de facto relationship (69% overall; 71% of females [Fs]; 66% of males [Ms]), with 22% of the sample single (21% of Fs; 23% of Ms) and the remaining 9% divorced, separated or widowed (8% Fs; 11% Ms).

Socio-Demographic Profile of CD Group

Forty percent of participants in the CD sample were employed full-time, 18% worked part-time, 11% were full-time students, a further 11% were retired (at an earlier than normal age in four cases), 10% described themselves as being involved full-time in home duties, 5% were receiving the disability pension and one person was unemployed when seen by the author.

The majority of CD participants were of medium-high socioeconomic status (SES), with 59% categorised as medium (40 females and 25 males) and 30% high (20 females and 13 males). The SES distribution was comparable with those recorded both in the chronic illness comparison (diabetes mellitus; DM) and healthy comparison groups, although above local community averages, as detailed by the ABS (2001). Different criteria for determining the socioeconomic level were considered during data collection, with post code and household income initially utilized. However, the method producing the figures reported was based on criteria used by Ciacci et al. (1998), for whom education and work were the key determinants of SES. The author of the present study adopted their approach,

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[3] Ninety-two percent of participants reporting detection of reduced BMD (osteopenia or osteoporosis) at interview had received a DEXA (Dual Energy X-ray Absorptiometry) scan in the preceding 5 years; 8% had had an earlier scan, measurement using a different technique (e.g., quantitative computerised tomography) or could not specify which modality was used, but recalled the diagnosis.

with a slight alteration in partitioning years of education to reflect usual Australian community levels. That only 10% of the CD group (12 females; 6 males) was subsequently classified in the low SES range reflected the author's general impressions of somewhat above average SES across the full CD group.

Sixty-four percent of the CD participants (61% of Fs; 68% of Ms) had children (94% biological; 6% adopted or via previous marriage), with 33% of the sample having two children, 15% three, 13% one and 4% having four (which was the maximum number reported). Just over one third of the sample (36%) had no children. The mean number of children of participants across the full sample was 1.36 (SD = 1.22), but for participants older than 30 years the mean increased to 1.75 (SD = 1.13), with 79% of women (and 81% of men) over the age of 30 years having at least one child. The mean number of children increased further to 1.95 (SD = 1.00) for those participants beyond the age of 40 years and to 2.20 (SD = 0.82) for people aged over 50 years.

Body mass index (BMI), both at diagnosis with CD and at study inclusion, was computed by the author, utilizing retrospective and current height and weight data in indoor clothing without shoes (minus 1 kg), as supplied by each participant. BMI is a measure of the height-weight ratio, obtained by dividing weight in kilograms by the square of height in metres (kg/m^2). Direct assessment of the bodily measurements comprising the BMI was not undertaken by the author, these being based on participants' knowledge or estimates. The mean BMI for CD participants was 23.5 (SD = 3.6; range 16.4 to 35.4) at the time when seen by the author and 22.3 (SD = 4.1; 13.7 to 39.0) at the time of CD diagnosis, which on average was 4.1 years earlier. The internationally accepted healthy or desirable BMI range is 18.5-24.9 (Tierney et al., 2002) with a BMI < 20 (in males, or about a point less in females) generally designating underweight status. People with a BMI of between 25 and 30 are usually classified as overweight, with the threshold for obesity marked by a BMI of $\geq$ 30. Minor adjustments for gender are sometimes advocated (e.g., Heading, 1999).

All participants were asked to denote their ethnicity or cultural background, with more than one category able to be marked (see Appendix C, page 6 of questionnaire). Using these criteria, it was

determined that that within the sample of 110 participants with CD, 99% were Caucasian and 1% were of Aboriginal (Koori or indigenous Australian) ancestry. More than 8 out of 10 (83%) of the sample identified themselves as British/ Irish, with a finer breakdown determining the weightings to be 30% English, 20% Irish, 18% Scottish, 7% Welsh and 8% as unspecified British. This result was not unexpected, with an Australia-wide observation of CD as most prevalent among Scot-Welsh-Irish groups previously reported (Barr et al., 1994). Sixteen percent of the sample categorised themselves as of European ancestry (7% German, 4% Italian, 2% French and 1% Russian/ Scandinavian), with nobody claiming to be of Asian descent. This represents an under-representation of Asians in the wider Victorian community, who comprise approximately 8% of the local population (McLennan, 1998). Thirty-eight percent of the sample claimed some degree of Irish heritage and 36% a proportion of Scottish descent, both relative over-representations compared to up-to-date demographic breakdowns of ethnic ancestry (ABS, 2001).

Screening Protocol for CD Group: Inclusion/ Exclusion Criteria

The sample was screened for acute illness at study enrolment, any history of previous head injury or neurological impairment, medical conditions that may contribute to neuropsychological impairment (e.g., known renal failure), English as a second language and severe psychiatric disorder. This process was prioritised to reduce the likelihood of participants being excluded after significant involvement in the assessment process.

Criteria for exclusion included a previous head injury requiring hospitalisation for more than 24 hours or unconsciousness for 5 minutes or longer, a medical condition history (as reported by the participant) that was very likely to have contributed to neuropsychological impairment (apart from being diagnosed with CD), uncorrected visual impairment or hearing loss, intoxication with illicit drugs or alcohol at the time of testing or a history of alcoholism, illicit drug or other substance abuse. Four male CD participants reported a history of recreational cannabis use, but three of these participants were working – and one was studying – full-time at study entry and none reported

cannabis use in the week prior to assessment. Medical/ psychiatric conditions considered exclusionary included those with documented neurological or neuropsychiatric sequelae (e.g., stroke or Alzheimer's dementia) and histories of psychosis or mental disorders other than those in the anxiety or mood disorder spectrum.

Previous or current diagnosis with an anxiety or affective disorder did not preclude inclusion in any of the three groups used in the study, nor did use of prescribed psychotropic medication at the time of recruitment or previously. Five participants in the CD group were prescribed with antidepressant medication at study entry, including one male participant undergoing long-term treatment for bipolar disorder whose mood was stabilized prior and subsequent to enrolment. Nine others had previously used antidepressant medication in their lifetime. Seven participants were medicated with anxiolytics or hypnotics (i.e., benzodiazepine class drugs), three primarily for anxiety and four to aid sleep, with an addition twelve others having used anxiolytic medication previously, typically for night sedative purposes.

Taking into account concurrent (or a history of either) antidepressant or anxiolytic medication use, nine CD participants (8% of sample) were taking psychoactive medication at study entry. An additional eighteen (16%) had been medicated previously. This equated to 23% of the CD sample having been prescribed with psychoactive or central nervous system (CNS) - relevant medication in their lifetime. A record and clinical investigation of these details were kept for each participant. Statistical analyses were performed both including and excluding participants prescribed with psychotropic medication at the time of assessment. No participants were (or reported having been) prescribed with antipsychotic, anticonvulsant or antineoplastic agents, nor had any participant ever been an inpatient at a psychiatric facility or received electroconvulsive therapy (ECT).

Varying proportions of the CD sample were taking, or had previously used, a range of other mild but CNS-relevant medications. Narcotic analgesics (typically paracetamol and less commonly codeine-containing painkillers) were being used on a daily basis by seven participants, were used "often" by another twenty-eight (25%), "occasionally' by sixty (55%) and "never" by only fifteen

(14%). Twelve CD participants (nine women) were using medication (typically Ventolin) to assist in controlling asthmatic symptoms and six (five women) were taking blood pressure lowering agents. Almost one quarter of the female CD participants were receiving hormone replacement medication, including a 31 year old, and 48% of coeliac women over the age of 45 years. Five women reported early onset of menopause (< 40 years) and, in total, twenty-six (39% of female CD participants) were post-menopausal. Non-steroidal anti-inflammatory (typically aspirin) use was commonly reported by male and female CD participants.

One participant with CD who reported a new diagnosis of diabetes mellitus (Type-2) three weeks after participating in the study was not included in the final sample (being excluded from statistical analysis). Two CD participants had a history of seizures but neither had a formal diagnosis of epilepsy and were included in the sample.

Thirteen percent of CD participants smoked cigarettes (approximately half the Australian community average), although males were twice as likely to smoke as females (18% cf. 9%). Twenty-six percent of the CD sample described themselves as previous smokers who had quit (21% of Ms; 30% of Fs) and 60% had never smoked (61% of both Ms and Fs). The sample-wise results were comparable to Vazquez et al (2001).

In relation to alcohol consumption, 46% of participants best described themselves as social drinkers, 24% typically only drank on special occasions (categorised as less than once per week), 15% were frequent but not heavy drinkers (less than four standard drinks at least four days weekly), 13% were lifelong abstainers, and one person best described himself as an occasional binge drinker, but there were no indications of associated health problems. People for whom drinking was – or used to be – a serious problem (according to WHO criteria; 1993) were not recruited to the study.

Mindful of the positive impact of pyridoxine on depression in CD (Hallert, Åström, & Walan, 1983), vitamin/ mineral supplementation was noted, with 26% of CD subjects regularly taking most or all of the B-group vitamins, 24% being periodic users (or regular recipients of partial formulations, e.g., folate/ iron) and 50% never or rarely being in receipt of nutritional therapy apart from the GFD.

Recruitment of CD participants

The majority of CD participants included in the study had initially contacted the author after reading advertisements about the project. They were primarily sought and recruited via calls for volunteers in the Victorian section of the Australian Coeliac Society's national magazine; "The Australian Coeliac" (see Appendix D), with the placement of six advertisements over 18 months in consecutive issues. In response to a promotion at the 2nd Annual Coeliac Seminar in Melbourne (May 1999), three dozen people with CD registered their interest by leaving contact details and were subsequently contacted by the author, with twenty-four meeting entry criteria and agreeing to participate.

Fifteen people relatively newly diagnosed with CD (identified by volunteer staff at the Coeliac Support Centre) agreed to be involved in the study after being contacted directly by the author. The remaining recruitment occurred via advertisements posted at the Coeliac Support Centre in Melbourne, the University of Ballarat and referrals directly from doctors, gastroenterologists and dieticians who were aware of the project.

Ninety-eight participants (i.e., 89% of CD sample) were current members of the Victorian branch of the Australian Coeliac Society, or in the process of joining, as in the case of those very newly diagnosed. A further five people were prior members who had not renewed their affiliation and two others were not affiliated themselves, but had family members who were diagnosed with CD and who were existing members. Seven potential CD participants who had appeared to meet general criteria for involvement in the study were excluded immediately prior to assessment on the basis of inadequate diagnostic criteria having been satisfied (e.g., serological testing compatible with CD, but endoscopy and jejunal biopsy not carried out). Unequivocal diagnosis with CD was essential prior to inclusion in the study, with all available medical results verified against Coeliac Society membership database records of these details and/ or directly perused by the author with each participant's consent.

All CD participants were initially seen by the author between June 1999 and April 2001, including the longitudinal cohort ($\underline{n} = 27$) followed up by the author 12 months after the initial meeting (see Chapter 5).

Diabetes Mellitus (DM) Participants

Fifty-three people with DM (31 female; 22 male) consented to involvement in the study, serving as an age-, gender-, education-, SES- and IQ-matched chronic illness comparison group. Matching with the CD group for the four socio-demographic variables was intentional, but the close IQ correspondence was incidental. A majority of individuals in this group (77%) lived in metropolitan Melbourne, with another eight living close to the University of Ballarat. Ethnic breakdown was comparable to the CD group, the sample being 98% Caucasian. British or Irish ancestry was predominant (85%). A significant minority were of European heritage (13%), primarily second or third generation.

The mean age of participants with diabetes mellitus (DM) was 44.4 years (SD = 19.3; range = 16 to 82) and they had a mean educational level of 12.8 years (SD = 2.7). Although not quite statistically significant upon t-test, females in the DM group were, on average, about nine years younger than their male counterparts (M = 40.7 years; SD = 16.1, versus 49.6; SD = 20.9). The female and male means for years of education were identical (M = 12.8; SD = 3.0 and 2.4 respectively) and the SES distribution across gender was comparable (medium: 16 Fs; 12 Ms; high: 10 Fs; 8 Ms and low: 5 Fs; 2 Ms).

Thirty-six people within the DM group had type-1 (previously called insulin-dependent or, more distantly, juvenile-onset) diabetes and seventeen had type-2 (previously called non-insulin dependent or adult-onset) diabetes. All participants in these subgroups had a previous general practitioner confirmed medical diagnosis of DM prior to study entry, based on ketonemia, ketonuria, or both in type-1 DM patients and consistently impaired fasting plasma glucose ($\geq$ 126 mg/dL) in all DM patients prior to treatment, the 75-g oral glucose test or other appropriate diagnostic procedures. Each DM participant was also receiving ongoing conventional medical assessment, including regular monitoring of glucose levels, glycosylated haemoglobin (HbA_{1c}), fasting lipid profiles and kidney function and standard reviews of individual treatment protocols. Each DM participant's own designation as type-1 or -2 at initial recruitment was closely examined at interview, in reference to their medical history and in light of current diagnostic and classificatory criteria (Masharani & Karam, 2002) prior to final study inclusion

In the type-1 subgroup, the majority of participants had a classic (abrupt and acute) onset of

hyperglycaemia in childhood or early adolescence, with proneness to ketoacidosis, insulopaenia and immediate dependence on injected insulin. Three participants were best described as having latent autoimmune diabetes, having not been initially diagnosed as type-1, but requiring insulin within two years of diagnosis. In the type-2 group, seven participants were insulin-assisted at the time of involvement in the study, another seven were medicated with oral hypoglycaemic agents and three were being treated solely via lifestyle modification (diet combined with aerobic exercise).

Initial recruitment of DM participants resulted in a preponderance of type-1 (over type-2) volunteers who were, on average, about 10 years younger than the CD group, and people with type-2 diabetes who were, not surprisingly, about 10-15 years older. Limiting the chronic illness comparison group to either type-1 or type-2 DM sufferers was not a fixed initial consideration. Also, matching the chronic illness comparison and CD groups on demographic grounds was enhanced by combining people type-1 and -2 DM. Therefore, this process was undertaken from the onset of recruitment.

The type-1 and type-2 DM subgroups were therefore combined as the chronic illness comparison group (referred to as DM) for the majority of statistical comparisons. These subgroups were also considered separately where appropriate. The mean age of participants with each of type-1 and type-2 DM were 37.44 years (SD = 17.1; range = 16 to 73) and 59.18 years (12.0; 41 to 82) respectively and they had a mean educational level of 13.17 (SD = 2.6) and 12.00 years (SD = 3.1). Across the range of demographic variables, independent samples t-test demonstrated that only age was significantly different between type-1 and -2 DM participants ($t = 4.70$, $p = .000$), with equal variance not assumed, given that Levene's test for equality of variances was positive ($p < .05$).

The mean age at the time of diagnosis with DM was 29.2 years (SD = 19.9; range = 4 to 70). In half the cases (51%, including all type-2 cases and nine of type-1) the diagnosis of DM had been made in adulthood (20+ years); in sixteen cases (all type-1) in childhood (4-12 years) and in the remaining eleven cases (all type-1) in adolescence (age 13-19 inclusive). The mean ages of diagnosis were, for type-1, 19.0 years (SD = 14.5; including nine at age 12-13) and, for type-2, 50.8 (SD = 9.8; with all

except four first detected in their 40s or 50s). A breakdown of age at diagnosis (with cases numbers, gender and diabetes type) is displayed in Table 5 (below).

The mean duration of DM across the full sample (since diagnosis) was 15.3 years (SD = 12.9 years); with a mean of 16.34 years (SD = 12.4) for females and 13.75 years (SD = 13.8) for males, a statistically non-significant difference. However, the mean duration of illness for the type-1 subgroup was significantly higher than for the type-2 subgroup (18.5 years; SD = 13.5 versus 8.5 years; SD = 8.5).

In addition to recording all socio-demographic factors, the type of diabetes, age at and time since diagnosis, the duration of symptoms prior to diagnosis was also noted, calculated or estimated during the face-to-face interview in consultation with each participant and all available medical records. Following an identical protocol to that used with the CD group to determine the total clinically symptomatic period pre-diagnosis, the mean pre-diagnosis symptomatic duration for the full DM was computed as 6.8 months (SD = 12.3 months). The type-2 subgroup reported significantly longer pre-diagnosis symptomatic periods (12.5 months; SD = 17.7 versus 3.2 months; SD = 5.0).

In 50% of type-1 cases the recalled symptomatic period was less than one month prior to diagnosis. Readers should also note that physiological changes may be occurring months and typically years prior to initial symptoms, especially in type-2 diabetes (Tierney et al., 2002).

Table 5

Diabetes Mellitus (DM) Diagnosis: Participants in Each Age Group by DM Type (i.e., Type-1 or -2)

	Number (and Gender) of Participants	
Age at Diagnosis	Type-1	Type-2
Childhood: Early (4-9)	7 (F = 6; M =1)	nil
Later (10-12)	8 (F = 5; M = 3)	nil
Adolescence: Early(13-14)	7 (F= 5; M = 2)	nil
Later(15-19)	4 (F = 2; M = 2)	nil
Adulthood: Young (20-34)	3 (F = 2; M = 1)	1 (M)
Middle (35-49)	4 (F= 2; M = 2)	6 (F= 5; M = 1)
Mature (50-64)	3 (all M)	8 (F = 4; M = 4)
Senior (65+)	nil	2 (both M)

The major symptoms of ill health experienced and reported by each DM participant at study entry, listed from most serious, troubling or uncomfortable were recorded. The top six nominated by all DM participants were weighted equally, with breakdowns according to diabetes type (and divided by the number in each subgroup to yield a percentage), as listed in Table 6. Three symptoms (anxiety or low mood, eye and foot-related complaints) were equally represented at 26% in the full DM sample. These are listed from highest to lowest ranked according to respondents' sequential rankings, giving a first-listed symptom a weighting of 6 down to 1 for the last listed (for those who listed six symptoms).

Table 6

Major/ Most Serious Symptoms of Ill Health Experienced Now, as Nominated by DM Participants, According to Diabetes Type (% of subjects)

Most Serious Symptom	Type-1 (n = 36)	Type-2 (n = 17)	Total DM Group (n = 53)
Lethargy/ fatigue	53	29	45
Hypoglycaemia	39	6	28
Anxiety/ Low mood	28	24	26
Eye	25	29	26
Foot related	33	12	26
Memory/ concentration problems	25	18	23
Weight[1]	19	12	17
Slow wound healing	17	12	15
Sleep	8	18	11
Other psychological (Fear of complications/ irritability)	8	12	9

Note: Figures are expressed as percentages of participants

[1] Gaining (or being unable to lose) weight was the key issue for all respondents except one male with type-1 diabetes, for whom lost weight was a major concern

It is important to note that the percentages reflect the number of people with DM (against diabetes type and total group) who themselves perceived the relevant symptoms to be serious, troubling or uncomfortable. Some of the figures tabulated do not necessarily correlate in a logical sense with other measures of the symptom in question. For example, a slightly higher proportion of people with type-1 (versus type-2) DM listed weight as a major symptom of ill health, despite a smaller proportion actually being overweight, using objective criteria such as body mass index (BMI).

Current BMI (kg/m^2) was computed from bodily measurement provided by all participants, with a mean of 26.3 (SD = 4.0) for the full DM sample, an almost identical figure for males and females. People in the type-2 diabetes subgroup had a significantly higher mean BMI than those in the type-1 subgroup (29.1; SD = 4.2 versus 25.0; SD = 3.2), with all except three participants with type-2 DM (82%) having a BMI of ≥ 25 (overweight) and almost half (47%) ≥ 30 (i.e., obese). In the type-1 subgroup 50% had a BMI in the normal weight range (20-25), with only three (8%) with a BMI above 30. The high proportion of overweight people in the type-2 subgroup was approximately representative of the community prevalence of overweight status in people with type-2 DM using BMI.

Medical Parameters at Study Entry

All except one DM participant (described later) were euglycaemic within an hour of scheduled psychological assessment, according to self-administered blood glucose recordings undertaken in front of or reported to the author. In addition, the most recent pathology report records of glucose levels, glycated haemoglobin (HbA_{1c}), fasting lipid profiles, as well as kidney and liver function test results (if available), were noted in the interviews of all DM participants where recalled. These details were not systematically recorded on a data file or subjected to statistical analysis, but were used primarily to exclude DM participants with a consistent recent history of very poor diabetic control, moderate to severe nephropathy or indications of serious hepatic complications. According to individual self-report, the majority of study participants had good to fair control in relation to HbA_{1c} levels, taken as an average of their most recently recorded tests in the 12 months immediately prior to study entry. Standard

reference intervals used for HbA_{1c} were Normal (non-diabetic): 4.0 – 6.0 %; Good Control: 6.1 – 7.0 % and Fair Control: 7.1 – 7.9 %. Eleven DM participants reported that their most recently assessed HbA_{1c} level was greater than 8.0% but each of these participants reported at least reasonable short to medium term glycaemic control preceding study entry, and an absence of severe DM-related health complications.

Perceived Self-Compliance With Diabetes Treatment

Each participant also self-rated their level of compliance with diabetic treatment at study entry from excellent (I'm doing almost everything I can to stay healthy) to very poor (I am not following my treatment plan at all). On this Likert-type scale (see Appendix E), 65% of the sample rated their treatment compliance as very good (39%) to excellent (26%), 8.7% each as good (I'm doing most things I can to stay healthy, but not everything) and fair (I'm doing a lot of things to stay healthy, but missing a few things) and 17% as poor (there are a lot of things I should be doing better to stay healthy). Reasonable concordance was apparent when perceived self-compliance with diabetes treatment was matched on a case by case basis with recent medical parameters (i.e., HbA_{1c}, fasting lipid profiles and available data regarding nephropathic and hepatic function). A further overall observation, pertinent to several cases, was that perceived compliance was excessively self-critical against supplied medical test data, especially in the case of those participants rating their compliance as poor. In all such cases, the recent test results suggested at least fair control regarding HbA_{1c} and an absence of anomalous results in other areas.

Glycaemic Status and Recent Hypoglycaemic Episodes

Despite variation in self-rated treatment compliance, almost all DM participants were successfully maintaining at least reasonable glycaemic control at the time of study inclusion, with a high degree of awareness of the short and longer-term health protective factors across the sample. Regular glucose testing was self-administered by all DM participants, except those with type-2 DM and reliant on diet alone. Across the sample, hypoglycaemia preparedness was typically sound. One DM participant who

experienced moderate hypoglycaemic symptoms during pre-assessment interviewing stabilized after provision of a snack and the passage of time, but cognitive testing was rescheduled.

A number of distantly diagnosed participants admitted poor or sporadic compliance earlier in life. There was a positive Pearson correlation between current participant age and diabetes compliance ($r = 0.48$; $p = .019$) and a negative correlation between compliance and state anger ($r = -0.43$; $p = .040$). Those expressing the greatest difficulty with glycaemic control were typically in new medicinal regimes at the time of study involvement.

Inclusion/ Exclusion Criteria for DM Group

Akin to the requirements for inclusion into the DM group, exclusionary criteria were strict, given the presence of complications, significant morbidity and severe later-state health implications encountered in diabetes (Williamson, Thompson, Thun, Flanders, Pamuk, & Byers, 2000). People with uncorrected visual impairment, renal or hepatic dysfunction, symptomatic cardiovascular disease and amputees were excluded from recruitment to the DM group. Furthermore, the aforementioned exclusionary criteria applied to participants in the CD group were also employed. These criteria were inclusive of a medical condition history (as reported by the participant) that was unlikely to have significantly contributed to neuropsychological impairment, over and above having been diagnosed with DM and having a history of mild to moderate complications associated with DM outside of the categories listed.

In addition, potential DM inclusions who had a history of classic clinical signs of CD – in particular GI symptomatology – and who had not had serologic testing and intestinal biopsy to rule out CD, were not included. One person fitting this description and another with a family history of CD were excluded, while a third person already recruited to the CD group later informed the author that she had been additionally diagnosed with DM after initial assessment. She was omitted from all statistical analyses.

As in the CD sample, psychoactive medication use was not uncommon in the DM group.

Combining a history of either antidepressant or anxiolytic medication use (or a concurrent prescription), four DM participants (8% of sample) were taking psychoactive medication at the time of assessment (one, an antidepressant; three other participants, sedatives). An additional six (11%) had been medicated in their lifetime prior to study entry, equating to 19% of the DM sample having been prescribed with psychoactive medication in their life. No DM participants reported having ever been prescribed with antipsychotic, anticonvulsant or antineoplastic agents, had ever been an inpatient at a psychiatric facility or been subject to ECT.

The author was reliant on information provided by each participant in response to detailed questionnaire items and discussions of medical histories and records during clinical interviewing, in determining the applicability of exclusionary criteria in each case. In a number of cases medical records were referred to by participants in the author's presence to clarify diagnostic information. No participants in the DM group were direct or distant blood relations (as far as could be ascertained) of anyone in either the CD or healthy control (NC) groups.

Twelve percent of the DM participants were cigarette smokers (cf. 13% of CD sample, 15.5% for Australian DM patients in a large scale study [Zimmet & Welborn, 1999] and about half the Australian community average, as aforementioned), 24% were previous smokers who had quit (cf. 26% of CD sample) and 63% had never smoked (60% for CD sample). Regarding alcohol consumption, 23% of participants described themselves as social drinkers (cf. 46% in CD sample), 31% preferred to drink on special occasions (i.e., < once per week; cf. 24% of CD sample), 26% were frequent but not heavy drinkers (< 4 drinks ≥ 4 days weekly; cf. 15% of CD participants) and 21% were lifelong abstainers (13% of CD group), with no DM participants describing themselves as binge or problem drinkers.

Given that there was a slightly greater proportion of participants in the DM group who were either frequent drinkers or abstainers, compared to the CD group, these two samples were viewed as approximately balanced overall regarding alcohol consumption. People for whom drinking was, or used to be a serious problem, were not recruited to the study.

Recruitment of DM Participants

Diabetes mellitus participants were primarily recruited via five consecutive advertisements in the quarterly national "Diabetes Today" magazine (Appendix F), the source of a large proportion of participants in older age brackets. From responses to each advertisement, several suitable participants (ranging in number from two to six) were selected who met diagnostic requirements and all inclusion and exclusion criteria.

The majority of younger DM participants were recruited via advertisements in a Victorian magazine (called "Reality Check"), published from the office of Diabetes Australia targeting the interests of teenagers and young adults with DM. An e-mail advertising the study was also sent to all electronic subscribers. Finally, the author personally addressed a young diabetic support group, after which several adolescent DM sufferers meeting selection criteria consented to involvement. A small proportion of middle-aged DM participants were recruited via advertisements posted at the Alfred Hospital in Melbourne, the Psychology Department notice board at the University of Ballarat and a mid-week advertisement placed in the largest selling Melbourne daily newspaper, the Herald-Sun. In all, eighty-one percent of DM participants were registered with (i.e., subscribers to) Diabetes Australia.

People in the DM group were recruited and assessed in the context of two sessions each (less than three weeks apart) between March, 2000 and December, 2001. Whilst light snacks and beverages were provided, all DM participants assessed away from their own residence were reminded of the estimated duration of assessment, separate from travel time, the day prior to study participation and encouraged to bring refreshments of their choice to ensure sustained glycaemic control.

Healthy Control Participants

A second control group of 69 age-, gender-, education-, SES- and IQ-matched healthy volunteers without a chronic illness (41 females; 28 males) comprised the normal control (NC) group. Selected to match the CD group as closely as possible in terms of age, gender, educational level and socio-economic status (all statistically achieved goals), close matching for full-scale WAIS-IQ incidentally

occurred, as happened in the DM sample. There was a comparable with-in group distribution of variance in all socio-demographic variables across gender. Most individuals in the NC group lived in metropolitan Melbourne (54 out of 69) or Geelong (two people), eight lived in proximity to the University of Ballarat, with the remaining five living in other regional locations within Victoria. The mean age of NC participants was 41.1 years (SD = 18.7; range of 16 to 81) and they had a mean educational level of 12.38 years (SD = 3.0).

The NC sample was almost exclusively of Caucasian extraction (99%), with people of British/ Irish background again most highly represented (82%) and European heritage accounting for almost for all the remaining variance (17% overall; Italian 4%, German 3%, Dutch 1%). For all NC participants, English was spoken at home from an early age.

No participants in the NC group were direct or distant blood relations of any participants in either the CD or DM groups. People with a family history of CD (but not diabetes mellitus) were excluded. According to their own reports in the context of answering a specifically designed questionnaire identical to the CD Questionnaire, except for the CD material (Appendix L), and clinical interviewing, none of the healthy volunteers included in the study had previous diagnoses, indications or current clinical signs of diabetes mellitus, CD or other gastrointestinal (GI) disorders, such as IBD. For example, people with a history of iron-deficiency anaemia who had not undertaken serologic and bioptic testing for CD were not included. However, medical testing to rule out CD or other medical conditions was not undertaken in asymptomatic volunteers. People with mild asthmatic conditions and minor medical ailments (e.g., high cholesterol in absence of symptomatic cardiovascular disease) were included, provided that there was not compelling evidence that such conditions may adversely affect cognitive functioning. Those with major and disabling or degenerative chronic diseases, other than mild cases of common processes (e.g., arthritis), were excluded. All healthy volunteers were also subject to the same general exclusionary criteria applied to CD and DM participants, as specified earlier.

Notwithstanding the clear exclusionary criteria utilised, 19% of the NC sample reported a lifetime history of occasional or mild GI symptoms. These figures were comparable to or below reported

community levels of lifetime upper GI symptomatology (Heading, 1999). The characteristics of the GI symptoms reported, in conjunction with general health factors, did not arouse suspicion of CD or IBD.

Psychoactive medication use was permitted in all study groups, including the NC sample, 4% of whom were prescribed with psychoactive medication at enrolment. Three NC participants were using anxiolytic medication (three for night sedation) and one was also using an antidepressant. In total, a further ten healthy controls (14%) had been prescribed psychotropic medication in their lifetime, a slightly smaller proportion than the DM and CD groups. As was the case in the CD and DM samples, no NC participants had ever been treated with antipsychotic, anticonvulsant or antineoplastic medications or been an inpatient at a psychiatric facility.

Various parameters of general health and life quality in the NC sample were in line with community norms, but a higher than expected proportion were non-smokers (58%), very similar to both the CD and DM groups. Alcohol consumption was also similar to the chronic illness groups. Mean BMI, at 24.5 (SD = 3.3), was not significantly different across gender, with 13% underweight (range of 17.5 to 19.4), 38% of the sample in the healthy range (20 to 24.9), 16% borderline (range of 25.1 to 25.99), 26% overweight (26 to 29.9) and two NC participants greater than 30 (30.1 and 32). There were no strong, pre-existing suspicions of DM in those designated overweight, with the person of highest BMI actually a fit young person with very high relative muscle mass and normal subcutaneous fat level (12%), as medically assessed. Less pronounced examples of this dynamic (relatively high muscle mass/ normal adipose levels) were apparent in a number of the NC males with a BMI greater than 25.

The NC participants were sought from three major sources. Recruitment occurred via general noticeboard and e-mail advertisements at the University of Ballarat and University of Melbourne, from amongst staff serving as correctional officers at Victoria's Port Phillip Prison (and/ or relatives of them) and also from general members of the public responding to an advertisement placed in the highest selling local daily newspaper, the Melbourne "Herald-Sun". The divergent recruitment protocol facilitated close matching of the NC group with both the CD and DM groups on socio-demographic

grounds and also resulted in a good spread of scores in most assessment/ test measures utilized in the study. Similar to the two chronic illness groups, the healthy controls, on average, were of medium to high SES.

After fully consenting, a 22 year old male university student was excluded from participating. He had scored 32 on the BDI-II, and a concomitant clinical interview established that this person had made a serious suicide attempt several days earlier. He voluntarily withdrew from the study and accepted a referral to a local psychologist after receiving counselling from the author.

All NC participants were seen once by the author between the period of June, 1999 and December, 2001, with a small subgroup accessed before March 2000 (n = 10) followed up for re-assessment one year later (see Chapter 5; Longitudinal Study).

Materials and Measures

Prior to assessment with a battery of psychological instruments in standardised order (as described in the prospective section), each participant read and signed a consent form (Appendix G), tailored according to their group (CD, DM or NC), in the presence of the author and an independent witness.

Beck Depression Inventory - 2nd Edition (BDI-II; Beck, Steer & Brown, 1996)

The BDI-II was the first psychological instrument administered to all participants in Study 1 in the presence of the author. It served a joint purpose, being used by the author as both; a) a screening test in establishing the likelihood or otherwise in all study participants of signs of a major mood disorder, and, b) it comprised the sole psychometric evaluation of depressive symptomatology used in Study 1. The Beck Depression Inventory has widespread previous use in screening for clinical depression in chronic illness, including diabetes mellitus (e.g., Lustman et al., 1997) and multiple sclerosis (De Luca, Barbieri-Berger, & Johnston, 1994), as well as the evaluation of mood in GI malabsorption and disturbance (Ledochowski, Widner, Bair, Probst, & Fuchs, 2000). The current BDI-II is a 21-item self-report questionnaire for measuring the severity of depression in adults and adolescents aged 13 years and older (Beck et al., 1996) and its constituent items were selected by Beck et al. (1996)

to correspond with the key criteria used for diagnosing depressive disorders outlined in the American Psychiatric Association's (DSM-IV; APA, 1994).

For each item in the BDI-II, the respondent indicates to what degree a particular depressive symptom (e.g., Sadness; Item #1) has been experienced in the *past two weeks, including today* by circling a score from 0 to 3. Each numerical score is self-evaluated as follows (using Sadness as an example): 0 = I do not feel sad; 1 = I feel sad much of the time; 2 = I am sad all the time; 3 = I am so sad or unhappy I cannot stand it. Possible total scores range from 0-63.

The author requested that each subject read the BDI-II instructions out loud in order to broadly ascertain the level of reading comprehension and capacity to fill the questionnaire without verbal guidance. The inventory took participants approximately 5-10 minutes to complete, as suggested in the BDI-II Manual.

For the purpose of interpreting scores on the BDI-II, the screening protocol advocated in the Manual uses a relatively low threshold for detecting depression in order to decrease the likelihood of false negatives. The cut score threshold guidelines based on patients diagnosed with major depression (as provided on page 11 of the Manual) are described by Beck et al. (1996) as minimal (total score of 0-13); mild (14-19); moderate (20-28) and severe (29-63). These thresholds were considered in relation to mean participant scores in each group in the study and the proportion of participants' scores within each range in each group.

The psychometric characteristics of the BDI-II, including its reliability and validity, are detailed in the BDI-II Manual. In summary, this test instrument is characterised by strong internal consistency, with high coefficient alphas and test-retest stability, the latter statistic of special pertinence to the longitudinal study of the present thesis (Chapter 5). Furthermore, all validity indicators are favourable, with clear content, construct and factorial validity.

Of particular relevance to the cross-sectional study, two major dimensions of self-reported depression were identified by Beck et al. (1996) following promax-rotated iterated-principal-factor standardised regression analysis using a sample of 500 psychiatric outpatients (see p. 30-31; BDI-II

Manual, 1996). Mutually exclusive sets of constituent BDI-II items were found to load onto one of each of these dimensions. These factors were described as Somatic/ Affective (Factor 1) and Cognitive (Factor 2). Many items on the second half of the inventory map onto Factor 1 (e.g., Tiredness or Fatigue and Loss of Energy) and those items appearing mainly on the first half of the inventory loading onto Factor 2 (e.g., Past Failure and Worthlessness). The correlation between these factors was 0.66.

The use of a reliable, valid and widely used measure of self-reported depression such as the BDI-II, with the capacity to discriminate between somatic/ affective and cognitive dimensions of depression, was considered to be of great relevance, especially given that the physical symptoms of depression in CD may mimic the somatic symptoms of depression, in addition to other reasons outlined in Chapter 2.

A final reason the BDI-II was chosen in the present thesis ahead of other measures of depression was that it contains just one item of possible direct gastroenteric or dietary significance, namely 18. Changes in Appetite. This situation compares favourably with the Zung self-rating depression rating scale, used (and modified) by other authors (e.g., Addolorato et al., 2001; Gasbarrini & Addolorato, 1997), which contained three items evaluating gastroenteric symptoms of depression prior to modification by those authors (decreased appetite, weight loss and constipation).

Coeliac Disease Awareness Screen

A new scale was developed by the author to measure CD participants' knowledge about CD (Appendix H). Ten questions comprising the scale tested awareness of facts about CD across diverse areas, including CD symptomatology (Question 4), the gluten-free diet (Question 5) and diagnostic criteria (Question 10). The screen was developed and refined over a six month period, involving consultation with Victorian Coeliac Society committee and other health care professionals associated with the Victorian Coeliac Society. The scale was also administered to society members, who provided feedback about item content and clarity. Following administration to a range of people with CD, from those newly diagnosed to those on the gluten-free diet for various periods of time, a scoring regime was developed (Appendix I), with tentative, preliminary descriptions of various score ranges.

For each of the ten questions comprising the scale, CD participants were instructed to circle the best answer or answers. Please note that in a number of questions more than one answer is preferable. Each question had from six to eighteen alternative answers. Every alternative answer to each question was given a score by the author. For incorrect answers a negative score was given if the item was selected, while for correct answers, positive scores were awarded or in some cases not selecting correct answers attracted negative scores. For example, the fifth question asked In the gluten free diet what foods can be safely eaten by people with CD. Of each of the 18 alternative answers, several attracted positive scores if selected (e.g., circling bananas = 1), selecting gluten-containing foods attracted negative scores, while one (correct) item attracted a positive score if selected and a negative score if not selected (circling monoglyceride = 2; if not selected = -2).

Whilst the scoring system was complicated, it was designed to maximise separation of scores (see Table 7), based simply on CD participants' knowledge of CD in the context of a brief inventory designed to be completed in less than 5 minutes. The author was present at all times during the administration of the CD Awareness Screen and emphasised the written instructions.

Table 7

Score Ranges and Proposed Level of Knowledge in the Coeliac Disease Awareness Screen

Level of Knowledge	Score Range
Highest possible score =	100
Excellent Knowledge:	**>60**
Broad Knowledge (>12 mths diagnosed/ updated awareness):	46-60
Average (Coeliac diagnosed for 12 months):	**30-45**
Low Knowledge (Newly diagnosed coeliac):	15-29
Very Low	**< 15**

Lowest possible score = Minus 100

The Coeliac Disease Awareness Screen was completed by CD participants immediately following the administration of the BDI-II. Theoretically, possible scores ranged from minus 100 to positive 100, with pilot testing suggesting a preliminary scoring range as outlined in Table 7. It was expected that

the majority of scores would fall between 0 and 80. The CD Awareness Screen took about 5 minutes to complete.

Health Status

Participants from each group completed a 6-point self-assessed health status rating in the presence of the author. They rated their health status (i.e., how good or bad they considered it to be) from *very poor* to *excellent* (Appendix J), with national community norms available for people with and without one or more medical conditions (McLennan, 1998).

This measure was based on the 5-point rating utilised in the Australian National Health Surveys of 1989-90 and 1995 (McLennan; Australian Bureau of Statistics; Pocket Year Book, 1998, p.44). In the present study an extra rating point ("very poor") was included to better accommodate a finer analysis of the perceived ill-health of people in the CD and DM groups.

Each NC participant rated their health on this scale once only, while those participants in the CD and DM groups rated their health according to two temporal scales; right now and prior to diagnosis/ treatment. Reading the instructions and completing this scale took participants less than 60 seconds.

Compliance with Treatment in CD and DM Participants

CD and DM participants rated their compliance with treatment via separate self-report processes, also with the author present. Participants with CD estimated how often they ate gluten-containing foods, whether deliberately, knowingly or accidentally, by selecting one of six categories based on frequency, ranging from Always, i.e., every day (score = 0) to Never (= 5).

This self-rating scale was designed by the author (Appendix J) and was intended to reflect actual behaviours, as opposed to intentions, beliefs or cognitions about a CD patient's perception of their degree of compliance, which are more susceptible to and dependent on temporal, situational, affective and memorial factors. Participants with CD were also required to describe recent occasions and circumstances when gluten-containing foods were knowingly or accidentally consumed.

Participants with DM rated their level of compliance with treatment (i.e., "the extent to which you

are doing what you can to stay healthy, based on the medical advice you have received") by selecting one of six categories from, ranging from Very Poor; i.e., I am not following my treatment plan at all; I'm not seeking help (score = 0) to Excellent, i.e., I'm doing everything I can to stay healthy (= 5). The compliance scale for participants with DM, like its CD counterpart, also emphasized behavioural evidence of treatment compliance. The brief CD and DM compliance scales were able to completed in less than one minute.

Compliance with GFD – Second Measure for CD Participants

The frequency with which CD participants deliberately, knowingly or accidentally ate gluten-containing foods, as the assessed by the previous scale, was considered the best brief self-report measure of compliance with the GFD. However, an alternative scale was also generated from a pool of 18 items (Appendix K), with two of four items based on items in a new GFD compliance measure developed by Buckfield (1997). The secondary scale subsumed distinct factors related to compliance, as identified by that author, including intentions to comply with and difficulty following the GFD, as well as self-reported compliant and non-compliant behaviours.

The author's scale was comprised of four compliance-related questions (two positively keyed and the other two negatively keyed), each of which yielded five possible scores from 0-4, based on a 5-point Likert scale (strongly disagree to agree), resulting in a total score of 0-16, with higher scores indicating increased dietary compliance. These four questions were selected from a list of 18 compliance-related questions administered to members of the Victorian coeliac society in a pilot exercise. They were selected primarily on the basis of encompassing key factors underlying dietary compliance with the GFD and were amongst the items that provided the greatest spread of scores during pilot testing. The questions were:

"I have made a firm commitment to follow the GFD" and "I follow the GFD strictly in all circumstances" (positively keyed) and "I have not always followed the GFD since being diagnosed" and "Because the GFD is difficult, sometimes it is not worth following" (negatively keyed).

Demographic and Health Questionnaire for all Participants

Participants in all groups completed a general 5-6 page pre-test general health and information questionnaire designed by the author (see Appendixes C, L and M), which yielded information about their socio-demographic profile, family information, medical and psychiatric history, smoking and drinking habits, medicinal use and ethnicity/ cultural background. The questionnaire was administered in the presence of the author and took an average of 15 minutes to complete. It was used conjunction with brief pre-assessment clinical interviewing. The screening process also verified each individual's inclusion in the study, assisted in matching the groups across key demographic factors and fortified the reservoir of background information relevant to the health-related, behavioural, affective and cognitive variables being measured.

The questionnaire was slightly different for each of the three groups, with those administered to the CD and DM participants including additional information about symptomatology and diagnostic details specific to CD and DM. In the CD questionnaire the specific diagnostic trajectory tracing initial symptoms to confirmed CD was requested. Primary and secondary reasons for referral leading to diagnosis and a retrospective record of which symptoms ameliorated following treatment with the GFD were clarified at interview following completion of relevant questions in the questionnaire.

Four key clinical variables were generated from information elicited via the questionnaire and clarified during the interview, these being 1) the precise age at diagnosis; 2) the days since diagnosis *and* being on the GFD; 3) the number of *distinct* symptoms at the time of diagnosis (referred to as "severity of illness") and 4) the total duration of time that each participant was symptomatic prior to diagnosis (persistently recalling experiencing at least one symptom of CD). The first three variables (i.e., age at diagnosis, time on GFD and number of symptoms at diagnosis) were able to be ascertained with a reasonable degree of confidence in almost all cases.

Calculating the fourth clinical variable (total duration of time that each participant was symptomatic prior to diagnosis) was very difficult in a large minority of cases and subject to many potential biases, not the least being how it was specified. The author defined "symptomatic" in the case

of this variable as any continuous period of time pre-diagnosis that the participant could recall having at least one distinct, unresolved, physical symptom of CD. For example, a participant diagnosed at age 20 years with definite GI symptoms their entire life (on an unbroken daily basis) prior to diagnosis would be designated as having been symptomatic for 20 years.

In the case of most participants who were diagnosed in adulthood, however, there was a sporadic history of CD symptoms experienced, with symptomatic periods often intensifying or increasing in length and frequency in the weeks, months and years just prior to diagnosis with CD. For many participants diagnosed in adulthood, early adolescence was recalled as being a completely symptom-free life stage. In the author's definition, if a participant's only symptom prior to diagnosis was, for example, anaemia, and this had remained unresolved up to the diagnosis of CD, the entire period between identification of anaemia and diagnosis with CD was recorded as the duration of time that that participant was symptomatic. In cases where periods of being symptomatic were preceded, broken by or alternated with completely asymptomatic stages, the symptom-free and symptomatic periods were each appraised and a total symptomatic duration was calculated by adding up each symptomatic period prior to diagnosis. Finally, possible non-physical symptoms of CD (e.g., depression) were not included in the calculation due to the increased inevitability of error in making retrospective diagnoses of psychiatric disorders.

There were a number of borderline judgements made where the definition of symptomatic was problematic. If the only symptom cited by a participant was "fatigue" or "tiredness" the relevant time periods were those in which the degree of lassitude clearly exceeded normality and treatment with the GFD had significantly increased energy levels. In the case of one participant for whom a history of debilitating migraines (which completely resolved after the GFD) and a brief anaemic period pre-diagnosis were the only distinct symptoms experienced, an estimate of the total time period during which migraine was experienced outside of the anaemic period was added to the duration of unresolved anaemia. In every case where a number of symptoms occurred simultaneously the continuous time period was only counted once.

Using the criteria described, in at least thirty cases out of the sample of 110 people with CD, converging on a final symptomatic time duration was most accurately described as an estimate with error margins that were impossible to quantify. A number of factors impinged on the best estimate able to be determined, including each participant's memory and own estimations (encompassing several decades in some cases), the clinical judgement of the author and the suggestibility of each participant in relation to the author's investigation. To guard against the latter source of potential contamination each participant completed the demographic health questionnaire prior to any input from the author and all available sources of collateral information were utilised. Wherever possible, medical records voluntarily supplied by the participant and information provided by family members (parents, siblings and spouses) were used to clarify time periods that were difficult or impossible to recall, let alone quantify accurately (e.g., infancy).

Undoubtedly in many cases, time periods excluded from the total symptomatic period may have encompassed unidentified symptomatic temporal stages (e.g., being anaemic but undiagnosed and not manifested clinically). On the other hand, it was impossible to rule out the inclusion of symptomatic periods that may have been attributable to unidentified causes other than CD. All unbroken periods of time inclusive of at least one symptom characteristic of CD were included in the calculation unless a more likely direct cause could be determined. After a total symptomatic duration pre-diagnosis was calculated or estimated for each participant, this variable, as well as the number of days since diagnosis and treatment with the GFD, were each partitioned into eight time periods.

State-Trait Anxiety Inventory (Form Y; Spielberger et al., 1983)

Participants in all groups completed the State-Trait Anxiety Inventory (STAI) in the presence of the author. Referred to as the Self-Evaluation Questionnaire, the S-Anxiety and T-Anxiety scales are printed on opposite sides of a single-page test form and are completed consecutively, each taking five minutes or less. Prior to administration, care was taken by the author to encourage participants to respond candidly, as outlined in the STAI Manual. They were reminded that their results would remain

confidential and they were informed that feedback about their test results would be made available.

Spielberger (1983) describes anxiety states as "characterised by subjective feelings of tension, apprehension, nervousness and worry, and by activation or arousal of the autonomic nervous system" (p.1; STAI Manual). The S-Anxiety scale (STAI Form Y-1) is designed to measure state (i.e., current) anxiety. Consisting of twenty statements (such as I feel worried)
that evaluate how respondents feel right now...at this moment...with no right or wrong answers, participants circled a number reflecting the degree to which each statement described present feelings best, from 1 (not at all) to 4 (very much so), in one-point increments.

Trait anxiety is described by Spielberger as referring to relatively stable individual differences in anxiety-proneness (p.1; STAI Manual). The T-Anxiety scale (STAI From Y-2) is also comprised of 20 statements, similar to those in Y-1, that assess how people generally feel, also rated from 1 (almost never) to 4 (almost always). Normative data for Form Y-1 and Y-2 of the STAI are available for working adults and other groups and will be referred to in the Results section of this chapter. The norms for working adults are based on a total of 1,838 employees of the Federal Aviation Administration (1,387 males; 451 females). Reliability data are presented in Table 11 (p.13) of the STAI Manual. The test-retest correlations for the T-Anxiety scale were reasonably high for college student (ranging from .73 to .86) but lower for groups of high school students (.65 to .75). The median reliability coefficient for the T-Anxiety scale for college and high school students were .765 and .695 respectively. For the S-Anxiety scale, the stability coefficients for college and high school students were *relatively low*, ranging from .16 and .62, with a median of just .33. However, "relatively low stability coefficients were expected for the S-Anxiety scale because a valid measure of state anxiety should reflect the influence of unique situational factors that exist at the time of testing" (p13). The internal consistency of the S-Anxiety scale, as measured by the alpha coefficient, was quite high, with a median of .93. For the T-Anxiety scale, a median coefficient of .90 was also reflective of uniformly high alpha coefficients. There is strong evidence of concurrent, convergent, divergent and construct validity of the STAI scales, as outlined in the STAI Manual.

Spielberger, Sydeman, Owen, and Marsh (1999) provide a detailed review of the underlying concepts and use of the STAI (and the STAXI; discussed below) for treatment planning and outcomes assessment in psychological testing. For a further in-depth review of 816 research articles utilising the STAI between 1990 and 2000 please see Barnes, Harp and Jung (2002).

State-Trait Anger Expression Inventory (STAXI; Spielberger, 1988, 1991)

The State-Trait Anger Expression Inventory (STAXI) provided a measure of the experience, expression and control of anger. It conceptualizes anger as having two main components – state and trait anger. State anger is defined as an emotional state marked by subjective feelings that vary in intensity from mild annoyance or irritation to intense fury and rage. State anger is generally accompanied by muscular tension and arousal of the autonomic nervous system. Over time, the intensity of state anger varies as a function of perceived injustice, attack or unfair treatment by others, and frustration resulting from barriers to goal- directed behaviour (Spielberger 1991). The 10 items comprising the State Anger scale ("How I feel Right Now") are statements such as "I feel angry" and respondents must fill in whether the statement applies to them Very much so (score = 4), Moderately so (3), Somewhat (2) or Not at all (1).

Trait anger is defined as the disposition to perceive a wide range of situations as annoying or frustrating, and the tendency to respond to such situations with more frequent elevations in state anger. Individuals high in trait anger experience state anger more often and with greater intensity than individuals low in trait anger (Spielberger 1991).

The 10 items comprising the Trait Anger scale (How I Generally Feel) are statements such as I am quick tempered and respondents must fill in whether the statement applies to them Almost always (score = 4), Often (3), Sometimes (2) or Almost never (1). Trait anger can be further subdivided into two subscales, Angry Temperament (T-Anger/T) and Angry Reaction (T-Anger/R). T-Anger/T (made up of 4 items) measures a general propensity to experience and express anger without specific provocation. T-Anger/R (also 4 items) measures individual difference in the disposition to express

anger when criticised or treated unfairly by other individuals.

Anger expression is conceptualized as having three major components (Spielberger et al., 1985). The first component involves the expression of anger toward other people or objects in the environment (Anger-Out). The second component of anger expression is anger directed inward – that is, holding in or suppressing angry feelings (Anger-In). Individual differences in the extent to which a person attempts to control the expression of anger (Anger Control) constitutes the third component of anger expression (see also Spielberger 1991).

Each of those three components of Anger Expression are comprised of eight statements such as "I control my anger" or "I express my anger". Respondents must note whether the statement applies to them Almost always (score = 4), Often (3), Sometimes (2) or Almost never (1) "when Angry or Furious".

Finally, when the three anger expression scales (-In, -Out and -Control) are combined a scale exists which provides a general index of the frequency that anger is expressed, regardless of the direction of the expression. The STAXI Manual suggests that adolescents and adults can generally complete all sections of the questionnaire in 10-12 minutes, which was the author's experience.

Normative data for the STAXI are contained in the Manual and are based on a sample size of 9,293 United States subjects from adult, adolescent and college student populations (5,521 males; 3,772 females). The groups represented included managerial, technical, clerical, sales and factory workers, as well as senior military officers and civilian personnel. One limitation was that normative data for the AX/ EX and AX/ Con scales were not available for females. The mean age of the adult sample was about 40 years, which was comparable to the mean age of all the groups used in this thesis (CD = 41.0, DM = 44.4 and NC = 41.1).

Age was the most pertinent demographic factor in score variation across all of the STAXI scales, with additional norms based on three age ranges justified. These were computed for 18-30 year olds, 31-40 year olds and subjects 41 and older. State anger and, to a lesser extent trait anger, AX/ Out, Ax/ In and AX/ EX decreased with age, while AX/ Con increased as a function of age.

Internal consistency reliabilities of the scales were described as satisfactory (p.3) by Spielberger

(1991) in the Manual and unaffected by age or gender, with alpha coefficients quite high for all scales except the 4-item T-Anger/ R subscale (0.69 for adult males and females). The STAXI author also noted that the "distributions of the S-Anger and T-Anger/ T scales are skewed in a direction that prevents these scales from discriminating among respondents with low scores" (p.5).

Correlations existed between the S- and T-Anger scales and their S- and T-Anxiety counterparts throughout STAXI scale development. Although in the final items comprising these scales the correlations were diminished Spielberger noted "an intrinsic relationship between anger and anxiety that may be difficult to eliminate from self-report measures of these constructs" (p.7), and "that feelings of anger and irritation were frequently associated with symptoms of anxiety in the subject samples (p. 8). Validity studies cited in the Manual referred to "low to moderate correlations between S-Anger and T-Anxiety" and "moderately high correlations between S-Anger and S-Anxiety" (p. 12).

Although gender was not a major factor in difference in S- and T-Anger differences, especially in older age groups, "highly significant F-ratios for the AX-In scale indicated that the males had higher scores than the females" (p.11), with no gender differences for the AX/ Out scale score. The Manual also noted "moderately high correlations of the AX/ Out scores with T-Anger and T-Anger/ T scores, suggesting that individuals who experience anger more frequently are more likely to express rather than suppress their anger" (p.13). Correlations between AX/ In and AX/ Out scales were "essentially zero" regardless of gender, with a lack of association between Ax/ In and Ax/ Con also. However, Ax/ Con and Ax/ Out were highly negatively correlated for both males and females (= -0.59 and -0.58 respectively). The AX/ EX scale was considered a "research scale" in the Manual (p.11), with its psychometric properties not yet "thoroughly investigated".

Finally, normative STAXI data for medical and surgical patients ($\underline{n}$ = 913; 56% male; mean age 50 years) were included in the STAXI Manual, 71% of whom were "tested shortly before undergoing cardiac catheterization procedures" (p. 24). However, the relevance of the scores to the CD and DM groups in this thesis may be quite limited, given that most of the medical/ surgical patients were hospitalised, awaiting intrusive medical procedures and possibly sedated with anxiolytic medication.

Wechsler Adult Intelligence Scale – III (Wechsler, 1997)

The Wechsler Adult Intelligence Scale - Third Edition (WAIS-III; Wechsler 1997) is the current version of the most widely used general intelligence scale used by mental health clinicians internationally (Kaufman, 1990). It consists of fourteen subtests (including one supplementary subtest), which each measure distinct, but interrelated, functions of cognition. Four broad aspects of intellectual functioning measured by the WAIS-III include Verbal Comprehension, Working (or immediate) Memory, Perceptual Organization (also referred to as analytic processing or non-verbal problem solving) and Processing speed. These indexes of general intelligence are made up of (between two to three unique) component subtests in the WAIS-III.

All standard subtests of the WAIS-III (thirteen in all, not including the supplementary Object Assembly) were administered to participants in each of the three groups of the study in the first session, if time permitted. In a small number of cases, due to either anticipated or unforseen time restrictions, the testing process was divided across two testing sessions (i.e., the first meeting and what normally constituted the second, feedback session). In no case was the divided testing process protracted beyond two weeks and scores were not pro-rated for any individuals, who all completed the 13 subtests.

The standardisation sample for the WAIS-III included 2,450 adults aged 16 to 89, divided into 13 age bands, and was stratified on key demographic variables, including age, sex, educational level and geographic region, according to the United States census data (U.S. Bureau of Census, 1995).

Exclusionary criteria for the standardisation samples included the conditions of exclusion used in the selection of participants in the CD, DM and healthy control groups in the present study, with additional caveats. These included consumption of more than three alcoholic beverages on more than two nights per week, seeing a doctor or other professional for memory problems or problems with thinking, additional medical or psychiatric conditions that could affect cognitive functioning (e.g., bipolar disorder) and currently taking antidepressant, anti-anxiety or antipsychotic medication. These are pertinent considerations when comparisons are made with WAIS-III norms, because exclusionary criteria used in the standardisation sample are slightly stricter than those used in the present study.

The psychometric properties of the WAIS-III are described in detail in the WAIS-III/ WMS-III Technical Manual. The average reliability coefficients for WAIS-III scales and indexes range from 0.88 to 0.97, whilst coefficients for individual subtests range from 0.7 to 0.9. Confidence intervals at the 90% and 95% level have been provided for all scale scores and the WAIS-III was demonstrated to possess adequate stability across time for all age groups. In test-retest intervals ranging from 2 to 12 weeks, 2.0 to 3.2 point increases in full-scale IQ were observed. Test-retest results across a 12 month period were not attempted by the authors of the WAIS-III, as conducted in the present study for newly diagnosed CD participants (n = 27) and a small NC subgroup group (n = 10; see Chapter 5).

There was a high magnitude of intercorrelations amongst the majority of the subtests of the WAIS-III, supporting the premise that these components are measuring general intelligence or intellectual functioning. Furthermore, there were intercorrelations between subtests comprising the indexes, verbal and non-verbal scales.

In line with expectations noted in the Manual, the WAIS-III took approximately ninety minutes to administer to the majority of participants in all three groups, including about 5-10 minutes of breaks, but the assessment of elderly participants, on average, tended to take about 20 minutes longer overall. All participants were informed of the expected length of assessment (and time involved in pre-assessment interviewing and questionnaire completion processes) at study entry and reminded the day before being seen. As testing generally occurred outside of their homes, they were encouraged to bring food/ snacks with them. Basic food (gluten-free and regular biscuits, rice cakes, cheese and fruit) and beverages (tea/ coffee, juice and water) were provided.

Given the overall length of interviewing and assessment prior to cognitive appraisal and significant travelling time for some participants, those with DM were encouraged to carefully self-monitor their blood sugar levels, including just prior to cognitive assessment, to allow the testing process to accommodate breaks for snacks. Although exact records of pre-test blood sugar levels were not systematically tabulated for every participant, all except one DM participants reported good glycaemic control just prior to (and throughout) cognitive assessment. One male experienced moderate

hypoglycaemia before testing occurred. Although he recovered sufficiently following the provision of a snack to comfortably complete the clinical interview, cognitive assessment was rescheduled. No other participants appeared distressed or adversely affected by any acute effects of DM, other medical conditions or preceding emotional events during intellectual assessment.

A standard administration and scoring protocol, as outlined in the Manual, was closely followed. Particular care was taken to avoid providing or alluding to correct answers after administration of items and subtests or during subsequent feedback sessions. Despite adherence to standard procedures, a number of participants expressed interest in knowing the answers to particular items, in particular word definitions and general knowledge questions, or whether their answers were correct. However, all participants, including those in the CD group pre-selected for longitudinal follow-up, were gently discouraged from endeavouring to seek answers to any test questions, in deference to prescribed administration procedures and also in view of test-retest validity.

Comprehensive reviews of test-retest research using the Wechsler scales are available (e.g., Kaufman, 1990; Matarazzo, Carmody, & Jacobs, 1980; Shatz, 1981; see also Sirois et al., 2002), although not in regard to the third version used in the present thesis. In the previous version, the WAIS-R, "gains for normal people...over a 1- to 2-month interval average 3 points in V-IQ, 8½ points for P-IQ, and six points in FS-IQ" (Kaufman, 1990, p. 298). Average IQ gains generally taper downwards over longer re-test intervals, to "4 points for a 4-month interval" (Kaufman, 1999, p.106), and so a one year interval, as used in Study 2 of the present thesis, may be expected to equate with an even smaller practice effect of several points or less.

Quality of Life Questionnaire (Evans & Cope, 1989)

The Quality of Life Questionnaire (QLQ) was developed to provide "a direct measure of life quality based on an individual's actions and behaviour in response to particular environmental domains", as opposed to other measures that "emphasize affective and cognitive perceptions of life quality" (Evans & Cope, QLQ Manual, p.1). It has been used in studies of many issues relevant to life

quality, including personality, marital, and occupational factors (Evans, Pellizzari, Culbert, & Metzen, 1993) and cognitive impairment in the elderly (Pilon, Arsenault, & Pare, 1997), as well as life quality in relation to proposed or actual medical interventions (e.g., prior to in vitro fertilization; Hearn, Yuzpe, Brown, & Casper, 1987, and after liver transplantation; Grant et al., 1987).

Fifteen content scales, or subdomains, of life quality (consisting of 12 statements each) are measured by the QLQ, which are subsumed within five major domains displayed below:

5 Domains	15 Scales/ Subdomains	Description of Scales
General Well-being:		
	Material Well-Being	Income/ living environment
	Physical Well-Being	Health seeking/ protective behaviours
	Personal Growth	Goals/ characteristics/ problem solving
Interpersonal Relations:		
	Marital Relations	Communication/ activities with partner
	Parent-Child Relations	Quality of involvement
	Extended Family Relations	Interactions with relatives
	Extramarital Relations	Social interaction/ friendships
Organizational Activity:		
	Altruistic Behaviour	Orientation towards helping others
	Political Behaviour	Current events/ electoral engagement
Occupational Activity:		
	Job Characteristics	Work challenging/ varied/ interesting
	Occupational Relations	Communication at work
	Job Satisfiers	Salary/ benefits/ training/ opportunities
Leisure/ Recreation Activity:		
	Creative/ Aesthetic Behaviour	Cultural activity/ hobbies
	Sports Activity	Participation/ attendance/ interest
	Vacation Behaviour	Relaxing/ flexible holidays

Emphasis on a behavioural measure of life quality was preferred by the author of the present thesis, given the use of a battery of inventories already assessing mood and cognition, self-assessed perceptions of health status and cognitions regarding locus of control. The QLQ was designed to be suitable for self-administration, with minimal supervision, in surveys and in both individual and group settings. It consists of 192 statements, each answered as either true (if the respondents agrees or finds it descriptive of themselves) or false, at the present time. Items that are not applicable to current life circumstances

(e.g., having children living with you) are not filled.

A total Quality of Life score is calculated by adding all valid individual scale (i.e., subdomain) scores and dividing by the number of valid scales. A scale is designated as invalid if > 9 out of 12 items making up the scale are unmarked (i.e., missing), as a result of being irrelevant to the person filling the QLQ. For example, if a person has no children then all 12 items of Parent-Child Relations scale would not apply. Similarly, for an unemployed person the three Occupational Activity scales would typically be irrelevant, unless a person involved in voluntary work (for example) perceived items in these scales as personally applicable. The scale Marital Relations was pertinent to people in de facto relationships, but respondents in less committed intimate relationships may interpret the majority of items from the perspective of being single and therefore not applicable.

The QLQ also includes a Social Desirability scale. Although the authors of the QLQ do not stipulate a cut-score regarding valid and invalid test results, they do suggest that very high social desirability scale scores may suggest stereotypical responding intended to hide true feelings, attempts to please the investigator and otherwise faking good. Nevertheless, a key strength of the QLQ is that actions and behaviours are being self-assessed, as opposed to mood, affect, cognitions or intentions in relation to life quality, presumably minimising the likelihood of response sets susceptible to dissimulation.

The normative data for the QLQ (p. 21; QLQ Manual) are based on two samples of individuals (N=163 and N=274) selected to represent the population of London, Ontario (Canada), collected during the summers of 1980-81. The total sample of 437 (60% female; 85% married) was aged 18 years or older and was determined to be highly representative of the population sampled. In 1980, London was a city of approximately 300,000 people and is situated south west of Toronto and Niagara Falls. Of primarily British background and middle-upper socio-economic status (compared to the Canadian population) the normative sample of the QLQ is highly comparable to all three groups of the present thesis, notwithstanding the twenty-year historical difference in data collection.

The psychometric properties of the QLQ, as outlined in the QLQ Manual, indicate good reliability and validity. Internal consistency, as measured by the Kuder-Richardson-20 coefficient, was generally

high and stable, ranging from .61 for Physical Well-Being to .96 for Occupational Relations in the item selection sample and from .55 for Physical Well-Being to .97 for Occupational Relations in the cross-validation sample.

Test-retest reliability for the QLQ, as assessed over a two week period by the authors, was acceptable, with reliability coefficients ranging from between .77 and .89. Furthermore, inter-correlations among the scales, their factor structure and cross-validation data are clearly presented in the QLQ Manual.

Using the interpretive guidelines for T-scores used by Evans and Cope (1989), the percentage of participants in each group falling into nine narrow ranges of QOL (from very much below to very much above average) may be calculated. For clarity, these nine intervals of QOL were collapsed by the author of the thesis into three broad ranges (i.e., below average – average – above average) so that the percentages of cases falling into different ranges of QOL could be ascertained.

The QLQ was completed by participants in each group of the study in their own time and mailed to the author, prior to the second, follow-up meeting. During the first meeting each participant was instructed to complete the questionnaire independently from the influence of family members and in an environment with minimal distractions. The purpose of the instrument was briefly described and the instructions about the QLQ booklet read to each participant. At that time a discussion of each individual's results was scheduled to be undertaken at the subsequent follow-up meeting, generally within a fortnight of the first meeting. Particular reference was made to scales that were not applicable to certain participants, such as Parent-Child Relations, which was most relevant to those participants with children living at home.

A subset of participants with below average literacy, as established during pre-test interviewing and the completion of preceding questionnaires, completed the QLQ in the presence of the author, who was available in person to answer any questions arising and verify that the correct response set was being adhered to. Those completing the QLQ in their own time were provided with a contact phone number of the author, should any difficulties arise.

At the time of the follow-up meeting, the QLQ answer booklet was checked by the author to ensure that all relevant questions were answered and the correct response set had been adhered to. Feedback from participants indicated that the scale took approximately half an hour to complete. Details, discussion and life quality inferences pertaining to each participants' scores ensued in the feedback session in general terms, with more specific details provided verbally on request to CD and NC participants not participating in the longitudinal study.

Multidimensional Health Locus of Control Scale (Becker & Rosenstock, 1984)

Form A of the Health Beliefs Questionnaire (Appendix N) was administered to gauge the extent to which participants in the three groups perceived their health to mediated by their own internal resources, by other people central to their lives, such as health professionals and family (powerful others) and by chance factors.

Scores for each of the three scales (internal, powerful others and chance health locus of control; I, P and C HLC) pertaining to these dimensions had ranges from 1 to 36. They were based on responses to six statements each, with respondents circling a number reflecting the extent to which they agreed or disagreed with each statement. There were six choices from disagree strongly (scored as one) to agree strongly (= six). Items from each of the three scales (totalling 18, i.e., 3×6) were interspersed through the questionnaire and unmarked regarding which subscale they belonged to.

The development of the multidimensional health locus of control (MHLC) scales (including Form A), normative data, internal consistency, reliability and validity indicators appear in Wallston, Wallston and DeVellis (1978).

Normative data was based on 115 returned and adequately filled questionnaires of 282 handed out to people over age 16 at a metropolitan airport near Nashville, Tennessee, in the United States. The sample corresponding to returned booklets was 51% female, 74% had "at least some college education" (p.163, Wallston et al., 1978) and the mean sample age was 42 years, similar in most respects to the groups studied in this thesis, especially in regard to age.

Internal consistencies of the three constituent scales of Form A were reasonable at 0.77 (Internal HLC), 0.67 (Powerful Others HLC) and 0.75 (Chance HLC). From correlational matrices provided in Wallston et al. (1978) it is evident that, in Form A, the Internal HLC scale is essentially statistically independent from the powerful others HLC scale ($r = 0.15$; $p > .05$) but negatively correlated with Chance HLC ($r = -0.34$; $p < 0.001$). Furthermore, on Form A (used in the present thesis) Powerful Others HLC is independent of Chance HLC ($r = 0.06$; $p > 0.05$). Powerful Others HLC (in Form A) had a statistically significant positive correlation with age ($r = .198$, $p < .05$) and negative correlation with educational level ($r = -.222$; $p < .05$), where $r_{0.05} = .183$ for the sample size used.

Wallston et al. (1978) described the scales as "three separate theoretically and empirically differentiated dimensions" (p.167) intended for use with adults with an eighth grade reading level. The author of the present thesis observed no difficulty in participants' understanding of the questionnaire, which took less than 5 minutes to complete for almost all respondents.

Procedure

Ethical Approval, Consent Process, Participation and Protocol

Ethical approval for the project (study design/ subject recruitment) was granted by the Human Research Ethics Committees of the University of Ballarat (June, 1999) and by Ballarat Health Services (August 1999). In addition, the executive committees of Victorian branches of the Australian Coeliac Society and Diabetes Australia sanctioned advertising for participants at their office premises, via their quarterly magazines, at associated conferences and workshops and through direct communication with health care practitioners recommended by the societies.

All newly admitted members of the Coeliac Society were informed of the project via their new membership kits. In addition, direct monitoring by the author of newly admitted members of the Victorian Coeliac membership register (and perusal of the recorded log of people making initial phone inquiries) was permitted from July, 2000, in order to increase the likelihood of adding newly diagnosed participants with CD to the study sample. A number of people very recently diagnosed with CD or

awaiting confirmation of biopsy results were directly contacted by phone, with details of the project mailed out if those contacted were receptive to possible involvement. In total, approximately one quarter of participants in the CD sample (and the majority of those newly diagnosed) were recruited via this procedure.

Other participants in the CD group, and those in the DM groups, contacted the author by phone, via the Coeliac Society of Victoria or Diabetes Australia in response to advertising requesting volunteers for the study, placed in quarterly national magazines. Details about each volunteer's potential involvement, participation and inclusion/ diagnostic requirements were explained by the author via telephone or e-mail (and in writing). First meetings with the author (for those meeting the study's selection criteria) were arranged via telephone for individuals who verbally consented. Prior to meeting with the author for the first time, the length of the assessment protocol was outlined and all participants were encouraged to ensure adequate sleep. On a few occasions participants fell ill or were otherwise inconvenienced prior to the first meeting, which was rescheduled in each case.

At the beginning of the first meeting the consent process and details of participation were again described in detail. People still wishing to participate read (and signed) a consent form attached to a plain language statement (Appendix G) in the presence of the author and an independent third person where possible.

Participants who lived in Ballarat were interviewed and assessed individually in rooms within the psychology department at the University of Ballarat, while those in Melbourne met the author at the Victorian Coeliac Society state office, which was relocated mid-way during testing (February 2000). An office was made available to the author for research/ interviewing purposes, at each venue, seven days per week, upon request.

People wishing to participate who were unable to attend these venues were also seen by the author in their own homes, if suitably lit rooms were available. In several cases, the author met participants at their place of employment during or after work hours. Meeting times and locations were at the mutual convenience of the participants involved and the author. Up to four participants were seen on several

occasions in back-to-back bookings, but in the majority of cases one participant was seen on a given day. In most cases (for those participants in the cross-sectional study) all interviewing, assessing and testing was completed in one session of approximately three and a half to four hours duration, including breaks. For about 20% of participants interviewing and assessment was spread across two meetings with the author, due to time constraints. These meetings generally occurred within one week of one another and never more than a fortnight apart. The same testing protocol was followed, regardless of whether assessment occurred in one or two sessions and irrespective of the venue.

The offices used for assessment at the University of Ballarat and Victorian Coeliac Society were well lit and ventilated, with drink/ snack facilities and lavatories in close proximity to the assessment venue. These features were minimum requirements of the alternative venues used by the author, including participants' homes, and were discussed prior to meetings being arranged.

As aforementioned, all participants were informed of the expected length of assessment (and time involved in pre-assessment interviewing and questionnaire completion processes) at study entry and reminded the day before being seen. If testing occurred outside of their homes, participants were encouraged to bring food/ snacks with them, but basic food provided by the author at all venues included gluten-free and regular biscuits, rice cakes, cheese and fruit, and standard beverages (tea/ coffee, juice and water).

Of those people visited by the author, one person with CD chose to withdraw from the study shortly after providing written consent. Another person newly diagnosed with CD who was visited at home had fallen asleep. He contacted the author two days later to inform that he had been hospitalised as a result of extreme exhaustion and - pending further medical investigation - chose to withdraw from participation.

Clinical Interview, Assessment and Follow-up Meeting

The eleven questionnaires and scales described in the preceding section, beginning in each case with the Beck Depression Inventory - II, were administered to each participant in each group in the exact

order in which they have been described, in the first of two meetings with the author. Participants in the healthy control group were not required to complete the compliance with treatment scales and only CD participants completed the Coeliac Disease Awareness Screen. The Quality of Life Questionnaire was completed (and mailed to the author in the self-stamped envelope provided) by the majority of participants between meetings.

During and following completion of the Demographic/ Health Questionnaire by participants in each of the three groups (Appendixes C, L and M), the author perused all information pertaining to the recent and retrospective symptomatology history (on p.2 of that questionnaire) and medical information (p.3 to 5 or 6), with particular reference to any history of anxiety or mood disorders.

In subsequent interviewing by the author it was explored and recorded whether each participant had been previously diagnosed with or treated for any type of mental disorder. Any history of treatment with psychotropic medication of any kind or visits to a mental health practitioner, including presenting symptoms, were noted retrospectively back to childhood. If a firm history of symptom clusters synonymous with anxiety or mood spectrum disorders was noted, a retrospective diagnosis with reference to DSM-IV criteria was attempted if sufficient information existed and the participant had an acceptable recollection of contemporaneous behaviours and events (e.g., being unable to work for a protracted period due to a traumatic experience, long-lasting sleeping problems, visits to general practitioner, etc.).

If sufficient criteria were fulfilled to justify diagnosis with a mood or anxiety spectrum disorder the applicable (albeit tentative and retrospective) diagnosis or diagnoses according to DSM-IV criteria were made by the author and included in the participant's data file. Borderline diagnoses were rejected.

Participants were encouraged to take a break of a minimum duration of 10 minutes per hour and a fifteen minute break and snack, if desired, prior to assessment with the WAIS-III. As part of the normal assessment protocol with the WAIS-III, participants were also encouraged to take breaks between subtests, as needed, throughout. The majority of participants chose to take one five minute break close to the middle of testing, effectively dividing the WAIS-III assessment into two consecutive sessions of

approximately forty minutes duration each.

Feedback about performance on the WAIS-III was provided either at the completion of the first meeting with the author if time permitted or during the follow-up session, within a fortnight of the first meeting. If time allowed, scoring of the WAIS-III was undertaken whilst participants completed the Multidimensional Health Locus of Control and started the Quality of Life Questionnaire, to allow for initial feedback.

The feedback session consisted of the discussion of questionnaire and test results, as well as any questions arising from the research. In a small number of cases, WAIS-III testing was completed in the follow-up session with the author, due to time constraints in the initial meeting. The feedback sessions were conducted in person with the author, generally at the same venue as the original meeting, except for a small percentage of feedback sessions for healthy controls that were conducted by telephone at the request and convenience of the participant.

Statistical Design

Group variables are generally expressed as a mean (M), with accompanying standard deviation (SD), unless otherwise indicated. For continuous variables, ranges are provided if applicable. The statistical software system SPSS for Windows (Version 10; 1999; Illinois, U.S.A) was used exclusively in all data analysis.

Since the CD, DM and NC group sample sizes all exceeded 50 cases (with group-wise matching across demographic variables successful) and the majority of statistical procedures were based upon group difference hypothesis-testing, parametric analyses of variance were utilized where applicable. Prior to all computations, assumptions of normality and homoscedasticity were assessed, using a variety of procedures. These included the Kolmogorov-Smirnov statistic for all data and the Shapiro-Wilk test prior to performing within group gender (or other) comparisons if case numbers were less than 50. Normal probability and detrended normal probability plots were also examined to test normality, with the Levene test used to determine the validity of assumptions of homogeneity of variance.

The unpaired (independent samples) t-test was computed for within-group comparisons between various subgroups of participants (e.g., males versus females, or type-1 versus type-2 participants in the DM group) and in several other analyses across groups (e.g., newly diagnosed CD patients versus healthy controls). Levene's test for equality of variances was computed in each analysis, with tests for unequal variance utilised in positive (significant) cases (i.e., $p < 0.05$). Differences between proportions, clinically more meaningful than comparing means in certain instances, were assessed via chi-square.

Primary comparisons between the CD, DM and NC groups were undertaken using parametric one-way analyses of variance (ANOVA) and a highly conservative, but flexible, post-hoc procedure, the Scheffé method (Scheffé, 1953), which provided protection for tests of every linear combination of means, including pair-wise differences between the three groups.

The dependent variables were demographic data and total scores and sub-scores on each of the questionnaires assessing mood and affect (i.e., the BDI-II, STAI and STAXI), cognition (WAIS-III), quality of life (QLQ), health status, the CD Awareness Screen and MHLC scales. This statistical paradigm was very similar to that utilised in a recent study which investigated depressive symptoms in adult CD (Ciacci et al., 1998) and most closely resembled the present thesis, in terms of the composition of comparison groups and the absolute and relative number of participants within each group. In Ciacci et al.'s, study, two clinical groups (92 CD patients and 48 Hepatitis C patients) and 100 normal controls were compared on the Zung Self-Rating Depression Scale. The statistical methodology used in that study and in the present thesis is regarded as appropriate, if not optimal, in the conventional evaluation of between-group effects and group-wise differences entailing group sizes of the absolute and relative magnitudes used in these studies (see Keppel, 1973; Tabachnick & Fidell, 1989), especially if prior research is lacking.

Following post-hoc analysis using the Scheffé method, a third procedure was applied to all results presented within the key domains studied (affect, cognitive functioning and quality of life), to further guard against inflated Type I error in the event of multiple testing within domains. These procedures are outlined by Tabachnick and Fidell (1989). Put simply, all results following post-hoc analysis were

recognised as significant only after falling within stringently set alpha (α) levels, appropriate to the number of comparisons made. These were decided on a Bonferroni basis where multiple comparisons between groups were made using several tests (or subscales within tests).

As a general rule, the .05 level was divided by the number of comparisons performed, unless there were compelling reasons not to do so. For example, if a single measure was used to assess functioning in a distinct area (e.g., quality of life), total mean group scores were compared without setting α levels below .05. Finally, confidence intervals (C.I.s) were noted wherever statistically significant differences in means were reported. Confidence interval sizes of 95% were reported throughout the thesis, unless otherwise indicated.

An alternative analytic approach to the three-step procedure (i.e., ANOVA => Scheffé post-hoc comparisons => indicated Bonferroni adjustments) outlined was the use of planned comparisons in the ANOVA. However, this approach was not considered suitable at the present time, given an absence of previous research with CD patients across several of the domains investigated, especially state and trait anger, and, to a lesser degree cognition, including neuropsychological functioning, and locus of control. Furthermore, the exploratory nature of the research increased the likelihood of unexpected findings and a very high number of comparisons between each primary group, and subgroups of CD participants with the comparison groups, were anticipated. Therefore, a systematic and conservative, but flexible, approach, best served by the three-step procedure outlined, was regarded as the most appropriate.

Since many components of the present study were exploratory, bivariate Pearson correlational analyses were also performed on all data, in order to establish the strength of any statistically significant and clinically relevant or important associations between variables. Significant correlations were also examined in order to assist in the process of ruling in or out the effects of within group factors (e.g., age, mood state, or compliance with diet in the CD group) if particular between group differences (e.g., neuropsychological functioning) were observed. Whilst attenuation of point-biserial significance has been described in cases where the proportion of individuals sampled in each category of the

dichotomous variable deviate markedly from 50% (see Day, Kane & Roberts, 2000), for gender the proportions of individuals within the smaller category (i.e., male) did not drop below 40%. In the development of all categorical variables or interval data, binary scales were avoided in preference to multiple gradation (e.g., number of symptoms at diagnosis), to maximise their predictive value.

Finally, discriminate function analysis was undertaken to determine the utility of combining static and dynamic clinical correlates (e.g., symptom number/ duration at diagnosis and dietary compliance) in predicting clinical outcomes (e.g., CD participants who were depressed or not at study entry).

Partitioning of CD Participants

As well as performing between-group analyses using the full CD group of 110 participants, the CD sample was subdivided according to the severity of CD at diagnosis, to assess whether this within-group factor impacted on mood, cognition and life quality in people with CD. Specifically, it was investigated whether CD participants who had numerous (2+), distinct symptoms at diagnosis (as opposed to being asymptomatic or having only one symptom) and classified as having moderate to severe symptoms - could be better understood as a distinct group. This was achieved by partitioning the CD sample according to the number of CD symptoms at diagnosis. The arbitrary criteria used by the author to determine the severity of CD at diagnosis was simply the number of observable clinical symptoms at the time of diagnosis, which were retrospectively recorded by each participant. The sample was partitioned as follows:

Severity of CD at Diagnosis....# Cases:

Asymptomatic.....6 (M=5, F=1)	
Monosymptomatic.....31 (M=17, F=14)	...*Oligosymptomatic*.....*37*

2-3 symptoms.....35 (M=10, F=25)	
>3 symptoms.....38 (M=12, F=26)	...*Multisymptomatic*.....*73*

Using these criteria, approximately one third of the CD sample was designated oligosymptomatic (those CD participants with one or no symptoms at diagnosis) and the remaining two thirds (n = 71) multisymptomatic ($\geq$ 2 symptoms at diagnosis). In a minority of borderline cases quantitative assessment of symptomatology was problematic.

Where the author was hindered by conflicting information, limitations in participants' recall of their diagnosis (e.g., those diagnosed in infancy) or data incongruous with the apparent severity of CD according to all other indicators as provided by the participant, clinical judgment and discretion was exercised in categorising the severity of CD. The method used to partition CD participants was the simplest available and congruent with the author's estimates of individual's severity of symptomatology, based on clinical data, in the majority of cases.

Classic symptoms (e.g., diarrhoea) were historically used in investigating and diagnosing CD. Partitioning was undertaken as it has become evident during the preceding decade that a growing percentage of newly diagnosed CD patients are relatively asymptomatic. With increased awareness of CD, a greater proportion of patients with minor or few, if any, symptoms are being identified.

It was suspected inclusion of oligosymptomatic cases in all statistical analyses may mask clinically important group differences, by weakening such effects. Preliminary analyses indeed demonstrated that CD participants in the oligosymptomatic subgroup were closer to NC participants than multisymptomatic CD participants, where group differences in affect were emerging. Other key within group factors were used in statistical analyses with the CD sample, including GFD compliance and the period of dietetic restriction, which was equivalent to the time since diagnosis in almost all cases.

Results of Study 1

Socio-Demographic Variables – Group Comparison

Age, years of education, general intelligence (WAIS-IQ), gender and socioeconomic status (SES) were comparable across the CD, DM and NC groups, with univariate analysis of variance (ANOVA) demonstrating no significant group differences (for age, education and IQ) and both gender and SES proportionately distributed group-wise. These demographic variables, with body mass index (BMI) at study entry, are summarized in Table 8. Age at and time since diagnosis (each in years) are also tabulated for the CD and DM groups.

Table 8

Demographic and Biomedical Characteristics of CD, Diabetes Mellitus (DM) and Healthy Control (NC) Groups; Means and Standard Deviations (SDs) for Age, Education, WAIS- IQ, Age At and Time Since Diagnosis and BMI; Percentages for SES and Group Numbers for Sex

Variable	CD	DM	NC
Group number (n)	110	53	69
Age (yrs; SD)	41.0 (14.3)	44.4 (18.6)	41.1 (18.7)
Education (yrs; SD)	12.6 (2.4)	12.8 (2.8)	12.4 (3.0)
WAIS-IQ (full scale; SD)	112.2 (13.2) (n = 108)	112.7 (12.6) (n = 51)	112.7 (13.8) (n = 62)
Sex (male/ female)	66 / 44	31 / 22	41 / 28
SES (% low/ med/ high)	(11/ 59/ 30)	(13 / 53/ 34)	(13 / 61/ 26)
Age at Diagnosis (yrs; SD)	36.9[a] (15.4)	29.2[a] (19.9)	n.a.
Years since Diagnosis (SD)	4.3[b] (8.2)	15.3[b] (12.9)	n.a.
BMI (kg/m^2; SD)	23.5[c] (3.6)	26.3[d] (4.0)	24.5[e] (3.3)

[a] Sig. difference at .01 level; CD > DM; [b] Sig. difference at .001 level; CD < DM;
[c,d,e] Sig. grp. difference at .001 level; Post-hoc Scheffé test: [c,d] CD < DM ($p < .001$); [d,e] NC < DM ($p < .05$)

The aim of matching the three groups of study participants across key demographic variables (age, education, SES and gender) was clearly achieved, with the almost identical WAIS-IQ mean scores somewhat fortuitous, but also a product of the close matching across other variables, especially education, as confirmed by the highly significant positive Pearson correlation (r [232] = .424, p = .000) between years of education and WAIS-IQ.

With regard to their defining illness, participants in the CD group had clearly been diagnosed at a significantly older age than DM patients (t = 2.50, degrees of freedom [df] = 82.92, p = .015, mean difference [m.d.] = 7.74, 95%, confidence interval [C.I.] = 1.57, 13.91) and had been diagnosed for significantly longer at study entry (t = 5.64, df = 72.76, p < .001, m.d. = 10.94, 96% C.I. = 7.07, 14.81), using t-test, with equal variances not assumed in either analysis. Levene's test for equality of variances was highly significant in both cases, especially in relation to the years since diagnosis analysis (F = 19.1, p < .001), in which the SD was almost double the size of the respective mean in the CD group. Table 8 shows that, on average, DM patients had been diagnosed for 15.3 years, compared to an average of 4.3 years for the CD group, The CD-DM differences in age at and time since diagnosis arose because the majority of CD patients (85%) were diagnosed in adulthood (≥ 20 years), while two thirds of the DM group were type-1 patients, of whom the majority (72%) had been diagnosed in childhood or adolescence (< 20 years).

Univariate ANOVA showed that there was a significant difference in BMI across the CD, DM and NC groups (F (2,229) = 10.394; p = .000). Post-hoc Scheffé testing was conducted to compare BMI between each pair of groups, with DM participants having a significantly higher BMI compared to both CD participants (p = .000) and, to a lesser extent, healthy controls (p = .025). The higher proportion of type-1 patients comprising the DM group may have limited the significantly elevated mean BMI compared to the two other groups, given that mean BMI is often higher in studies of type-2 patients. Participants with CD did not have a significantly different BMI to healthy controls (p = .235). However, a subgroup 27 relatively newly identified CD patients (diagnosed within ten weeks of study entry) had a significantly lower BMI than the NC group; t = 3.254, df = 94, p = .002, m.d. = 2.43, C.I. = .94, 3.9).

Coeliac Disease Awareness

Scores on a new scale developed by the author to measure CD participants' knowledge about the illness were compared against the four levels of severity of CD, as shown in Table 9. A favourable spread of scores was observed. There were no differences across CD subgroups, including when the four subgroups were collapsed into oligosymptomatic and multisymptomatic subgroups.

Table 9

*Means, Standard Deviations (SDs) and Ranges of CD Awareness Scores Across CD Subgroups**

	Asymptomatic (n = 6)	Mild (n = 31)	Moderate (n = 35)	Severe (n = 38)
Number of CD Symptoms:	0	1	2-3	4+
	Oligosymptomatic		Multisymptomatic	
N	6	31	35	38
Mean (SD)	23.50 (17.9)	38.48 (18.8)	41.11 (15.2)	41.47 (15.3)
Range	2 to 49	-4 to 70	10 to 74	-4 to 74

* Asymptomatic = no symptoms at CD diagnosis; Mild = single symptom at CD diagnosis; Moderate = 2 symptoms at CD diagnosis; Severe = 3 or more symptoms at CD diagnosis

When CD awareness scores were correlated against key demographic and test outcome measures, positive bivariate Pearson correlations were identified with years of education (r [110] = .25 (p < .01), WAIS-III IQ (r [110] = .41 (p < .01) and two measures of dietary compliance (p < .05), as hypothesised, but not depression or quality of life, with close to zero association observed.

Affective Functioning

Depressive Symptomatology: Group Comparisons

The Beck Depression Inventory – 2nd Edition (BDI-II) was used to measure various components of depressive symptomatology in the three experimental groups in Study 1. In addition to total BDI-II scores, individual item and Factor 1 (i.e., Somatic/ Affective) and Factor 2 (i.e., Cognitive) sub-scores were tabulated for each group. Univariate analysis of variance (ANOVA), with post-hoc Scheffé testing in the event of a significant effect across groups, was computed to compare scores pair-wise.

Full BDI-II score was the first dependent measure compared. Alpha level was fixed at $p = .05$, with no Bonferroni adjustment required, given that only one measure of depression was utilised in Study 1. ANOVA demonstrated that there were no significant differences across groups (F [2, 229] = 1.86, p = .158). Descriptive statistics for total BDI-II scores across groups are reported in Table 10.

Table 10

*Means, Standard Deviations (SDs) and Ranges of the BDI-II Scores in the CD, DM and NC Groups**

	CD	DM	NC
N	110	53	69
Mean (SD)	8.92 (7.13)	9.36 (8.03)	7.09 (6.82)
Range	0-34	0-32	0-27

* CD = coeliac disease; DM = diabetes mellitus; NC = normal controls

Notwithstanding a slight gender disparity between mean BDI-II scores across all study participants (9.01 for females [n = 138]; 7.70 for males [n = 94]), in the direction of the trend towards mood disorders being identified more often in females, the difference was not significant overall, or within any of the three groups, including the CD group, in which the female mean (9.58, SD = 7.34) was 1.64 points higher than the male mean (7.93, SD = 6.77), also negligible from a clinical perspective.

The proportion of participants in each group falling into the four ranges of depression outlined in the BDI-II Manual are displayed overleaf. It was evident that about four fifths of the full cross-sectional CD group (78.2%) did not show substantial signs of depression according to BDI-II cut score criteria, compared with about three out of four DM participants (75.5%) and almost nine out of ten NC participants (87%). In the CD group, 21.8% were in the mildly to severely depressed range at assessment (compared to 24.5% of DM and 13% of NC participants) and 10% of CD participants (compared to 15.1% of DM and 4.3% of NC participants) were in the moderately to severely depressed range.

None of the group-wise proportional comparisons were statistically significant, using the Crosstabs function of SPSS to perform chi-square tests using pairs of groups or all three groups in the analysis

(asymptotic significance > .05 using each of the Pearson chi-square, continuity correction, likelihood ratio and Fisher's exact test). As noted earlier, one potential NC participant who was assessed to be in the severely depressed range did not continue in the study due to concerns about his high degree of suicidal ideation and recent behaviour. Symptoms of suicidality were not features of the of the CD or DM participant in the elevated ranges of depression who participated in Study 1.

Table 11

Number (and Percentages) of Participants with Full BDI-II Scores in the Four Ranges of Depression (Absent/ Minimum to Severe) Across the Three Groups

		CD	DM	NC
Total BDI-II Score	Range of Depression			
0-13	Absent/ Minimal	86 (78.2%)	40 (75.5%)	60 (87.0%)
14-19	Mild	13 (11.8%)	5 (9.4%)	6 (8.7%)
20-28	Moderate	10 (9.1%)	7 (13.2%)	3 (4.3%)
29-63	Severe	1 (0.9%)	1 (1.9%)	Nil
		Totals: 110 (100%)	53 (100%)	69 (100%)

In summary, the categorisation in Table 11 indicates that 24 out of 110 (or about one in five) CD participants were depressed at the time of assessment, using cut score criteria used by the BDI-II authors to screen for major depression, compared to one in four people with DM and just under one in eight NC subjects. All except one CD participant categorised as depressed fell within the mild to moderate depression range, an interval of depression that may be broadly referred to as dysthymic Beck et al. (1996).

Following the comparison of the three groups using all participants in Study 1, the CD sample was subdivided on the basis of the number of CD-related symptoms at CD diagnosis (severity of illness), as outlined in the previous chapter. This subdivision resulted in the initial partitioning of the full CD sample into four subgroups, for which mean BDI-II scores were calculated (see Table 12 overleaf).

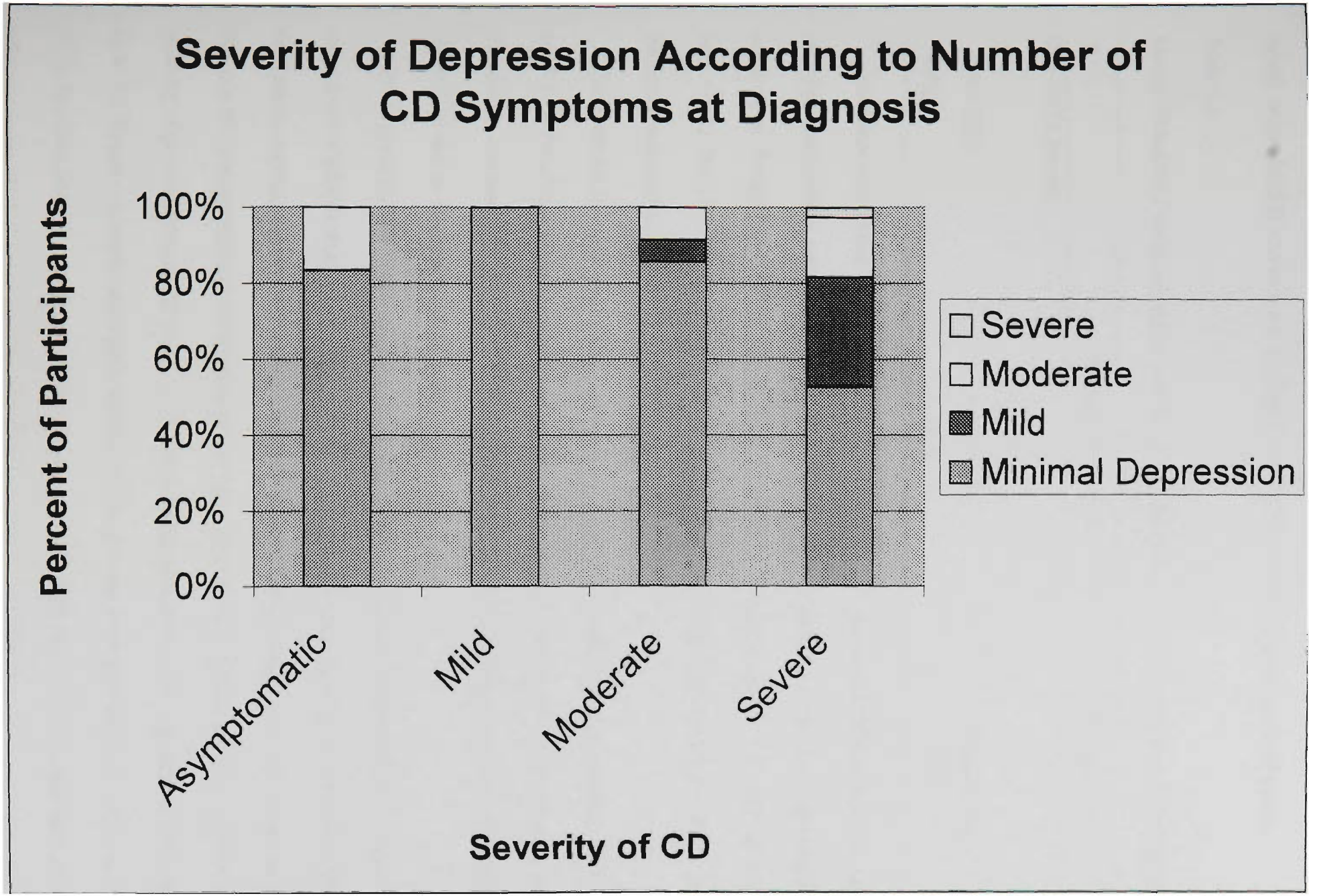
Table 12. *Means, SDs and Ranges of the BDI-II Scores Across the Four CD Subgroups**

	Asymptomatic (n = 6)	Mild (n = 31)	Moderate (n = 35)	Severe (n = 38)
Number of CD Symptoms	0	1	2-3	4+
	Oligosymptomatic		Multisymptomatic	
N	6	31	35	38
Mean (SD)	5.17 (7.7)	5.03 (4.1)	8.34 (6.5)	13.21 (7.4)
Range	0-20	0-13	0-26	0-34

* Asymptomatic = no symptoms at CD diagnosis; Mild = single symptom at CD diagnosis; Moderate = 2 symptoms at CD diagnosis; Severe = 3 or more symptoms at CD diagnosis

There was a significant Pearson correlation (r [110] = .458, p = .000) between the severity of CD (i.e., across the four CD subgroups) and BDI-II depression. Figure 3 (overleaf) graphically illustrates the increased proportion of depressed patients in the moderately (compared to mildly) symptomatic sub-group and especially in those severely symptomatic at diagnosis. In the latter subgroup, 18 out of 38 patients (i.e., 47%) were in the clinically depressed range, with 18% moderately or severely depressed. This result prompted consideration of the possibility that a less symptomatic proportion of the full CD group may have substantially contributed to a "normalisation" of the mean overall level of depression in the full CD group, masking statistically and perhaps clinically relevant differences bet-ween the more symptomatic portion of the CD group and healthy controls, if not the DM group as well.

The small number of asymptomatic cases precluded their inclusion as a separate subgroup in any justifiable parametric statistical analysis. They were instead combined with the monosymptomatic cases to create an oligosymptomatic subgroup (of 6 + 31 = 37 cases), an amalgamation also defendable on clinical grounds. Notwithstanding the immediate creation of three similarly sized subgroups (oligosymp-tomatic, moderately and severely symptomatic) highly suitable for subsequent comparison from a statistical viewpoint, there were minimal differences from a clinical perspective between CD patients with at least two CD-related symptoms at diagnosis and those participants with three or more. Therefore, these groups were also combined to form a multisymptomatic subgroup (of 35 + 38 = 73


Severity of Depression According to Number of CD Symptoms at Diagnosis
Percent of Participants
100%
80%
60%
40%
20%
0%
Asymptomatic
Mild
Moderate
Severe
Severity of CD
Severe
Moderate
Mild
Minimal Depression

cases). Mean BDI-II scores were tabulated for these two subgroups, as reported below.

Table 13

Means, Standard Deviations (SDs) and Ranges of the BDI-II Scores Across Primary CD Subgroups

	Oligosymptomatic	Multisymptomatic
BDI-II (21 items)		
N	37	73
Mean (SD)	5.05 (4.72)	10.88 (7.36)
Range	0-20	0-34

An independent samples t-test was computed in order to compare the BDI-II mean scores between the oligosymptomatic and multisymptomatic subgroups, setting alpha at .05, given the single procedure undertaken. A significant difference occurred between these subgroups, $t = 4.37$, $df = 101.93$, $p = .000$; m.d. = 5.82, 95% C.I. = 3.18, 8.46). Since Levene's test was positive ($F = 6.61$, $p = .011$), equal variances were not assumed.

Furthermore, it was revealed that, in the oligosymptomatic subgroup, only one CD participant out of 27 (= 2.7% of that subgroup) had a total BDI-II score above 13, the cut-point of absent/ minimal depression, compared to 22 out of 73 (= 30%) participants in the multisymptomatic subgroup, who had full BDI-II scores ranging from 14 to 34.

Given the significant difference between oligosymptomatic and multisymptomatic subgroups in the mean level of BDI-II depression (underpinned by the substantially higher proportion of mildly and moderately depressed participants who were multisymptomatic), a second ANOVA comparing the full DM and NC groups with the multisymptomatic CD subgroup was undertaken. This re-analysis, omitting oligosymptomatic CD participants, did not require a Bonferroni adjustment, with alpha again set at .05. Results showed a significant difference between the three groups (F [2, 192] = 4.733, p = .010). Post hoc Scheffé testing revealed only one pair-wise difference, with the multisymptomatic CD subgroup mean BDI-II score significantly higher than the mean NC score ($p = .010$; m.d. = 3.79, 95% C.I. = .739, 6.841).

The 21 items of the BDI-II may be subdivided into two factors. As noted in the preceding chapter, twelve load onto a Somatic/ Affective dimension and the other nine onto a Cognitive dimension (p. 31; Beck et al., 1996). Table 14 lists the means and standard deviations of the nine Cognitive dimension items, with symptomatic percentages for each item (i.e., percent of participants endorsing a 1, 2 or 3 point response, as opposed to a zero response).

Table 14

Means (SDs) of Item Scores and Percent (%) Symptomatic (Item score of ≥ 1) for Each BDI-II Item in the Cognitive Dimension Across the Three Groups

	CD (n =110)		DM (n = 53)		NC (N=69)	
Symptom (Item)	M (SD)	%	M (SD)	%	M (SD)	%
Sadness	0.17 (0.4)	17	0.23 (0.4)	23	0.20 (0.4)	20
Pessimism	0.28 (0.5)	27	0.51 (0.7)	43	0.33 (0.5)	32
Past Failure	0.33 (0.6)	26	0.49 (0.7)	36	0.39 (0.6)	32
Guilty Feelings	0.30 (0.5)	29	0.38 (0.5)	38	0.39 (0.6)	35
Punishment Feelings	0.12 (0.4)	10	0.20 (0.6)	13	0.23 (0.5)	20
Self-Dislike	0.34 (0.6)	29	0.49 (0.8)	34	0.29 (0.5)	28
Self-Criticalness	0.39 (0.7)	29	0.38 (0.6)	32	0.43 (0.6)	38
Suicidal Thoughts/ Wishes	0.06 (0.2)	6	0.23 (0.4)	23	0.13 (0.3)	13
Worthlessness[1]	0.15 (0.4)	15	0.43 (0.8)	30	0.13 (0.4)	12

[1] Significant differences across groups ($p < .01$); DM > CD and NC

Univariate analysis of variance was computed to compare BDI-II item scores across the three groups, with the alpha level pre-adjusted to $p = .01$, due to the multiple comparisons. ANOVA demonstrated that the only significant differences at this alpha level across groups was on Worthlessness (F [2, 229] = 6.870, $p = .001$). Post hoc Scheffé testing showed that the DM group mean score on this item was significantly higher than the mean score of both the CD group ($p = .004$; m.d. = .28, 95%, C.I. = .07, .49) and the NC group ($p = .005$, m.d. = .30, 95% C.I. = .08, .53).

Table 15 lists the means and standard deviations of the twelve Somatic/ Affective dimension items, with symptomatic percentages for each item (i.e., percent of participants endorsing a 1, 2 or 3 point response). Univariate analysis of variance was computed to compare BDI-II item scores across the three groups, with the alpha level again pre-adjusted to $p = .01$, due to the multiple comparisons. ANOVA demonstrated that the only significant differences at this alpha level across groups was on Changes in Appetite (F [2, 229] = 9.162, $p = .000$). Post hoc Scheffé testing showed that the CD group mean score on this item was significantly higher than the mean score of both the DM group ($p = .006$; m.d. = .41, 95% C.I. = .10, .71) and the NC group ($p = .001$, m.d. = .43, 95% C.I. = .15, .71).

Table 15

Means (SDs) of Item Scores and Percent (%) Symptomatic for Each BDI-II Item in the Somatic/ Affective Dimension Across the Three Groups

Symptom (Item)	CD (n =110) M (SD)	%	DM (n = 53) M (SD)	%	NC (N=69) M (SD)	%
Loss of Pleasure	0.44 (0.6)	40	0.34 (0.5)	32	0.21 (0.5)	20
Crying	0.33 (0.7)	25	0.25 (0.6)	17	0.23 (0.5)	19
Agitation	0.50 (0.8)	37	0.34 (0.6)	30	0.41 (0.6)	36
Loss of interest	0.40 (0.6)	36	0.36 (0.7)	27	0.30 (0.6)	28
Indecisiveness	0.43 (0.8)	32	0.30 (0.6)	25	0.30 (0.6)	26
Loss of Energy	0.80 (0.7)	64	0.83 (0.6)	70	0.58 (0.6)	54
Sleeping Pattern Changes	0.85 (0.9)	56	1.02 (1.0)	62	0.58 (0.9)	38
Irritability	0.45 (0.7)	35	0.28 (0.5)	26	0.33 (0.6)	28
Changes in Appetite[1]	0.76 (0.9)	55	0.36 (0.7)	28	0.33 (0.6)	28
Concentration Difficulty	0.63 (0.8)	46	0.55 (0.6)	47	0.33 (0.5)	33
Tiredness or Fatigue	0.71 (0.7)	56	0.79 (0.7)	68	0.52 (0.6)	46
Loss of Interest in Sex	0.45 (0.8)	30	0.70 (1.0)	40	0.45 (0.8)	29

[1] Significant differences across groups ($p < .01$); CD > DM and NC

Following perusal of individual item means across the three groups, each of the twelve BDI-II items loading onto factor 1 (i.e., the Somatic/ Affective dimension) and the nine items loading onto Factor 2 (i.e., the Cognitive) were averaged to create mean sub-scores pertaining to the Somatic/ Affective dimension and Cognitive dimensions, as outlined Table 16.

Table 16

Means, Standard Deviations (SDs) and Ranges of the BDI-II Somatic/ Affective and Cognitive Factor Scores Across the Three Groups

	CD (n =110)	DM (n = 53)	NC (N=69)
Somatic (12 items)			
Mean (SD)	0.56 (0.47)	0.51 (0.40)	0.38 (0.37)
Range	0 – 2.08	0 – 1.50	0 – 1.50
Cognitive (9 items)			
Mean (SD)	0.24 (0.26)	0.37 (0.40)	0.28 (0.33)
Range	0 – 1.11	0 – 1.56	0 – 1.22

Univariate analysis of variance was undertaken to compare the mean Somatic/ Affective dimension and Cognitive dimension factor scores across the three groups. The alpha level was set at $p = .025$, in relation to two comparisons being performed, but also acknowledging that this was a conservative perspective, given that these factors were composite scores based on the averages of 12 and 9 BDI-II items respectively, each individually having strong, built-in reliability coefficients. ANOVA demonstrated that there was a significant differences across groups on the Somatic/ Affective factor scores (F [2, 229] = 3.782, $p = .024$). Post hoc Scheffé testing showed that this overall difference could be attributed to the CD group mean score being significantly higher than the mean score of NC group ($p = .025$, m.d. = .18, 95% C.I. = .02, .34).

There was not a significant difference across the three groups relative to the Cognitive dimension. Since there was a significant positive Pearson correlation (r [110] = .356, p = .000) between the severity of CD and the Cognitive dimension of BDI-II depression, consecutive ANOVA was conducted across the NC, DM and increasingly severely symptomatic CD subgroups groups to determine if a significant difference emerged between groups. It was interesting to note that even when the severely symptomatic CD subgroup (≥ 3 symptoms at CD diagnosis; n = 38) was used in the ANOVA there was not a significant difference across groups (F [2, 157] = 1.376, p = .256). This result clearly demonstrated that depression underpinned by Cognitive, as opposed to Somatic/ Affective factors, was not significantly more prevalent in the CD sample than either of the control groups used in Study 1, even amongst the most symptomatic third of the CD group.

State and Trait Anxiety: Group Comparisons

The State-Trait Anxiety Inventory (STAI) was used to measure the levels of state and trait anxiety in the three groups. Univariate analysis of variance (ANOVA) was undertaken, with post-hoc Scheffé testing performed if significant group effects were identified. Mean state STAI scores, standard deviations and ranges across groups are reported below in Table 17.

Table 17

Means, Standard Deviations (SDs) and Ranges of State Anxiety in the CD, DM and NC Groups

	CD	DM	NC
N	110	53	69
Mean (SD)	35.79 (12.5)	32.81 (10.0)	30.04 (9.2)
Range*	20-76	20-64	20-57

* Possible score range of 20-80, with individual scores > 40 indicating elevated state anxiety

There was a significant effect across groups on state anxiety (F [2, 229] = 5.814, p = .003), with Scheffé testing showing that the CD group reported significantly greater state anxiety than the NC group (p = .004; m.d. = 5.74, 95% C.I. = 1.56, 9.94). There were no other pair-wise differences. Upon gender

partitioning, statistical significance across groups was only maintained among female CD patients (F [2, 135] = 3.40, p = .036), with the CD – NC pair-wise difference also maintained (p = .037; m.d. = 5.67, 95% C.I. = .27, 11.06). If only multisymptomatic CD cases were considered, the same significant group effect was maintained regardless of gender, with the mean multi-symptomatic CD state anxiety score rising to 39.15 (SD = 13.2) – near the cut-off of 40 designating elevated state anxiety – from 35.79 (12.5) in the fill CD group. Using this cut score criteria, corresponding to the 70-85th percentile, depending on age (Spielberger et al., 1983), 28% of the CD sample scored greater than 40, compared with 18.9% of DM patients and 14.5% of NC participants. There was not a statistical difference between male and female CD patients regarding state anxiety upon t-testing.

There was not a significant difference across groups in trait anxiety, mean scores for which are displayed in Table 18. Using equivalent cut score criteria, corresponding to the 72-88th percentile, again depending on age (Spielberger et al., 1983), 38% of the CD sample scored greater than 40, compared with 37.7% of DM patients and 30.4% of NC participants.

Table 18

Means, Standard Deviations (SDs) and Ranges of Trait Anxiety in the CD, DM and NC Groups

	CD	DM	NC
N	110	53	69
Mean (SD)	38.39 (10.79)	37.04 (10.9)	34.61 (10.76)
Range*	20-71	20-62	20-63

* Possible score range of 20-80, with individual scores > 40 indicating elevated trait anxiety

When the previously mentioned multisymptomatic CD subgroup was substituted for the full CD sample in the ANOVA, a significant difference across groups arose (F [2, 192] = 7.88, p = .001), with only the CD – NC pair-wise difference significant (p = .001; m.d. = 7.12, 95% C.I. = 2.62, 11.61). Upon t-testing, a slight statistical differences emerged between male and female CD patients in trait anxiety (F [108] = .06, p = .041, m.d. = 4.29, C.I. = .19, 8.4); female CD patients mean = 40.11, versus male CD patients = 35.82), with the assumption of equal variance made as Levene's test was negative.

State and Trait Anger: Group Comparisons

The State-Trait Anger Expression Inventory (STAXI) was used to evaluate various aspects of anger in each of the three groups. Mean state anger levels are shown in Table19. There were no differences across groups, but a small significant difference occurred when the multisymptomatic subgroup was used (F [2, 192] = 4.08, p = .018), with only the CD – NC pair-wise difference significant (p = .019; m.d. = 1.79, 95% C.I. = .23, 3.35). It is doubtful, however, whether this small statistical difference – approaching two points in a range of possible scores between 10 and 40 – is clinically meaningful.

Table 19

Means, Standard Deviations (SDs) and Ranges of State Anger in the CD, DM and NC Groups

	CD	DM	NC
N	110	53	69
Mean (SD)	11.91 (4.2)	11.57 (2.8)	10.85 (2.8)
Range*	10-31	10-22	10-30

* Possible score range of 10-40, with individual scores > 20 indicating elevated state anger

Neither Angry Temperament nor Angry Reaction (each subscales of state anger) were significantly different across groups, even after consideration of only multisymptomatic CD patients, a result repeated in relation to trait anger, which is reported in Table 20 below.

Table 20

Means, Standard Deviations (SDs) and Ranges of Trait Anger in the CD, DM and NC Groups

	CD	DM	NC
N	110	53	69
Mean (SD)	17.65 (5.8)	17.32 (4.46)	17.22 (5.0)
Range*	10-31	10-29	10-33

Other Anger Functions: STAXI Anger-In, -Out, Control and Expression

Four other functions of anger assessed by the STAXI, namely Anger – In (often abbreviated to Ax-In when reported), Anger – Out (Ax-Out), Anger Control (Ax-Con) and Anger Expression (Ax – Ex). These are displayed in Table 21, with possible score ranges footnoted.

Table 21

Means, Standard Deviations (SDs) and Ranges of Anger – In, Anger – Out, Anger Control and Anger Expression on the STAXI in the CD, DM and NC Groups

	CD	DM	NC
Anger – In			
Mean (SD)	16.92 (3.7)	16.45 (4.4)	14.53 (3.5)
Range[1]	9-26	9-29	8-22
Anger – Out			
Mean (SD)	14.08 (3.2)	13.42 (2.7)	14.4 (3.4)
Range[2]	8-25	8-32	9-28
Anger Control			
Mean (SD)	22.92 (4.7)	24.21 (4.7)	24.71 (5.0)
Range[3]	14-32	8-32	12-32
Anger Expression			
Mean (SD)	24.08 (7.9)	21.66 (7.1)	20.24 (7.9)
Range[4]	6-41	6-39	2-46

[1]Possible score range of 8-32; [2]Possible score range of 8-32;
[3]Possible score range of 8-32; [4]Theoretical range of 0-72 (derived from Ax-In/ -Out/ -Con.)

The only significant effect across groups occurred for Anger – In (F [2, 228] = 3.82, p = .023), with only the DM – NC pair-wise difference significant (p = .026; m.d. = 1.92, 95% C.I. = .18, 3.66). Given the possible range of scores of 7-30, the difference was regarded as clinically irrelevant. If alpha level was adjusted to p = .007, decided on a Bonferroni basis by considering an overall .05 level for each score divided by the five STAXI sub-scores compared across groups, this difference also disappeared.

When the multisymptomatic CD subgroup was used in the ANOVA the significant effect across groups was stronger (F [2, 191] = 7.45, p = .001), with a significant difference involving the CD-NC comparison, as well as DM – NC pairing (p = .001 and p = .025 respectively). However, the m.d. of 2.38 (C.I. = .74, 2.07) between the multisymptomatic CD and NC group remained clinically unremarkable.

A somewhat more notable affect across groups occurred in Anger Expression, with multisymptomatic CD patients expressing anger (regardless of the direction of expression) significantly more often than NC participants (F [2, 191] = 4.26, p = .016), with only the DM – NC pair-wise difference significant (p = .017; m.d. = 3.85, 95% C.I. = .56, 7.13).

Using the t-test, there was only one significant gender difference (at an α level of .05) in any of the seven functions of anger within the CD group, with Anger – In higher in female CD patients, but only marginally (t [108] = 2.08, p = .04, m.d. = 1.52, C.I. = .07, 2.98). In view of the small mean difference – and multitude of comparisons undertaken increasing the likelihood of type 1 error – this result was not viewed as particularly clinically important.

Cognitive Functioning

Neuropsychological Assessment: Group Comparisons

The WAIS-3 was used to measure various components of cognitive functioning in the cross-sectional study. Univariate ANOVA with post-hoc Scheffé testing was computed to compare performance across the three groups. The dependent measures consisted of the seven major scores on the WAIS-3. These were full-scale IQ, verbal IQ, performance IQ and the four index scales; verbal comprehension, perceptual organisation, working memory and processing speed.

Alpha level was fixed at p = .007, decided on a Bonferroni basis by considering an overall .05 level for each score divided by the seven WAIS-3 scores compared across groups, to markedly reduce the likelihood of Type 1 errors.

There were no significant differences across groups on the WAIS-3 full-scale, verbal and performance IQ scores (F [2, 218] = .04, .607 and 2.617 respectively and p > .05 in each case). Mean scores, SDs and ranges for these measures across groups are reported below in Table 22.

Table 22

Means, Standard Deviations (SDs) and Ranges of Full Scale, Verbal and Performance IQ Scores Across the Three Groups

	CD	DM	NC
WAIS-IQ (Full Scale)			
Mean (SD)	112.19 (13.2)	112.71 (12.6)	112.69 (13.8)
Range	75-145	81-143	72-145
Verbal IQ			
Mean (SD)	109.56 (12.1)	111.45 (12.5)	111.53 (14.1)
Range	72-138	88-147	75-140
Performance IQ			
Mean (SD)	113.30 (15.0)	112.33 (12.6)	111.96 (15.4)
Range	76-153	77-140	73-155

Neuropsychological Index Performance

Regarding the four WAIS-IQ index performance scores, no significant differences occurred across groups on the WAIS-3 Verbal Comprehension (VC) or Perceptual Organisation (PO) indexes (F [2, 218] = .61 and 2.62 respectively, p > .007 in each case), despite the mean PO score in the CD group being 5.4 points higher than the mean NC PO score.

However, significant differences occurred across groups for the two other WAIS-IQ indexes; Working Memory (F [2, 218] = 9.13, p = .000) and Processing Speed (F [2, 218] = 14.60, p = .000. The mean scores, standard deviations and ranges for the four WAIS-3 index scores across groups are reported overleaf in Table 23.

Table 23

Mean, Standard Deviation (SDs) and Ranges of IQ Index scores; Verbal Comprehension, Perceptual Organisation, Working Memory and Processing Speed, Across the Three Groups

	CD	DM	NC
WAIS-III Index	(n = 108)	(n = 51)	(n = 60)
Verbal Comprehension			
Mean (SD)	112.4 (12.2)	113.2 (11.9)	110.7 (13.8)
Range	76-138	84-136	80-140
Perceptual Organisation			
Mean (SD)	116.4 (15.1)	113.3 (13.3)	111.0 (16.7)
Range	76-150	72-142	69-150
Working Memory			
Mean (SD)	101.7 (13.3) [a]	104.3 (12.8) [b]	110.9 (14.6) [a,b]
Range	71-144	69-150	71-144
Processing Speed			
Mean (SD)	99.6 (13.5) [c]	104.1 (12.8) [d]	110.8 (12.7) [c,d]
Range	69-137	76-137	81-148

[a] CD < NC ($p < .001$); [b] DM < NC ($p < .05$); [c] CD < NC ($p < .001$); [d] DM < NC ($p < .05$)

For Working Memory (WM), CD participants performed at a significantly lower level than healthy controls ($p = .000$; m.d. = -9.20, 95% C.I. = -14.52, -3.88). Participants in the DM group also performed at an inferior level to NCs ($p<.05$), but not significantly so after a Bonferroni adjustment ($p > .007$).

In the Processing Speed (PS) index, there was a similar, but even more salient result ($F = 14.60$, $p = .000$), with CD participants again performing at a significantly lower level than NCs ($p = .000$, m.d. = -11.28, C.I. = -16.43, -6.13). The performance of DM participants was not significantly different to NCs following the Bonferroni adjustment. Across the four IQ indexes, the performance of CD and DM participants was not significantly different. The strength of already clear WM and PS results increased slightly when the multisymptomatic CD group was used in the ANOVA, with the mean WM and PS scores in the CD group dropping a further 2.17 and .65 points respectively. Statistical significance held when the CD sample was subdivided into low, medium or high subgroups, based on total IQ, age at study entry, age or number of symptoms at CD diagnosis and time on or compliance with the GFD.

In regard to gender, the PS difference was slightly accentuated in male, compared to female, CD participants, using the independent samples t-test, with equal variance assumed ($t = 2.08$, $p = .040$, m.d. = 1.52, 95% C.I. = .07, 3.0).

Finally, covariate ANOVA was performed using a number of dependent variables (measuring indices of mood and other psychological factors) that may impact on memorial functioning and speed of information processing. When total BDI-II scores were used as the covariate, significant differences across groups remained for WM (F [2, 218] = 7.68 [cf. 9.13], $p = .001$ [cf. .000]) and PS (F [2, 218] = 12.97 [cf. 14.60], $p = .000$ [no change to third decimal point]). Similar results were obtained when state anxiety was the covariate for WM (F [2, 218] = 6.85 [cf. 9.13], $p = .001$ [cf. .000]) and PS (F [2, 218] = 11.50 [cf. 14.60], $p = .000$ [no change]). Although space does not permit the reporting of all covariate analyses undertaken, none using other measures of mood or quality of life changed the existence of significance pertaining to the WM and PS group differences.

Index Performance: Discrepancy Analysis in CD Group

Given the significant mean decrements in the WM and PS indexes of the WAIS-3 in the CD group compared to the NC (but not DM) group, further analysis was undertaken to determine in what percentages of the three groups these indexes were significantly low – or high – compared to the VC and PO indexes. Table 24 (overleaf) displays these percentages. The cut score criteria used were those published in the WAIS-III Administration and Scoring Manual. Differences required for statistical significance are based on the standard errors of measurement of each Index at each age and calculated using the following formula:

$$\text{Difference Score: } Z \sqrt{SE_{Ma}^2 + SE_{Mb}^2},$$

where Z is the normal curve value associated with the desired significance level and SE_{Ma} and SE_{Mb} are the standard errors of measurement of the two scales (Wechsler, 1997). In practice, the required magnitude of difference that is statistically significant at the .05 level varies by several points, being between 9 and 11 points for the VC-WM comparison and 11-14 points for the PO-PS comparison.

Table 24

WAIS-III Index Score Differences for VC-WM and PO-PS Pairings Across Groups: Percentage of Cases Involving a Significant Difference at .05 Level (Each Direction) and No Statistical Difference

	CD	DM	NC
Index Pairing	(n = 108)	(n = 51)	(n = 60)
VC-WM			
% VC < WM	13.0 %	3.9 %	30.6 %
% No statistical difference	33.3 %	47.1 %	46.8 %
% VC > WM	53.7 %	49.0 %	22.6 %
PO-PS			
% PO < PS	3.7 %	7.8 %	17.7 %
% No statistical difference	37.0 %	49.0 %	56.5 %
% PO > PS	59.3 %	43.1 %	25.8 %

According to the WAIS-III Technical Manual, significant differences between Index scores are expected to occur in approximately 40-60% of people, depending on the full-scale IQ range. The direction of these differences is balanced. Therefore, examining Table 24, it is evident that, in both the CD and DM groups there are a greater than expected number of cases in which WM < VC (53.7 % and 49.0 %) and in which PS < PO (59.3 % and 43.1 %), compared to the NC group (22.6 % and 25.8 % respectively). These proportions are congruent with the significant mean index score differences found in the CD compared to the NC, but DM, group.

One again, the PS index result was the most pronounced in the CD group, with PS < PO in more than half of all cases (59.3 %) versus the converse (i.e., PO > PS) in only four cases out of 108 (= 3.7 %). These results confirm that there are relative weaknesses in both the WM and PS indexes in CD, relative to the two other core indexes, and that this result is especially salient in the case of Processing Speed. It was interesting to note that the CD result did not vary according to CD severity, as determined by the number of symptoms at diagnosis. For the multisymptomatic subgroup the VC-WM difference percentages were 8.3 (VC < WM)/ 33.3 (no difference)/ 58.3 (VC > WM), versus 22.2/ 33.3/ 44.4 for the oligosymptomatic subgroup, whilst for the PO-PS pairing the respective results were 2.8/ 34.7/ 62.5 versus 5.6/ 38.9/ 52.8.

Neuropsychological Subtest Performance: Descending Order

The reliability coefficients of the WAIS-III IQ and Index scores (ranging from .88 to .97) are consistently higher than those of the 14 subtests, which ranges from .70 (Object Assembly – not used in thesis) and .74 (Picture Arrangement) to .93 (Vocabulary, Digit Span, and Information). Therefore, the analyses of discrepancies in performance between groups focussed on differences between Index Scores. However, having identified the deficits in WM and PS in the CD group, a straightforward exercise undertaken was listing the descending order of performance in each of the three groups. These orders are displayed in Table 25.

Table 25

Means and SDs of Subtest Scores, in Descending Numerical Order of Performance Across Groups

	CD (n = 108)	DM (n = 51)	NC (n = 60)
Best	WAIS Subtest (Mean, SD)	WAIS Subtest (Mean, SD)	WAIS Subtest (Mean, SD)
1	Vocabulary (13.51, 2.7)	Matrix Reas. (13.14, 2.9)	Vocabulary (12.19, 2.6)
2	Matrix Reas. (13.32, 2.7)	Information (12.96, 2.1)	Information (12.16, 2.7)
3	Picture Comp. (12.57, 2.8)	Vocabulary (12.84, 2.5)	Digit Sym. Cod. (12.13, 2.3)
4	Comprehension (12.16, 2.9)	Comprehension (12.51, 2.4)	Matrix Reas. (12.13, 3.0)
5	Block Design (12.01, 2.8)	Block Design (11.92, 2.5)	Comprehension (12.02, 2.7)
6	Information (11.93, 2.5)	Picture Arr. (11.63, 2.4)	L-N Sequenc. (11.97, 2.6)
7	Picture Arr. (11.78, 2.8)	Picture Comp. (11.49, 2.1)	Arithmetic (11.95, 2.7)
8	Similarities (11.39, 2.4)	Similarities (11.47, 2.4)	Picture Comp. (11.74, 2.6)
9	Arithmetic (10.52, 2.6)	Arithmetic (11.23, 28)	Symbol Search (11.76, 2.8)
10	L-N Sequenc. (10.43, 2.6)	L-N Sequenc. (10.96, 2.3)	Digit Span (11.65, 3.0)
11	Digit Span (10.14, 2.9)	Digit Sym. Cod. (10.84, 2.4)	Similarities (11.50, 2.8)
12	Symbol Search (10.00, 2.5)	Symbol Search (10.73, 2.8)	Block Design (11.45, 3.0)
13	Digit Sym. Cod. (9.94, 2.8)	Digit Span (10.23, 2.9)	Picture Arr. (11.14, 2.4)
Worst			

It is apparent from Table 25 that in the CD group, the five numerically lowest mean scores were the two PS subtests, followed by the three WM subtests. In terms of statistical significance, the mean scores

for the CD group's two worst performed (PS Index) subtests, Digit Symbol–Coding (= 9.94) and Symbol Search (=10.00) were each statistically different ($p < .05$) from the mean scores in both Vocabulary (m.d.'s = 3.57 and 3.51; required differences at .05 level = 2.80 and 3.20 respectively) and Matrix Reasoning (m.d. = 3.38 and 3.32, required difference = 3.01 and 3.39).

The next three numerically lowest subtest scores in the CD group (Digit Span, Letter-Number Sequencing and Arithmetic, comprising the WM Index) were also significantly lower than performance on Vocabulary (m.d.'s = 3.37, 3.08, and 2.99; with the respective required differences at the .05 level being 2.48, 2.98, and 2.57). Mean scores on two out of the three, Digit Span and Arithmetic, were also significantly lower than performance on Matrix Reasoning (m.d.'s = 3.18 and 2.80; with the respective required differences being 2.64 and 2.80).

A similar pattern of results (WM and PS Index subtests comprising bottom five) was found in the DM group, but statistical significance only occurred in regard to the pairing of Digit-Span with the highest three DM subtest scores. Within the NC group there were no significant discrepancies in mean performance between any pairs of subtests, even at the .15% level of significance, with the m.d. between the highest and lowest subtest performance scarcely one point and the next greatest m.d. = .74. Furthermore, the PS and WM Index subtests were evenly distributed regarding descending numerical mean score order, occupying ranks equal third through to tenth. These comparative NC results underline the significance of the CD findings.

Health Status and Life Quality

Comparisons of Health Status Across Groups

Self-assessed health status was recorded at study entry for all participants. In the case of CD and DM participants, health status was rated retrospectively in relation to two time periods; prior to and after diagnosis/ treatment with either CD or DM. For the NC group, the health status rating corresponded to the exact time of study entry. Since the ratings corresponding to the CD and DM groups relate to different temporal durations and points than the NC ratings, statistical comparisons were limited to the

CD and DM groups. However, the NC ratings provide a useful background perspective. The percentages of participants in all three groups rating their health according to one of six rating categories (from very poor to excellent), are displayed in Table 26. The only missing data involved two CD participants who were unable to rate their health status after diagnosis with CD as they had not received confirmation of CD at study entry.

Table 26

Health Status Before/ After Diagnosis with CD or DM and at Study Entry for NC Participants (%)

	CD	DM	NC
Rating (% of Sample)	Before/ After	Before/ After	Study Entry
1: Very Poor	25.5% - 0%	0% - 3.8%	0%
2: Poor	28.2% - 0.9%	2.0% - 9.4%	2.9%
3: Fair	22.7% - 19.4%	18.0% - 11.3%	8.7%
4: Good	9.1% - 38.9%	52.0% - 54.7%	30.4%
5: Very Good	11.8% - 25.9%	22.0% - 17.0%	36.2%
6: Excellent	2.7% - 14.8%	6.0% - 3.8%	21.7%

From Table 26, it is evident that three-quarters (76.4%) of the CD sample rated their health as very poor to fair prior to diagnosis, where as four-fifths (79.6%) rated their health as good to excellent after diagnosis and treatment with the GFD. The shift towards an improved health rating pre-post diagnosis in the CD group was exemplified by the observation that no CD participants rated their health in the period since diagnosis as very poor, compared to one-quarter of the CD sample (25.5%) pre-diagnosis. Those rating their health as poor also fell from 28.2% to 0.9% (i.e., just one case). Health ratings in the very good to excellent categories increased from 14.5% to 40.7%.

In contrast, about half of the DM group rated their health status as good both prior to and after diagnosis with DM (52% and 54.7% respectively). More DM patients rated their health as poor to very poor post diagnosis (13.2%, compared to 2% pre-diagnosis) and fewer DM patients rated their health as very good to excellent after diagnosis (20.8% compared to 28% pre-diagnosis). Unlike in the CD

group, where there was a marked increase in the percentage of participants who reported increases in health pre-post diagnosis, the opposite trend occurred in the DM group, although to a lesser degree.

In both the CD and DM groups there was a greater percentage of participants who rated their health, both pre- and post-diagnosis, in the lower three categories (very poor to fair) compared to the NC group at study entry. These percentages were, for the CD group, 76.3% and 20.3% (pre-post diagnosis), for the DM group, 20% and 24.5% (pre-post) and 11.6% at study entry for the NC group. These results were comparable to Australian National Health Survey data (McLennan, 1998, 2000), in which 3.3% of people without a medical condition surveyed rated their health as poor to fair and 18% of people with one or more medical conditions (recent and/ or long-term) were in the same range. However, a 5- rather than 6-point scale was used in the National Health Surveys of 1989-90 and 1995, with the scale used in this thesis including an additional category (very poor) in view of the focus on people with at least one medical condition (CD or DM). Therefore, comparisons are somewhat limited, although the differences between people with and without a medical condition were notable. In both the National Health Surveys and the DM and NC groups in the present thesis, there were no gender differences in health status. However, in the CD group, females rated their health status as lower than males, as shown in Table 27.

Table 27

Means and Standard Deviations (SDs) of Self-Assessed Health Status Prior to and Since Diagnosis in Male and Female CD Participants

	Male CD	Female CD
Health Status Prior to Diagnosis		
Mean (SD)	2.86 (1.5)	2.45 (1.3)
Health Status Since Diagnosis		
Mean (SD)	4.67 (1.0)	4.14 (1.0)

Independent samples t-test showed that the difference in health status was only significant in relation to the period since diagnosis, with $t = 2.81$, $p = .006$, m.d. = .53, 95% C.I. = .15, .90).

Table 28 displays the mean health status scores prior to and since diagnosis for the CD and DM participants and the NC scores at study entry.

Table 28

Means, Standard Deviations (SDs) and Ranges of Self-Assessed Health Status Prior to and Since Diagnosis in relation to CD and DM Patients and at Study Entry for NC Participants

	CD	DM	NC	
Health Status Prior to Diagnosis				
Mean (SD)	2.62 (1.4)	4.12 (.8)		
Range	1-6	2-6		
			Mean (SD)	4.65 (1.0)
Health Status Since Diagnosis			Range	2-6
Mean (SD)	4.34 (1.0)	3.83 (1.1)		
Range	2-6	1-6		

Health Rating Score Range Key:

1: Very Poor 2: Poor 3: Fair: 4: Good 5: Very Good 6: Excellent

Using ANOVA with retrospectively reported pre- and post-diagnosis CD and DM scores, and with NC health status scores at study entry in each analysis, there was a difference across groups in health status both pre-diagnosis; F [2, 226] = 68.86, p = .000) and post-diagnosis F [2, 227] = 9.91, p = .000). Post-hoc Scheffé testing showed that pre-diagnosis CD health status scores were significantly lower than pre-diagnosis DM scores (p = .000, m.d. = 1.50, 95% C.I. 1.00, 2.00) and NC scores (p = .000, m.d. = 2.03, 95% C.I. = 1.58, 2.48). Post-diagnosis, DM scores were significantly lower than both NC scores (p = .000, m.d. = .82, 95% C.I. = .37, 1.28) and, to a lesser degree, CD scores (p = .012, m.d. = .51, 95% C.I. = .09, .93).

There was not a significant difference between the CD and NC scores, although when the multi-symptomatic CD subgroup was used in the ANOVA, a significant effect still occurred across groups (F = 11.596, p = .000) and the multisymptomatic subgroup's score was significantly lower than the NC score (p = .003, m.d. = .58, 95% C.I. = .17, .99). Upon gender partitioning, statistical significance only held in the analysis isolating female participants (p = .022, m.d. = .57, 95% C.I. = .07, 1.08).

Within-group analyses were also undertaken. Using paired samples t-test, there was a significant increase pre- to post-diagnosis in CD scores (t [107] = 13.12, p = .000) and a smaller, although still significant, decrease pre- to post-diagnosis in DM scores (t [49] = 2.13, p = .038). The lack of perceived health improvement in the chronic illness comparison group pre- to post-diagnosis was attributed to the almost inevitable, eventual deterioration of health associated with DM, as distinct from CD, in which a remission of health problems is generally observed following consistent adherence to the GFD.

Further analysis of the increase in health status in the CD group (pre- post-diagnosis) showed that this result was significant in both the multisymptomatic participants, with an average increase of 1.85 points (or almost two categories) in that subgroup (t [71] = 11.35, p = .000, m.d. = 1.85, 95% C.I. = 1.52, 2.17) compared to 1.58 points in the oligosymptomatic group (t [35] = 6.68, p = .000, m.d. = 1.58, 95% C.I. = 1.10, 2.06), These results are shown in Table 29.

Table 29

Means, Standard Deviations (SDs) and Ranges of Self-Assessed Health Status Prior to and Since Diagnosis in the Multisymptomatic and Oligosymptomatic CD Subgroups.

	Multisymptomatic CD	Oligosymptomatic CD
Health Status Prior to Diagnosis		
Mean (SD)	2.23 (1.1)	3.31 (1.5)
Range		
Health Status Since Diagnosis		
Mean (SD)	4.07 (0.9)	4.89 (0.9)
Range		

There was not a significant difference in health status between the oligosymptomatic CD subgroup and NC participants.

Quality of Life

Quality of life (QOL) was assessed using the Quality of Life Questionnaire. Table 30 displays the mean QOL and major domain scores across the three groups. Using ANOVA, there was no difference in overall QOL between groups.

Table 30

Means, Standard Deviations (SDs) and Ranges of Quality of Life (QOL) and Major QOL Domain Scores Across the Three Groups

	CD	DM	NC
QOL (Total score)			
N	107	53	60
Mean (SD)	104.76 (22.6)	103.83 (22.8)	111.28 (21.0)
Range	54-162	30-153	49-158
General Well-being			
N	107	53	60
Mean (SD)	7.96 (1.7)	7.55 (1.8)	8.28 (1.6)
Interpersonal Relations			
N	69	23	28
Mean (SD)	7.78 (2.0)	7.55 (1.8)	7.67 (1.6)
Organisational Activity			
N	105	53	60
Mean (SD)	5.92 (2.0)	6.11 (2.3)	5.54 (2.1)
Occupational Activity			
N	78	34	49
Mean (SD)	6.68 (2.6)	7.05 (2.4)	7.33 (2.2)
Leisure and Recreation Activity			
N	106	53	60
Mean (SD)	6.04 (2.2)	6.17 (1.9)	7.54 (2.2)

Major domains		**Subdomains**
General Well-being	=	Means of Material & Physical Well-being & Personal Growth
Interpersonal Relations	=	Means of Marital, Parent-Child, Extended Family & Extramarital Relations
Organisational Activity	=	Means of Altruistic & Political Behaviour
Occupational Activity	=	Means of Job Characteristics, Occupational Relations & Job Satisfiers
Leisure/ Recreation Activity	=	Means of Creative/ Aesthetic Behaviour, Sports Activity & Vacation Behaviour

In the subsequent analyses of variance involving the five major QOL domain scores, alpha level was fixed at p = .01, decided on a Bonferroni basis by dividing the standard alpha level of .05 by five – corresponding the five major domain scores – to limit Type 1 errors. The only significant difference across groups occurred in Leisure/ Recreation Activity (F [2, 216] = 10.59, p = .000), with both the mean CD group score significantly lower than NC group score (p = .000, m.d. = 1.50, 95% C.I. = .67, 2.34) and the DM group score also lower than NCs (p = .003, m.d. = 1.37, 95% C.I. = .40, 2.35).

Further perusal of the subdomain scores comprising this major domain (i.e., Creative/ Aesthetic Behaviour, Sports Activity and Vacation Behaviour) showed that there was a significant effect across groups (F [2, 217] = 11.77, p =.000), with the NC group significantly more involved in sporting activity than both the CD group (p = .000, m.d. = 2.60, 95% C.I. = 1.25, 3.94) and the DM group (p = .004, m.d. = 2.17, 95% C.I. = .60, 3.75).

In the consideration of subdomain score differences, which involved 15 analyses, a further Bonferroni adjustment was made by dividing alpha by 15 (= .003), with only significant differences below this level reported. Using this adjustment, only one other significant subdomain difference was detected between groups, namely Parent/ Child Relations (F [2, 127] = 6.46, p = .002). Post-hoc analysis showed only one pair-wise difference between the CD and DM group, with CD participants reporting significantly better Parent/ Child Relations (p = .004, m.d. = 2.10, 95% C.I. = .54, 3.49). No difference across groups occurred on the Social Desirability scale, and the mean scores in each group were well within acceptable limits, indicating that responses were not biased towards social desirability.

There were no significant male-female differences in any of the three groups using the Bonferroni adjustments, except for Sporting Activity in the CD group, where males (M = 6.35, SD = 3.7) were significantly more involved than females (M = 4.02, SD = 2.7) with CD (t [70.69] = 3.58, p =.001, m.d. = 2.33, 95% C.I. = 1.12, 3.55). Equality of variances could not be assumed, as Levene's test was significant.

Life Quality Lower in Multisymptomatic CD

When the multisymptomatic CD subgroup was used in an ANOVA using the DM and NC groups, a significant difference emerged across groups (F [2, 181] = 5.91, p = .003). Post-hoc Scheffé analysis showed that the multisymptomatic CD subgroup reported significantly lower QOL than the NC group (p = .003, m.d. = 13.10, 95% C.I. = 3.69, 22.51). In another ANOVA using the oligosymptomatic CD subgroup with the DM and NC groups, there was also a significant differences across groups (F [2, 146] = 4.71, p = .010). Post-hoc Scheffé analysis showed that the oligosymptomatic CD subgroup reported significantly higher QOL than the DM group (p = .012, m.d. = 13.89, 95% C.I. = 2.54, 25.24), but not the NC group. Mean scores for the multisymptomatic and oligosymptomatic subgroups are shown with DM and NC group scores in Table 31.

Table 31

Mean, Standard Deviations (SDs) and Ranges of Quality of Life QOL in the Multisymptomatic and Oligosymptomatic CD Sub-Groups, DM and NC Groups

	Multisymptomatic CD	Oligosymptomatic CD	DM	NC
N	71	36	53	60
Mean (SD)	98.18 (21.5)	117.72 (19.1)	103.83 (22.84)	111.28 (21.0)
Range	54-146	69-162	30-153	49-158

High versus Low Scorers on the Quality of Life Questionnaire

Another approach to examining possible group differences in QOL was to consider the percentages of cases falling into different ranges of QOL using the T-scores published in the QOL Manual. Using the interpretive guidelines for T-scores used by Evans and Cope (1989), the percentage of participants in each group falling into nine narrow ranges of QOL (from very much below to very much above average) were able to be calculated. For clarity, these nine intervals of QOL were collapsed into three broad ranges (i.e., below average – average – above average) and are shown overleaf in Table 32, with the multisymptomatic CD subgroup added to demonstrate the

relative increase in cases at the lower QOL range within the CD group.

Table 32

Percentage of QOL Scores in the Low, Average and High Ranges for the Multisymptomatic CD Subgroup, the Full CD Group and the DM and NC Groups, Using T-Scores

	Multisymptomatic CD	Full CD Group	DM	NC
N	71	107	53	60
High QOL (T ≥ 61)	5.6%	7.5%	5.7%	8.3%
Average QOL (T = 41 to 60)	55%	63.5%	66%	78.7%
Low QOL (T ≤ 40)	39.4%	29%	28.3%	13%

From Table 32 it is evident that the percentage of participants reporting average to high QOL are roughly equivalent across groups. However, more than twice as many CD and DM participants reported low QOL than NC participants and this increased to three times in the multisymptomatic CD group. These results are reminiscent of the depression results reported earlier, in which there are no mean score differences across groups (unless the multisymptomatic CD subgroup is isolated), but a greater proportion of low scorers are found within the CD group compared to the NC group.

Unlike the data sets used in preceding analyses, in which missing data was minimal, several of the major QOL domains (especially Interpersonal Relations and Occupational Activity) involved the measurement of aspects of QOL inapplicable to a large minority of participants in each group (e.g., marital relations for those who were single and job characteristics for the retired, unemployed or females with full-time home duties). As a result of close matching across demographic factors, though, equivalent proportions of the three groups were affected. Also, standard adjustments to the scoring regime of the QOL questionnaire in cases of missing data are described in the Manual (Evans & Cope, 1989). Power was nevertheless reduced where lower sample sizes were used.

It was notable that the mean QOL score for the NC group (111.28, SD = 21.0) and oligosymp-

tomatic CD subgroup (117.72, SD = 19.1) were comparable to the mean normative total score for the QOL Questionnaire (113.15, SD = 20.4), especially in view of the fact that the demographic characteristics of all three groups were similar, notwithstanding historical and geographic differences.

Multidimensional Health Locus of Control

No significant differences were found between groups in the three Multidimensional Health Locus of Control sub-scales, which are displayed in Table 33.

Table 33

Mean, Standard Deviations (SDs) and Ranges of Multidimensional Health Locus of Control Scores (Internal, Powerful Others and Chance) Across the Three Groups

	CD	DM	NC
Internal HLOC			
Mean (SD)	24.98 (4.7)	24.36 (5.1)	25.51 (4.8)
Range	12-36	14-35	8-34
Powerful Others HLOC			
Mean (SD)	16.29 (4.9)	18.08 (5.2)	16.06 (6.1)
Range	6-34	6-33	6-34
Chance HLOC			
Mean (SD)	16.39 (4.5)	16.36 (5.1)	16.81 (5.0)
Range	7-26	6-31	8-29

There were also no significant differences between the mean scores for any of the three groups and normative data published by Wallston, Wallston and DeVellis (1978), although the CD and NC group scores on Powerful Others HLOC were a few points lower than two decade old United States community levels. As hypothesised, internal HLOC was negatively correlated with BDI-II depression in the CD, DM and NC groups (r [110] = -.192, $p < .05$, r [53] = -.331, $p < .05$, and r [68] = -.317, $p < .01$ respectively) and positively correlated with health status since diagnosis (r [110] = .277, $p < .01$) and quality of life (r [107] = .251, $p < .01$. However, Internal HLOC was not correlated with GFD compliance, reminiscent of the lack of association between CD awareness and GFD compliance.

Correlation Matrices Within CD Group

A selection of bivariate Pearson correlational analyses are displayed in Table 34. These highlight numerous positive correlations between the test measures used in Study 1 and two important demographic variables, age and educational status.

Table 34.

Bivariate Pearson Correlations Within CD Group Between the Variables Age, Education and Test Scores

Variable	Age	Education	BDI-II	Anx.(S)	Anx.(T)	Ang.(S)	Ang.(T)	WAIS-IQ	QOL
Age	-	-.11	-.125	-.20*	-.20*	-.24*	-.25*	.11	.17
Education	-.11	-	-.22*	-.20*	-.10	-.04	-.20	.46**	.29**
BDI-II	-.13	-.22*	-	-.61**	.63**	.47**	.40**	-.20*	-.53**
Anxiety (State)	-.20	-.20	.61**	-	.73**	.52**	.54**	-.24*	.60**
Anxiety (Trait)	-.20*	-.10	.63**	.73**	-	.42**	.51**	-.19	-.60**
Anger (State)	-.24*	-.04	.47**	.52**	.42**	-	.66**	.16	-.60**
Anger (Trait)	-.25**	-.20*	.40**	.54**	.51**	.66**	-	.54**	-.41**
WAIS-IQ	.11	.46**	-.20*	-.24*	.19*	-.16	-.23*	-	.22*
QOL	.17	.29**	-.53**	-.60**	-.60**	-.38**	-.41**	.22*	-

Note: N = 110, except in case of WAIS-IQ (N = 108) and QOL (N=107) and IQ/ QOL (N = 105)

Correlation are statistically significant at * $p < .05$ and ** $p < .01$.

The highly significant positive correlations between measures of affect (e.g., the BDI-II, STAI and STAXI) were expected, given the clinical overlap in the mood and anxiety spectrum disorders and anger functions, as described in Chapter Two. There was a modest positive correlation between WAIS-III IQ and BDI-II depression (r [108] = -.203, $p < .05$). Further analysis isolating the four WAIS-III Index scores showed that just one of the four indexes, Working Memory, was negatively correlated with BDI-II depression (r [108] = -.22, $p < .05$). As noted earlier, however, Working Memory was still reduced in the CD group compared to the NC group even after controlling for the effects of depression, the overall level of which was not significantly different across each full group. Table 34 shows that

lowered mood, increased anxiety and anger are all negatively correlated with quality of life. Finally, self-rated Health Status (not in Table) was significantly negatively correlated with BDI-II depression in participants across all three groups (r [230] = -.54, $p < .001$), and within each group ($p < .001$ in each case), indicating a robust association between poor general health and depression. The effects of demographic variables, including age, years of education and gender, have been tested and generally noted within preceding sections. There was no correlation, nor trend towards an association, between gender and either of the two measures of dietary compliance.

As a prelude to discriminant function analysis, the four DQ variables, described earlier in Study 1, were used in a correlational analysis with BDI-II scores for all CD participants, as shown in Table 35. Each of the four DQ variables had been proposed to have a directional association with the hypothetical level of depression.

Table 35

Bivariate Pearson Correlations Within CD Group Between BDI-II Depression and the DQ Variables

Variable	BDI-II Score (0-64)	CD Symptoms at Diagnosis (1-4+)	Time Symptomatic Pre-Diagnosis (# Months)	Time Since Diagnosis (Days)	GFD Compliance[1]: Measure 1 (1-5)	Measure 2 (1-16)
BDI-II Score	-	.46**	.43**	-.12	-.13	-.11
CD Symptoms At Diagnosis	.46**	-	.40**	.02	-.05	.07
Time Symptomatic Pre-Diagnosis	.43**	.40**	-	-.02	-.15	.07
Time Since Diagnosis	-.12	.02	-.02	-	.05	.08
GFD Compliance[1]: Measure 1 (Freq. gluten)	-.13	-.05	-.15	0.05	-	.50**
Measure 2 (Questionnaire)	-.11	.07	.07	-.08	.50**	-

[1] A higher score = greater compliance; Results statistically significant at * $p < .05$ and ** $p < .01$.

The two greatest correlations ($p < .01$) occurred between BDI-II depression and each of two static disease correlates; CD Symptoms Pre-diagnosis and Time Symptomatic Pre-diagnosis. A strong significant correlation between the latter two variables indicates that, in the CD group used in Study 1, people who retrospectively reported a higher number of CD-related symptoms at diagnosis also tended report having experienced a greater duration of symptoms pre-diagnosis. These two variables were unrelated to the elapsed time period since diagnosis with CD and GFD duration. Dietary compliance, as measured by two separate scales, was not significantly related, overall, to any other variables, except one another. The hypothesis that higher dietary compliance would be associated with lower levels of depression was not confirmed, although the trend in each case was in the expected direction. Although only two out of four DQ variables were significantly associated with BDI-II depression, each of the others were in expected directions and so the DQ model incorporating combinations of all four variables was tested via discriminant function analysis.

Discriminant Function Analysis

Utility of Theorised Damage Quotient Model in Predicting Depression in CD

A systematic series of discriminant function analyses were performed using combinations of all, and subsequently three, of the within-CD group hypothetical damage quotient (DQ) variables, as equally weighted predictors of membership of two outcome groups, namely 1) absent/ minimal depression (BDI-II ≤ 13), and 2) at least mild depression (BDI-II > 13). Prior to analysis, each of four DQ variables were converted to standard scores, as outlined. There were pragmatic and actuarial motivations for subdivision of the CD group using static clinical parameters (i.e., disease severity) and dynamic behavioural and temporal correlates (e.g., dietary compliance and time since diagnosis), as a prelude to discriminant analysis. As well as Study 1's observation that the prevalence of depression in CD was higher in multisymptomatic than oligosymtomatic CD patients, previous reports in the literature support the view that non-demographic, CD-related factors may predispose to the development of both physical and psychological sequelae.

These findings justified the pooling of all readily obtainable clinical information underpinning the DQ, to determine whether this information had clinical utility in predicting which CD patients may be expected to be at risk of suffering from clinically significant depression post-diagnosis. Given the increasingly heterogeneous spectrum of CD worldwide (Fasano & Catassi, 2001) and exposure of the less symptomatic portion of the CD iceberg, plus Study 1's finding of unremarkable levels of depressive symptomatology in oligosymptomatic cases, it was also considered important to be able to determine in which circumstances screening for depression in CD is actually justified. With shrinkage of affordable health care proportionate to the ageing of western populations and rising competition for these resources due to increased awareness of mental health issues in many chronic illnesses (e.g., DM), specification of risk profiles within the greater CD population was deemed important in justifying which CD patients may warrant and potentially benefit from early specialist intervention in the area of mental health.

All 110 CD participants were used in a series of direct discriminant function analyses (DFAs), with a selection of four of the most accurate analyses (regarding predicted group membership) reported, in order to highlight which DQ variables were most clinically useful in predicting significant levels of depression in CD.

How Accurately Did the DQ Variables Identify Depressed CD Patients?

The first DFA used each of the four DQ predictor variables previously described and all CD participants were included. Depressed and non-depressed CD participants on the BDI-II were the two groups used. There were 86 CD patients in the non-depressed group and the 24 remaining CD patients constituted the depressed group. The first measure of dietary compliance was used (i.e., frequency of gluten intake). No items were removed as a result of missing data. The Mahalanobis distance method (Coakes & Steed, 1999; Tabachnick & Fidell, 1996) was applied to probe for multivariate outliers, but none were identified.

Relationships between predictor variables within groups were examined for linearity and serious violations were not observed. Since significant correlations were observed between several

independent variables, the possible effects of multicollinearity were monitored, but did not prove to be problematic. Box's M test was used to assess equality of covariance and was found to be non-significant ($\underline{M} = 6.92$, $\underline{p} > .001$), verifying homogeneity of variance-covariance matrices. Finally, DFA "is quite sensitive to the ratio of sample size to the number of predictor variables", with "a ratio of 20 observations for each predictor variable" suggested (Hair, Anderson, Tatham, & Black, 1992, p. 106). Clearly, this recommendation was met.

The first DFA was significant; $\chi^2 (4, \underline{n} = 110) = 24.40$, $\underline{p} = .000$, accounting for 20.6% of between-group variability. It was noted that, in testing "the null hypothesis that the means of all the variables across groups are equal" Lambda "provides little information regarding the success of the model for classifying cases" (The SPSS Base 10.0 Application Guide, 1999, p. 255). This was certainly the case, as three-quarters of CD patients (75.5%) were correctly classified, exceeding at a statistically significant level the classification accuracy expected by chance. This was determined by using Press's Q statistic, calculated using a standard formula[1] (Hair et al., 1992, p. 104), with $\underline{Q} = 28.51$, where the critical value at the .01 significance level = 6.63.

Closer inspection revealed that, in the larger, non-depressed CD subgroup, 73.3% of cases were correctly classified and, in the depressed subgroup, 83.3% of cases were grouped correctly. Together, the results indicated that that the DFA used demonstrated a reasonable degree of specificity and high sensitivity in correctly identifying depression, as assessed by the BDI-II.

Further examination the standardised canonical discrimination function coefficients shown in Table 36 (overleaf) demonstrate that the number of symptoms at diagnosis was most influential in discriminating depressed from non-depressed CD patients and that the measure of dietary compliance appeared irrelevant.

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[1] Press's $\underline{Q} = \dfrac{[\underline{N} - (n \times K)]^2}{N (K - 1)}$

N = total sample size, n = number of observations correctly classified, K = number of groups (Hair at al., 1992).

Table 36

Discriminant Function Analysis using Four DQ Variables, as Predictors of Depression

Predictor (independent) Variable	Canonical Discrimination Function Coefficients	Tests of Equality of Group Means	
		Univariate F	Sig.
CD Symptoms At Diagnosis	1.07	19.01	.000
Time Symptomatic Pre-Diagnosis	-.23	3.58	.061
Time Since Diagnosis	.535	3.13	.080
GFD Compliance Measure 1	.125	.81	.370

The second DFA was identical except that the alternate measure of dietary compliance (i.e., the brief questionnaire) was substituted to determine whether either of the two key goals of classification, specificity and sensitivity to depression, could be improved. This DFA was also significant; χ^2 (4, $\underline{n}$ = 110) = 27.04, $\underline{p}$ = .000, accounting for 22.5% of between-group variability and all assumptions of the analysis were again met. Not surprisingly, the standardised canonical discrimination function coefficients were very similar. Overall, the classification rate improved numerically, by two cases, to 77.3% (from 75.5%), as did the classification accuracy pertaining to he non-depressed group (up to 76.7%, from 73.3%, an improvement of three cases), but the correctly predicted depressed patients fell marginally to 79.2% (from 83.3%, equivalent to one case). Since both dietary compliance measures had almost negligible discriminant function coefficients, this DQ was removed from the next analysis.

It has been previously noted that "often a model with fewer variables is more useful for classifying new cases than one with more variables" (The SPSS Base 10.0 Application Guide, 1999, p. 260). In the third DFA, three DQ variables (excluding either measure of dietary compliance) and all 110 cases were used. This DFA was significant, with χ^2 (3, $\underline{n}$ = 110) = 24.18, $\underline{p}$ = .000, accounted for 20.3% of the between-group variability and 74.5% of cases were correctly classified. The best predictor for distinguishing between depressed and non-depressed CD patients at study entry was again the number

of CD-related symptoms at diagnosis. The three DQ variables used in the final DFA were not only successful in grouping about three-quarters of CD patients correctly, but seven out of ten non-depressed CD participants (70.9%) were correctly classified in this DFA (a slight decrease), almost nine out of ten (87.5%) patients who were depressed were identified. This was a very important finding.

Can the DQ Model Still Discriminate at Lower Thresholds of Depression?

A fourth DFA was computed, identical in its use of the three DQ variables used in the preceding DFA, except that the cut score criteria for depression was lowered from ≥ 14 to ≥ 8, which may be regarded as a subthreshold or subclinical level of depression. The new subgroup ($n = 59$), inclusive of subthreshold levels of depression, outnumbered the non-depressed group ($n = 51$). In the final DFA (χ^2 $(3, n = 110) = 32.91$, $p = .000$, accounting for 26.6% of the between-group variability) the same 74.5% overall classification rate was achieved. Press's Q statistic was significant ($Q = 26.51$, $p < .01$). The correct predicted group membership percentages for non-depressed and depressed patients were 70.6% and 78%. These figures demonstrated that a comparable degree of accuracy was maintained via the use of the same DQ model at lower, subclinical levels of depression.

Discussion of Study 1: Key Results

Study 1 was a cross-sectional analysis of mood, intellectual functioning, health status and quality of life in a large CD sample, compared to people with DM, who served as a chronic illness comparison group, and a sample of healthy people without a significant chronic medical condition. The comparison groups were gender balanced and closely matched to the CD group socio-demographically, in regard to age, years of education, SES, general intelligence, occupational status and urban versus rural habitation. Each group was principally of Anglo-Celtic ethnicity. Participants recruited to the CD group primarily included Coeliac Society members (all with biopsy-confirmed CD using ESPHAGN criteria) who volunteered on the basis of successive magazine advertisements and interest generated at local conference proceedings. Several consequent idiosyncrasies were observed in the CD and matched

samples. Notably, age, SES and general intelligence were each slightly above general community levels, notwithstanding considerable ranges. A relatively high degree of compliance with the GFD was also noted among CD participants.

In other respects, the CD sample developed over two years was decidedly heterogenous, which was a primary goal. The CD group's heterogeneity enabled arbitrary partitioning of the full CD group on the basis of the number of CD-related symptoms at diagnosis, with separation into multisymptomatic and oligosymptomatic subgroups undertaken prior to many of the statistical procedures. This subdivision hinged on the assumption that CD patients with few, if any, symptoms of illness may be indistinguishable from a self-perceived health perspective and other respects from the NC group, and potential between-group differences using the full CD group may be masked or weakened by the presence of oligosymptomatic patients. This supposition seemed justified, given that in many analyses of variance using the three groups and test scores as dependent variables, significant between-group differences were only found after the oligosymptomatic CD cases were omitted. Further evidence was supplied by the DFA results, in which the number of symptoms at diagnosis was the most important predictor variable in discriminating depressed from non-depressed patients at study enrolment.

Two thirds of the DM sample had type-1 diabetes, with the remaining third classified as early-middle stage type-2 patients on the basis of previous general practitioner confirmed medical diagnoses of DM prior to study entry and status reviews, based on self-reported, up-to-date medical information at study entry in the context of current diagnostic criteria (Masharani & Karam, 2002). Overall, the DM participants were generally compliant with their medical treatment regimes, euglycaemic prior to study entry and free from debilitating diabetic complications. The choice of a suitable chronic illness comparison group was made on the basis of shared similarities with key features of CD and approximate equivalence regarding severity of disease.

Most of the hypotheses about psychological functioning in CD were contingent on expectations of differences with healthy people – who provided a baseline against which to evaluate changes in CD – but not necessarily in relation to patients with DM, who served as a yardstick in evaluating the strength

of any identified changes, over and above the affects of having a serious, but treatable, chronic illness, and in identifying any changes unique to the coeliac condition. The three groups were assessed across three primary domains of psychological functioning, namely clinical symptomatology (mood, anxiety and anger), life quality and neuropsychological aptitude.

Cognition: Neuropsychological Performance

The hypothesis that general intellectual ability would not be significantly different across groups was confirmed, supporting previous findings (De Maria et al., 1997; Hallert & Åström, 1983). However, the most salient result of Study 1 was the identification of a modest, but consistent, neuropsychological test performance pattern. This was evident in both DM and CD patients, but, in several respects, statistically different to healthy controls only in the CD group.

Fortuitously close and chiefly incidental matching in general intelligence permitted the direct comparison of WAIS-III Index profiles across groups, in addition to the Wechsler scale's well-elaborated test norms. During early data collection a trend was observed in the CD group indicative of relative decrements in performance on subtests in the Working Memory (WM) and Processing Speed (PS) Indexes, compared to normative expectations after test scores were standardised, as previously reported (Grech et al., 2000). This tendency was sustained throughout data collection, with sixty-four out of one-hundred and eight CD participants (i.e., 59%, compared to 43.1% of DM and 25.8% of NC participants) having a discrepancy in Index performance consisting of their PO Index score significantly exceeding their PS Index score in the Performance Scale. The converse (PS > PO) was true in only four CD cases (i.e., 3.7% of the CD group).

Similarly, the WM Index score was lower than the VC Index score in 53.7% of CD participants (compared to 49.0% of DM and 22.6% of NC participants), with the opposite occurring in only 13% of CD patients. This result provided evidence in support of Pavone et al. (1997). Conversely, though, in relation to those authors' findings of impaired visual discrimination, especially in patients non-compliant with the GFD, the CD performance in Perceptual Organisation was certainly not inferior to

that of NC or DM patients in the present study. Furthermore, no evidence was found that dietary compliance significantly affected overall intellectual functioning or specific Index performance. Comparable lack of diminution in the PO Index in DM compared to NCs was also consistent with previous DM research (Ryan & Geckle, 2000).

Deficits in the CD group, compared to NC but not DM patients, in the areas of WM and PS, as highlighted by the proportions of CD patients with VC-WM and PO-PS discrepancies, were not predicted. This outcome was also more prominent than could be expected on the basis of Pavone et al.'s (1997) suggestive, but inconclusive, findings.

Advantages of the present study were use of a sensitive, reliable, and well-standardised cognitive assessment measure and the generation of large sample sizes, each defining aspects which permitted elaboration of the distinct neuropsychological profile which emerged. With a much smaller sample size of less than about twenty cases per group (which characterises almost all other studies in this area), simulated testing using random samples of cases drawn from the present study's full participant pool showed that the mean aforesaid WM/ PS differences lost statistical significance at the .05 level, even assuming homogeneity of variance and similarly sized comparison groups. In less ideal control conditions, upwards of thirty cases would be required to elicit statistical significance, based on trialling incremental analyses using arbitrarily sized samples comprised of real, randomly selected test results.

Initially, it seemed conceivable that elevations in the level of depression and/ or state anxiety, as observed in the CD group, and which may be associated with psychomotor slowing, distractibility and reduced output under time pressure (Kaufman, 1990), may have influenced the observed WM and PS results. However, when BDI-II depression and STAI state anxiety scores were made covariates in analyses of variance, between-group significance remained in relation to the WM/ PS differences, with only a slight diminution of $\underline{F}$ values. Corresponding relative differences in WM and PS between the CD and NC groups were only fractionally reduced. Using a range of other covariates (e.g., quality of life) also resulted in small $\underline{F}$ value decrements and marginal changes in the relative WM and PS means, but in every case the between-group statistical significance was unchanged.

The PS Index result was accentuated in male, compared to female CD patients. This result was in agreement with others' general observations of neurological impairment in both CD (e.g., Ciclitira, 2001) and temporal lobe epilepsy (Briellmann, Berkovic, & Jackson, 2000). Frodl et al. (2002) found that hippocampal changes in patients with a first episode of major depression were "more pronounced in male patients" (p. 1112), further noting that "a substantial number of brain disease seem to affect male patients more severely than female patients" (p. 1115). Explanations of these gender differences include the finding that "estrogen protects while testosterone exacerbates" neurotoxic processes (Nishino et al., 1998, p. 303).

These distinctive patterns of performance were also evident in DM patients, although not to quite the same degree. The WM and PS results translated into lowered mean scores in those indexes in both CD and DM compared to healthy controls but, while the CD-NC result was unequivocal ($p < .000$), the DM-NC result was statistically marginal. In broad terms, the DM performance was approximately mid-way between the CD and NC scores. The hypothesis that the DM group would perform at a significantly lower level than the NC but not the CD group in the WM Index was confirmed.

Although the results pertaining to WM may have neurological underpinnings related to a subtle degradation in hippocampal structure in DM (Hershey et al., 1997), connecting the neuropsychological findings of reduced immediate memory and psychomotor slowing in CD to brain structure is neither straightforward, nor justified on the basis of what is presently known. Unlike in DM, cerebral atrophy, where found in CD, has been more diffuse (Gobbi et al., 1998), although generalised, mild damage to multiple sites has been implicated in psychomotor slowing in a number of other disease processes (Kolb & Whishaw, 1990; Lezac, 1983). Furthermore, the Digit-Symbol subtest of the WAIS-III, on which the CD patients performed especially poorly, is sensitive to mild, generalized deficits (Crowe et al., 1999). More research is needed in this area.

As noted, a plausible alternative explanation for the pattern of neuropsychological results observed in the CD and DM, compared to the NC group, was that higher levels of depression or anxiety, each known to be related to psychomotor slowing, distractibility and reduced output under time pressure

(Kaufman, 1990), may have caused or contributed to the observed WM and PS results. However, given that a significant difference in performance between the CD and NC groups remained after the minimal effect of depression was controlled, alternative explanations must be sought to determine the cause of these subtle, but consistent, neuropsychological changes, which, at least statistically, impinged on about half of the CD sample to at least a mild degree. It may be premature to speculate on the clinical significance of these findings until such time as they are replicated by others, but for a significant minority of the CD sample, the gap between general intellect and WM or PS (or both) was large by any criteria. This result was reflected in anecdotal observations of a somewhat increased frequency of apprehension or general concern expressed to the author about cognitive performance in relation to memorial functioning by CD and DM patients during testing compared to NC participants.

Affective Functioning: Depressive Symptomatology, Anxiety and Anger

The general hypothesis that levels of depression would be higher in CD patients than in people without a chronic illness received qualified support. Across the full CD sample, mean BDI-II depression was not significantly different to healthy participants or people with DM. However, the level of depressive symptomatology was higher in the multisymptomatic CD subgroup than in the NC group. The related hypothesis that depression would be higher in CD patients who were multisymptomatic, compared to oligosymptomatic at diagnosis, was also confirmed. An even finer-grained analysis, after further subdivision of the CD sample, showed that about half of the CD participants who were severely symptomatic at diagnosis ($\geq$ 3 symptoms) were clinically depressed using BDI-II cut criteria at study entry. In around one in five of this highly symptomatic subgroup the level of depression was moderate to severe in intensity.

In contrast to the reports of others (Holmes, 1997; Nielsen et al., 1985; Pellergrino, 1995), symptoms of suicidal ideation or behaviour were not prominent features of the CD or comparison participants in the elevated ranges of depression who participated in Study 1. During participant recruitment, however, the author was contacted by three people displaying varying degrees of suicidality. One person was a

young man without any chronic physical illnesses, who reported a very recent suicide attempt by hanging, but had not come to the attention of a general practitioner or mental health care professional. He received immediate – and ongoing – counselling and was not included in the healthy comparison group, due to more immediate, serious concerns for his personal safety.

The other two people referred to above were CD patients. They consisted of a middle-aged woman with longstanding health problems – possibly CD-related – who was included in Study 1, and a young man who had been diagnosed with CD within days of contacting the author. This man was asleep at the time of his initial meeting regarding study participation and it was not possible to reschedule an appointment. The author was later contacted by his housemate, who had driven the young man to hospital several days later following a disclosure of suicidal intent and detailed plans. Follow-up, involving psychiatric outpatient care arranged at the hospital and provision of information from the Coeliac Society by the author, was implemented, but this man was not subsequently contactable.

Although each of the three cases involve isolated examples of apparently severe depression in CD, the final case is notable in that the CD statistics pertaining to Study 1 do not include his information, as he was unable or uninclined to participate, with his immediate health obviously of paramount concern. However, he is by no means the first example to come to the author's direct attention of troubled young men with CD who fail to avail themselves to support mechanisms such as the Coeliac Society. It is the author's belief that single men, in particular, are over-representative of people with CD who fail to undertake or maintain treatment with the GFD, let alone commit themselves to medical follow-up. Their subsequent invisibility may also lead to underestimates of psychological difficulties amongst males with CD, with their problems less discernible given increased female representation in diagnoses of both mood disorders and CD.

The hypothesis that there would be no difference in the prevalence of Cognitive versus Somatic/ Affective depression within the CD group, or compared to either comparison group, was rejected. It was instead found that the increase in depression in the multisymptomatic CD subgroup was due to an increase in the Somatic/ Affective, as opposed to the Cognitive dimension, of self-reported depression.

This result contrasted with other suggestions (Ciacci et al., 1998), but was in partial support of a previous study's findings of increased subjective depression (D1), psychomotor retardation (D2) and Physical Malfunctioning (D3) in the elevation of Scale 2 on the MMPI, using the Harris subscales (Hallert & Åström, 1982).

The present study's finding of an increased level of somatic rather than cognitive symptoms of depression in those affected and an escalating proportion of depressed patients among those increasingly affected by CD-related symptoms, may help to explain moderate variation in the reported prevalence of depression in groups of CD patients worldwide, over and above the impact of idiosyncratic differences in the choice of measures and local protocols used in data collection. Carefully defining background parameters of CD-related symptomatology and correlates of general health is especially important in CD research given the protean clinical picture and possible diffusion of the significance or strength of future results owing, inevitably, to greater inclusion of minimal-symptomatic cases corresponding to the CD iceberg floating higher in the water. A potential danger is that patients whose health and well-being is complicated by genuine depressive processes – related to CD or otherwise – may not receive specialised clinical attention commensurate with the intensity, chronicity or specificity of mental health difficulties.

Anxiety levels were higher in multisymptomatic, compared to oligosymptomatic, CD patients, as well as NC participants, but neither state nor trait anxiety was higher in the full CD group, compared to NCs. Support for the hypothesis that state, but not trait, anxiety would be greater in the CD group was provided by the observation of an increase in state anxiety in the multisymptomatic CD group compared to NCs, which held after gender partitioning. This result differed somewhat from Addolorato et al.'s (2001) findings of normalised state anxiety following one year's GFD intervention, although a comparison of mean STAI scores (not provided by Addolorato et al.) between the two studies would be useful. However, the present thesis' sample of CD patients was more heterogenous regarding time since diagnosis, so direct comparisons with Addolorato et al.'s longitudinal group may be limited by cross-study variations in the duration of illness.

State, but not trait, anger was also higher in the multisymptomatic CD subgroup in the present thesis compared to the NC group. Considered together, the findings of elevated state, as distinct from trait, anxiety and anger in the multisymptomatic CD subgroup, support Gasbarrini and Addolorato's (1997) suggestion that differences in affective functioning in CD may be attributed to reactive processes, rather than personality traits.

Health Status and Quality of Life

No difference in overall QOL was found between groups. Conforming to a familiar pattern, though, QOL was significantly lower in the multisymptomatic CD group compared to NCs. Furthermore, the oligosymptomatic CD subgroup reported significantly higher QOL than the DM group, but not the NC group. A significant difference also occurred across groups occurred in Leisure/ Recreation Activity, with both the mean CD and DM group scores significantly lower than the NC group score. Further inspection of the subdomain sub-scores comprising this major domain revealed a significant effect across groups, with the NC group significantly more involved in Sports Activity than both the CD and DM groups. Given the utility of regular, vigorous and/ or weight bearing physical activity in the treating both depression and osteoporosis, each major concerns in CD, it would seem prudent to encourage inactive CD patients to participate in sport or exercise suitable to their needs, preferences and capacity.

In the consideration of other subdomain score differences, CD participants reported significantly better Parent/ Child Relations than DM patients. There were no significant male-female differences within any of the three groups, except for Sports Activity in the CD group, in which males reported significantly more involvement, activity and interest than females.

The percentage of participants reporting average to high QOL was equivalent across groups, yet more than twice as many CD and DM participants reported low QOL than NC participants. There was a threefold increase in low QOL in the multisymptomatic CD subgroup, compared to the NC group. These results were similar to the aforementioned depression results, in which there were no mean score differences across groups unless the multisymptomatic CD subgroup was isolated. The hypotheses that a

major domain of QOL, General Well-Being, and a sub-domain, Physical Well-Being, would be decreased in CD, compared to the NC group, was not supported.

In results paralleling the QOL findings, retrospectively self-reported health status was reduced in the multisymptomatic CD subgroup, compared to the NC group, as hypothesised. Across the full CD sample, health status was markedly lower prior to diagnosis in relation to each comparison group. Unlike participants with DM, whose self-rated health status declined slightly pre- to post-diagnosis, a significant increase in subjective health status was reported in the CD group following diagnosis. Nevertheless, the multisymptomatic subgroup still rated their health status following diagnosis (i.e., at study enrolment) as below healthy control levels. Upon gender partitioning, statistical significance only held for females, supporting Hallert et al.'s (2002) findings. The lack of perceived health improvement in the chronic illness comparison group pre- to post-diagnosis was attributed to the almost inevitable, eventual deterioration of health associated with DM, as distinct from CD, in which a remission of health problems is typically observed following consistent adherence to the GFD.

CD Awareness, GFD Compliance and Health Locus of Control

The hypothesis that increased CD awareness and knowledge in CD patients would be positively correlated with greater compliance with the GFD was confirmed, but the scores on the awareness screen developed by the author were not meaningfully associated with depression or self-reported QOL. Ciacci et al. (1998) observed a trend towards an inverse correlation between depression and their patients' level of knowledge about CD, prompting those authors to reasonably propose that "depressive symptoms may prevent patients from reaching a high level of knowledge of the disease or, conversely, that a good level of knowledge about the disease could play a role in reducing the depression level" (p. 249-250). The present study's results do not discount Ciacci et al.'s hypothesis, since a proportion of highly depressed CD patients may have an unusually in-depth awareness of their illness, or vice versa, a result which, if superimposed upon the result corresponding to Ciacci et al.'s hypothesis, would tend to cancel any correlation between CD awareness/ knowledge and

depression across the full CD group.

A possible mix of inter-relationships such as these, which may underpin both direct and circuitous associations between variables, could help to explain the lack of association – *overall* – between GFD compliance and several variables of interest in the present study. As well as pointing to complex relationships, the lack of correlation between dietary adherence and other key indices also highlights the reality of individual variation and fluctuations in attitudinal beliefs at different stages of CD.

There were no differences between the mean MHLOC sub-scores across any of the three groups or in relation to normative data published by Wallston, Wallston and DeVellis (1978). As hypothesised, Internal MHLOC was negatively correlated with BDI-II depression in the CD, DM and NC groups and positively associated with health status since diagnosis and quality of life, but not GFD compliance. The hypothesis that Internal MHLC would be lower and Chance MHLC higher in CD and DM patients, compared to NC participants, was not confirmed.

Depression Prediction Using Discriminant Analysis

Using equally weighted static and dynamic diagnostic, dietary and temporal correlates as predictor variables, DFA was undertaken to determine if a combination of readily available or obtainable clinical information was useful in forecasting depression in CD. This process correctly predicted group membership of three in four CD participants, each classified beforehand as either non-depressed or above the minimum cut score denoting BDI-II depression at study entry. The same result was replicated at sub-threshold levels of depression.

Of major clinical relevance was the high sensitivity and reasonable specificity of this straightforward procedure. Seven out of ten non-depressed CD participants were correctly classified, with identification of more than eight out of ten CD patients who were depressed at study enrolment. Basic clinical information, obtainable without difficulty, was utilised. False positives – comprising just under one third of those assessed as not depressed at study entry – could be screened via psychometric assessment or clinical interviewing and need not pose a serious problem in the use of this system. Therefore, this

accurate, brief, cost-effective procedure, used to identify CD patients most likely to experience clinical depression post-diagnosis, would appear to have significant practical utility as an adjunct in mental health intervention considerations in CD patient care.

In the next chapter, a subset of one-quarter of the cross-sectional CD group – who were newly diagnosed at entry into Study 1 (i.e., at T_1) – are tracked and re-assessed one year later (at T_2), in order to evaluate the nature of changes in psychological functioning, including depression, intellectual ability and QOL over time in response to the GFD.

Chapter 5 – Study 2: Longitudinal One-Year Follow-Up

A major goal of the thesis was to re-evaluate any newly diagnosed CD participants, willing to continue their involvement beyond the cross-sectional study (i.e., at T_1) one year later (T_2), using the full assessment protocol. The purpose of re-assessment was to determine if any of the major domains of psychological functioning that were the subject of the thesis changed over time (from T_1 to T_2) in people with CD, whether in response to GFD treatment, or as a result of other factors, such as changes in mood state.

It was conceded from the outset of data collection in Study 1 that any changes in functioning detected at T_2 in newly diagnosed CD participants already on the GFD at T_1 would not be able to be attributed to the GFD alone, regardless of the degree of detail kept regarding dietary compliance. Furthermore, it was evident that the capacity to ascribe any observed changes to the GFD would proportionately diminish in relation to the elapsed period of treatment with the GFD at T_1. In view of the further anticipated difficulty of capturing CD participants yet to begin the GFD at T_1 within the limitations of the planned recruitment protocol and period of data collection, a large window was initially maintained regarding suitability for inclusion in Study 2 in reference to time elapsed since CD diagnosis and beginning the GFD. This period was subsequently set at *nine weeks or less*, in response to balancing the needs of an early capture of newly diagnosed CD participants in Study 1 with the practical requirement of developing a longitudinal cohort of sufficient size.

Hypotheses

Ten primary hypotheses, pertaining to the longitudinal cohort regarding psychological functioning one year post-diagnosis and GFD implementation, were made on the basis of limited previous longitudinal research, principally four key studies discussed in Chapter 2 (Addolorato et al., 2001; Hallert & Åström, 1982; Hallert, Åström, & Walan, 1983; and Lohiniemi et al 1998). The major hypotheses were:

1. Levels of depression, as measured by the BDI-II, would not change significantly within the CD group between T_1 to T_2 in the absence of any specific interventions other than the GFD.

2. State, but not trait anxiety, on the STAI, would decrease significantly within the CD group between T_1 and T_2 in response to compliance with the GFD.

3. State, but not trait anger, on the STAXI, would decrease significantly within the CD group between T_1 and T_2 in response to compliance with the GFD (an exploratory hypothesis, as no prior research was available).

The preceding hypothesis was made on the basis of overlap between the constructs of anger, anxiety and depression, as well as anecdotal reports of irritability reported in the early stages of CD at or immediately following diagnosis. The expectation was that the level of several measures of mood state, as opposed to traits, would change across several domains. The Profile of Mood States (McNair, Lorr, & Droppleman, 1971; described on pp. 218-220 of this chapter) was used to assess specific dimensions of mood state, namely Tension-Anxiety, Depression-Dejection, Anger-Hostility, Vigor-Activity, Fatigue-Inertia and Confusion-Bewilderment. It was hypothesised that:

4. Tension-Anxiety, Anger-Hostility, Fatigue-Inertia and Confusion-Bewilderment would decrease significantly within the CD group between T_1 and T_2 in response to compliance with the GFD.

5. Vigor-Activity would significantly increase within the CD group between T_1 and T_2 in response to compliance with the GFD.

6. Depression-Dejection would not change within the CD group between T_1 and T_2 in the absence of any specific interventions other than the GFD.

Collin et al (1997) concluded their investigation of dementia and CD with a call for a "cross-

sectional study of the intellectual ability of new and earlier diagnosed CD patients" (p. 288), an exercise undertaken in Study 1. Those authors further noted that "the impact of the gluten-free diet on intellectual ability must be evaluated" (Gobbi et al, 1997, p. 288). In order to monitor retesting effects in the Wechsler Adult Intelligence Scale (at T_2, compared to T_1) the re-assessment of a demographically matched subgroup of healthy controls (drawn from Study 1) was also planned.

Although comprehensive reviews were available regarding test-retest findings using previous Wechsler scales (e.g., Matarazzaro, Carmody, & Jacobs, 1980; Shatz, 1981) and findings pertaining to 1-year intervals using previous versions (e.g., Sirois et al., 2002) and other measures of cognition (e.g., Ivnik et al., 1999), there were no studies available regarding one-year follow-up testing using the Wechsler Adult Intelligence Scale – Third Edition. The possibility of a small increase in IQ due to a practice effect, especially in the Performance Scale, was anticipated on the basis of previous research. Therefore, a small group of NC participants was also re-assessed to monitor the magnitude of any changes due to a practice effect. Given the stability of the construct of global intelligence it was hypothesised that:

7. General intelligence, as measured by the WAIS-III, would not change significantly within the CD group between T_1 to T_2 regardless of compliance with the GFD, over and above a practice effect, if the latter occurred.

8. Mean WAIS-III Index scores would not change, in absolute or relative terms, within the CD group between T_1 and T_2.

On the basis of Lohiniemi et al.'s (1998) findings regarding quality of life, and the author's observations of retrospectively reported changes in perceived health status, it was hypothesised that:

9. Health status would increase within the CD group in response to compliance with the GFD.

10. Total QOL would increase in response to compliance with the GFD.

Method

Selection of Newly Diagnosed CD Participants from Cross-Sectional Pool

Twenty-seven people (14 females, 13 males), who had been diagnosed with CD within nine weeks of enrolment in Study 1 (i.e., first time point: T_1), were selected for assessment at 12 month follow-up (second time point: T_2). These relatively newly diagnosed patients formed the longitudinal CD (LCD) group, who were the focus of Study 2. Although a much shorter duration than nine weeks between CD diagnosis and initial assessment at T_1 was preferable, this generous arbitrary cut-off was established with the practical consideration of generating an adequate longitudinal sample size, given that very few of the first fifty CD participants enrolled cross-sectionally had been diagnosed with CD within a few weeks of Study 1 entry (T_1). Another consideration was the number of T_1 entrants willing and available to be re-assessed.

The proactive recruitment of very newly diagnosed CD participants from mid-2000 was facilitated by immediate identification of new member applications via the Victorian Coeliac Society. This process continued until March, 2001 (final T_1 study entrant). From September 2000, the cut-off point of nine weeks since diagnosis at T_1 had been determined to be inclusive of sufficient CD participants already seen and permitted the development of the eventual longitudinal group of twenty-seven, with the addition of an increasingly greater proportion of newly diagnosed CD participants to the cross-sectional pool, from which the LCD patients were chosen.

Newly Diagnosed CD Group: Demographic Characteristics

For the 13 males and 14 females comprising the longitudinal group, the mean age was 39.0 years (SD = 16.7; range 16-84), only two years younger, on average, than that of the full CD sample and not significantly different according to independent samples t-test at .05 level. Longitudinally tracked females (mean age of 34.4; SD = 12.6; range 18-56) were somewhat younger than their male counterparts (42.5; SD = 19.6), although not significantly so (t = 1.28, p > .05). Mean years of

education for the longitudinal group was 12.3 (SD = 2.4), equivalent to the full CD sample. Females in the LCD group had, on average, completed an extra year and a half of formal education (13.1 years; SD = 2.7) than LCD males (11.5; SD = 1.9), but this was not a significant difference. As noted in the previous chapter, the seventh year of education corresponds to the first year of high school, 12 = the last year of high school and 15 = completion of an undergraduate degree at university.

The extent of matching across all demographic variables within the LCD group by sex and in comparison to the full CD sample was entirely incidental, the overriding consideration being to maximize the LCD sample size via recruitment of newly diagnosed CD participants. Nevertheless, the original consideration given to matching the cross-sectional group, which spawned the LCD subgroup, conferred sex-wise equivalence to the latter subgroup across all demographic variables apart from the minor differences in age and years of education. These are summarized in Table 37, with general intelligence (full-scale WAIS IQ) and body mass index (BMI) at the time of initial inclusion in the study (T_1).

Table 37

Demographic Characteristics (Means/ SDs) at T_1 of Newly Diagnosed CD group (n = 27), the Remaining CD participants (n = 83[1]) and Full CD sample (n = 110)

Demographic	T_1CD (n = 27)	Other CD at T_1 (n = 83[1])	Full Sample at T_1 (n = 110)
Age (Yrs/ SD)	38.3 (16.6)	41.9 (13.5)	41.0 (14.3)
Male	42.5 (19.6)	42.5 (13.7)	42.5 (15.4)
Female	34.4 (12.6)	41.6 (13.4)	40.1 (13.5)
Gender (Male - Female)	13 - 14	31 - 52	44 - 66
Education (Yrs/ SD)	12.3 (2.5)	12.7 (2.5)	12.6 (2.4)
Male	11.5 (1.9)	12.7 (2.6)	12.3 (2.5)
Female	13.1 (2.7)	12.6 (2.4)	12.7 (2.4)

Table 37 (Cont.)

Demographic	T_1CD (n = 27)	Other CD at T_1 (n = 83[1])	Full Sample at T_1 (n = 110)
SES: Low-Med-High (%)	15 - 63 - 22	10 - 58 - 33	11 - 59 - 30
Male	15 - 62 - 23	13 - 55 - 32	14 - 57 - 30
Female	15 - 64 - 21	8 - 60 - 33	9 - 61 - 30
WAIS-IQ (full scale/ SD)	108.1 (15.5)	113.6 (12.2)	112.2 (13.2)
Male	107.0 (14.6)	115.4 (12.1)	112.8 (13.3)
Female	109.1 (16.8)	112.5 (12.1)	111.8 (13.2)
BMI (in kg/ m^2/ SD)	22.1 (3.3)	24.0 (3.6)	23.5 (3.6)
Male	22.1 (1.6)	24.4 (3.2)	23.7 (3.0)
Female	22.0 (4.3)	23.8 (3.9)	23.4 (4.0)

[1] Includes female participant diagnosed with CD 8 weeks prior to being initially seen (T_1) who had moved interstate at time of follow-up 12 months later (T_2) and could not be contacted

All except one participant in the newly diagnosed group were urban dwellers, residing in metropolitan Melbourne or – in two cases – in the city of Geelong. The socioeconomic status (SES) of the CD subgroup longitudinally tracked was comparable to the full CD sample from which it was drawn, with four participants (2 M; 2 F) classed as low, seventeen as middle (8 M; 9 F) and six of high SES (3 M; 3 F). In addition to almost identical matching for SES by sex, fortuitously close correspondence was observed regarding general intelligence, with newly diagnosed males equivalent to new females (mean male WAIS-IQ being 107.0, SD = 14.6, versus 109.1, SD = 16.8 for females).

The mean number of days since CD diagnosis at T_1 was 31.3 (SD = 23.2), with six participants having been diagnosed with CD for a week or less, another three between 8-14 days and a further five between 15-30 days. The remaining participants included in the longitudinal study had been diagnosed with CD between 31-63 days inclusive when initially interviewed and assessed, as shown in Table 38.

Table 38

Number of Days Since CD Diagnosis for LCD Group at T_1: Number and Percentage of Group

	Days since Diagnosis with CD				
	3 days or Less	4-7 Days Inclusive	8-14 Days Inc.	15-30 days Inc.	31-63 Days
N	3	3	3	5	13
%	11.1%	11.1%	11.1%	18.5%	48%

These newly diagnosed CD participants (designated "T_1CD" at time of first assessment and distinct from the full CD group at T_1) represented about one quarter of the full CD sample. They were re-assessed using all test measures and interview procedures within 11-13 months of initial assessment (at that point designated "T_2CD", denoting 2nd time assessed).

The greatest deviation from 12 month follow-up was a participant seen 12 months and three weeks after his first assessment, due to difficulties contacting him and scheduling a follow-up appointment. All other participants were re-interviewed and re-assessed within a fortnight of exactly 12 months later.

Two participants pre-selected as longitudinal study inclusions, having been diagnosed with CD within nine weeks of being first seen, were not re-assessed. One woman diagnosed for two weeks at T_1 contacted the author three weeks later, informing that she had subsequently been diagnosed with diabetes mellitus, in addition to CD. She was removed from the CD sample and her results deleted from the database, being excluded from all analyses in Study 1.

Another female participant who had been diagnosed with CD eight weeks after being first seen by the author had moved interstate within Australia during the subsequent 12 month period. She was unable to be contacted and could therefore not be included in the follow-up study.

All T_1CD participants received a definitive, biopsy-confirmed diagnosis of CD – 93% prior to initial recruitment into study – according to European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) criteria (1990), based on clinical, immunological and bioptical features, as outlined in Study 1. In the case of two T_1CD participants, diagnostic confirmation

occurred within several days of study involvement, with prior serological testing having being highly suggestive of CD at the point these participants were initially assessed.

Histologic normalisation or improvement on the GFD was proven within eight months of dietary intervention in all T_1CD cases included in data analysis, although clinical improvement was unable to be accurately gauged in two people who were asymptomatic at diagnosis. All T_1CD participants were also re-interviewed at 12-month follow-up regarding their response to the GFD and any miscellaneous diagnostic developments. In summary, all T_1CD participants selected for follow-up and included in statistical analysis remained medically confirmed CD patients at T_2.

A breakdown of the number of CD symptoms at diagnosis and pre-diagnosis symptomatic duration in the T_1CD subgroup, compared to the both the remaining CD participants in the full CD sample and the total sample, are shown in Table 39.

Table 39

Number and Duration of Symptoms at CD Diagnosis (as recalled at T_1) of Newly Diagnosed CD Group Who Were Followed Up (n = 27), the Remaining CD Participants (n = 83) and Full CD Sample (n = 110)

	T_1CD (n = 27)	Other CD at T_1 (n = 83)	Full Sample at T_1 (n = 110)
Symptom number at diagnosis; # Cases in each category			
nil (= Asymptomatic)	1 (1 M)	5 (4 M, 1 F)	6 (5 M, 1 F)
1 (= Mild)	9 (6 M, 3 F)	22 (11 M, 11 F)	31 (17 M, 16 F)
2-3 (= Moderate)	8 (3 M, 5 F)	27 (7 M, 20 F)	35 (10 M, 25 F)
4 (= Severe)	9 (3 M, 6 F)	29 (9 M, 20 F)	38 (12 M, 26 F)
Symptomatic Duration (Months/ SD)	66.4 (79.7)	52.1 (78.2)	55.6 (78.4)
Male	69.2 (98.4)	43.0 (82.7)	50.7 (87.3)
Female	63.9 (61.3)	57.6 (75.6)	58.9 (72.4)

Although symptomatic duration in the T_1CD subgroup was not remarkably different from the full CD sample, the proportion of asymptomatic cases was smaller. The author's explanation of this difference was based on a simple, anecdotal observation noted during recruitment. Rather than representing any trend related to contemporary or local CD diagnosis practices, the newly diagnosed CD participants directly invited to participate in the study who actually agreed to involvement were more likely to believe their participation may be personally valuable if they had endured more CD-related symptoms prior to diagnosis. Volunteers at the Victorian Coeliac Society and the author himself observed that people recently diagnosed who were asymptomatic typically perceived there to be less value, including personal benefit, in study participation and generally declined involvement.

All T_1CD participants were re-screened for head injury or neurological impairment and any new medical conditions emerging in the preceding year that may have contributed to neuropsychological impairment or the development of severe psychiatric disorders. None of the T_1CD participants were excluded on the basis of these criteria.

Two CD participants in the longitudinal group were using psychoactive medication at both T_1 and T_2. One male in the longitudinal group had been undergoing long-term treatment for bipolar disorder and was of stabilized mood at Study 1 entry (T_1). His medication regime had changed four months prior to follow-up (antidepressant medication discontinued; replaced with *Epilim*, also known generically as sodium valproate). A female LCD participant had been prescribed with benzodiazepine medication to assist sleep at initial assessment (T_1) but reported reduced dosage and intermittent use at T_2. Two other T_1CD participants had reported previous use of psychotropic medication at initial assessment, but did not report any use in the year preceding follow-up.

The author re-assessed all T_1CD participants between July 2000 and March 2002. Throughout this chapter, the group of 27 people with CD who were subsequently re-assessed are referred to as either the LCD group, or as "T_1CD" participants when the time point is initial study entry (i.e., first assessment) and "T_2CD" participants when the time point is one year later.

Healthy Control Participants

Ten healthy control participants were re-interviewed and re-assessed with the BDI-II, the WAIS-III and QOL Questionnaire within 11-13 months of initial participation in the study. These normal controls followed up (T_1NC participants) were selected from the full sample of 69 healthy volunteers without a chronic illness to match the T_1CD participants as closely as possible across key demographic factors, as displayed in Table 40.

Table 40

Demographic Characteristics (Means, SDs & Ranges) at T_1 of Healthy Controls Followed Longitudinally (n = 10), Compared with Newly Diagnosed CD Group (n = 27)

	T_1NC (n = 10)	T_1CD (n = 27)
Gender (Male - Female)	4 M - 6 F	13 M - 14 F
Age (Yrs/ SD)	39.2 (21.9); Range 18-82	38.3 (16.6); Range 16-84
Male	37.3 (14.2); Range 23-55	42.5 (19.6); Range 16-84
Female	40.5 (27.1); Range 18-82	34.4 (12.6); Range 18-56
Education (Yrs/ SD)	11.9 (2.8); Range 7-15	12.3 (2.5); Range 9-18
Male	12.3 (2.1); Range 10-15	11.5 (1.9); Range 9-16
Female	11.7 (3.4); Range 7-15	13.1 (2.7); Range 9-18
SES: Low-High (# cases)	L=2; Med.= 6; High=2	L=4; Med.=17; High=6
(Male, Female)	(2F); (3M, 3F); (1M, 1F)	(2M, 2F); (8M, 9F); (3M, 3F)
WAIS-IQ (full scale/ SD)	109.5 (11.0); Range 86-125	108.1 (15.5); Range 75-145
Male	112.3 (5.7); Range 104-116	107.0 (14.6); Range 75-131
Female	107.7 (13.8); Range 86-125	109.1 (16.8); Range 88-145
BMI [kg/ m^2]/ SD	22.7 (2.9); Range 17.7-26.0	22.1 (3.3); Range 18.0-31.1
Male	24.5 (1.2); Range 23.2-26.0	22.1 (1.6); Range 18.8-24.3
Female	21.5 (3.2); Range 17.7-25.5	22.0 (4.3); Range 18.0-31.1

Data collected from the T_1NC participants at T_1 and T_2 was compared using single sample (i.e., dependent) t-test to help establish whether practice effects impacted on the re-assessment results of the T_1CD participants, in particular in the case of full scale, index and subtest WAIS-III scores. Although slight increases in IQ upon re-testing are reported in the WAIS-III Manual (p.56), these are in reference

to follow-up periods of 2-12 weeks, much briefer than the 12 month follow-up pertaining to Study 2. The NC group also completed the BDI-II, which served as a check to monitor and guard against any significant changes in mood across the group, or individuals, between $T_1$and T_2, in order to ensure that any changes in the NC WAIS-IQ profile could indeed be assumed to be related to a practice effect, rather than mood changes. Finally, the QOL questionnaire was re-administered as normative data regarding re-assessment with this measure was not available. Using a healthy comparison group, albeit one of limited size, also helped control for any other intangible factors, unrelated to CD or practice effects, that may have impacted on changes between $T_1$and T_2 in the LCD group.

Consent Process, Materials and Measures

Prior to initial assessment with a battery of psychological instruments, and cognitive assessment, each participant in the study read and signed a consent form (Appendix G) in the presence of the author and an independent witness. In addition, participants who had been diagnosed with CD within one-hundred days of being seen by the author were also asked if they were willing to be contacted 12 months later with a view to being re-interviewed and re-assessed, according to exactly the same protocol as outlined in Study 1. All T_1CD participants who were asked about follow-up participation expressed a willingness to be contacted one year from the time of initial assessment.

All participants in the NC group were also asked at the time of their initial inclusion in the study whether they were willing to be contacted one year later with a view to being re-interviewed and re-assessed. Those who expressed willingness had their files marked as potential follow-up candidates. Twelve out of sixty-nine NC participants, well matched demographically to the emerging T_1CD sample, were subsequently contacted and ten were available or obliged to be re-assessed. The twenty-seven T_1CD and ten NC participants re-tested at T_2 were subject to the same battery of measures used at T_1, as described in Chapter 4. These were the demographic and health questionnaire, BDI-II, WAIS-III and QLQ, and, for the T_1CD sample, the CD Awareness Screen, STAI, STAXI, Multidimensional Health Locus of Control Scale (Form A) and an additional measure, unique to Study 2, described overleaf.

Profile of Mood States (POMS)

The Profile of Mood States (POMS; McNair, Lorr, & Droppleman, 1971) is a psychometrically sound, easy to understand, self-response inventory. It has longstanding acceptance as a reliable measure of transient mood state (Peterson & Headen, 1984). From the outset of cross-sectional data collection, the POMS was administered to all CD participants considered eligible for future inclusion in the longitudinal study, by virtue of having been diagnosed with CD for less than one year when first seen. After September 2000, when a cut-off point of nine weeks since diagnosis at T_1 was determined to be the longitudinal entry criteria, administration of the POMS was limited to CD participants in this category. All 27 participants diagnosed with CD for less than nine weeks at T_1 who were included in the longitudinal sample completed the POMS for a second time at follow-up one year later (T_2).

At both T_1 and T_2, CD participants used a 5-point Likert scale to rate the degree to which each of 65 adjectives comprising the POMS described their mood in the preceding week, including the day of assessment. Non-overlapping combinations of these adjectives contribute to six separate factors or mood scales. These scales are Tension-Anxiety (T), Depression-Dejection (D), Anger-Hostility (A), Vigor-Activity (V), Fatigue-Inertia (F) and Confusion-Bewilderment (C). The dimensions consist of between seven (scale F) and fifteen (scale D) unique questions.

According to the POMS' authors, factor T is "defined by adjective scales descriptive of heightened musculoskeletal tension" and factor D "appears to represent a mood of depression accompanied by a sense of personal inadequacy". Anger-Hostility (factor A) represents "a mood of anger and antipathy towards others" (POMS Manual, p.7).

Vigor-Activity (V) is "defined by adjectives suggesting a mood of vigorousness, ebullience and high energy". Conversely, fatigue-Inertia (F) represents a "mood of weariness, inertia and low energy level", classically typical of people with undiagnosed CD. Finally, Confusion-Bewilderment (C) appears "characterized by bewilderment and muddleheadedness" (POMS Manual, p.7).

Summing the scores across all six factors (and weighting Vigor-Activity negatively) provides a single global estimate of affective state, known as the Total Mood Disturbance (TMD) score. Norms and

validity data are unavailable for TMD, but the authors of the POMS Manual encourage research into this variable, which was calculated by the author of the present study.

Different time-periods for ratings have been used in various applications of the POMS. As aforementioned, the author of the present study used the standard one-week reference frame. Reasons for using a one-week period were twofold; 1) to be able to compare the longitudinal CD group experimental data against POMS normative data and 2) because one week was judged to be most appropriate in capturing a consistent picture of mood state soon after and 12 months post-diagnosis.

Norms have been developed for two groups by McNair et al (1971); mixed gender psychiatric outpatients (n = 1,000; 65% female) and undergraduate college students (n = 856; 60.3% female). Correlations between scales ranged from -.49 (F versus V) to .76 (D vs. T, in both cases among female psychiatric outpatients). Most correlations were in the vicinity of .50 to .70, ignoring V, which is negatively weighted when considered in conjunction with total mood scores. McNair et al (1971) note that "correlations between Tension-Anxiety (T) and the other mood scales tend to be lower in the normal group than in the outpatient group, suggesting a clearer distinction between T and other moods in normals" (POMS Manual, p. 9). Internal consistency reliabilities (K-R $_{20}$) of the POMS, measuring the extent to which individual items within the six mood scales measure the same factor, were consistently high. Using psychiatric outpatient normative data, K-R $_{20}$ indices ranged from .87 (factor C) to .95 (factor D).

Test-retest reliability was measured using a sub-sample of the normative psychiatric outpatient group (n = 100; approximately two-thirds female) accepted for treatment at a university medical center psychiatry clinic. They were reassessed on the POMS immediately prior to their first therapy session (with a median time of 20 days; range 3-110 having elapsed since intake) and after six weeks after treatment. The reliability estimates for these periods across the six scales ranged from .66 to .74 (20 day period) and from .43 to .53 (6 week period). McNair et al (1971) noted that the first time frame involved seeking and finding a source of psychiatric treatment for these patients, in itself probably associated with change in emotional states, and that the correlations are therefore "probably lower-bound estimates

of reliability" (POMS Manual, p. 10).

According to McNair et al (1971), the six factor analytic replications in the development of the POMS may be taken as evidence of the factorial validity of the six mood factors. The results were indeed very consistent for the various patient and non-clinical samples and across the different rating time periods.

Using the psychiatric outpatient norms, correlations were reported in the POMS Manual between demographic variables and scale scores. In summary, all POMS factors except A were significantly related to sex, with female outpatients obtaining significantly higher scores than males on T, D, F and C, and males reporting significantly higher V scores. Correlations with age were small, with older patients (primarily those > 40 years) scoring lower on A and C. In female patients, small positive correlations existed between education and each of T, D, V and C, while for males there was a slight but significant positive correlation between education and F. The POMS took participants approximately 10-15 minutes to complete.

Participation Procedures and Protocol

The T_1CD participants were originally interviewed and assessed in accordance with exactly the same procedures as all members of the full CD sample. At the time of follow-up (T_2) twelve months after the initial meeting with the author, precisely the same protocol was adhered to in re-interviewing and re-assessing each participant selected and contacted to be a member of the longitudinal study. A second consent form was signed by all T_1CD participants according to the same procedures used at the time of their original participation. If practicable, re-interviewing and testing was scheduled for the same venue and time of day as occurred at the original session one year earlier.

In view of the relatively small sample size of the longitudinal group, a particularly detailed record at initial and follow-up testing was kept in relation to situational factors that may have impacted on mood state and test results. Foe example, one participant reported being "a bit sadder than normal", having attended a funeral of a relative five days prior to re-assessment, but she was included in statistical analysis.

The ten healthy control (T_1NC) participants who were matched demographically to the T_1CD participants were re-interviewed and re-assessed 12 months following their original inclusion in Study 1 and were also subject to the same protocols. They re-rated their health status and completed all sections of the demographic and health questionnaire except static information (e.g., date of birth). However, these participants were only re-tested with a subset of the full battery of psychological inventories, namely the BDI-II, WAIS-III and QOL Questionnaire.

Statistical Design

In the case of the BDI-II, WAIS-III and QOL measures, in which both the LCD and NC groups were re-assessed, a standard between and within-subject repeated measures ANOVA was used to determine whether changes between T_1 and T_2 in the LCD group were able to be attributed to being on the GFD (or other possible CD-related factors), or whether the change was due to chance or systematic factors unrelated to CD (e.g., re-testing or practice effects). Using this model, the test scores at T_1 and T_2 comprised the within-subjects factor and group (CD or NC) was the between-subjects factor, with the interaction between group and the series of within-subject factors of primary interest.

Where the NC group was not re-assessed, within-group comparisons of the CD participants between T_1 and T_2 were conducted using a paired comparison (or dependent) t-test. Test scores and measures used in the cross-sectional study, plus POMS scores, served as dependent variables. These included various demographic data and major scores on the STAI and STAXI, Health Status, the Multidimensional Health Locus of Control scale (Form A) and the Coeliac Disease Awareness Screen.

Where multiple testing occurred within domains, suitable Bonferroni adjustments were undertaken (i.e., division of alpha by tests executed), as in Study 1. Standard tests of normality and equality of variance (Levene's test) were undertaken prior to each analysis. In some instances, case by case observations about – and feedback from – individual patients were made, where these elucidated any of the findings reported. Finally, several cases were described highlighting the marked improvement in general well-being observed in a number of patients who had been highly symptomatic at diagnosis.

Results of Study 2

Nutritional Considerations: Compliance with GFD and Orthomolecular Findings

In general, the longitudinal LCD group reported initial GFD compliance, which had been sustained at reassessment. Using both scales of GFD compliance (frequency of gluten intake and the brief questionnaire of beliefs, intentions and behaviours), there were no significant changes across the LCD group between T_1 and T_2.

There were also no significant changes in vitamin and mineral supplementation, with 33.3% of the LCD group regular B-group vitamin users at T_1 (and 25.9% at T_2), another quarter being periodic users or regular recipients of partial formulations, such as folate/ iron (25.9% at T_1 and 29.6% at T_2) and half never or rarely being in receipt of nutritional therapy apart from the GFD (40.7% at T_1 and 44.5% at T_2). In summary, there were no systematic changes in supplement use, whether prescribed by a health care professional or initiated by LCD participants.

Coeliac Disease Awareness

The mean scores in the questionnaire reflecting knowledge of CD increased significantly between between T_1 and T_2 in the LCD group ($t = 4.93$, $p = .000$; m.d. = 8.36, SD = 5.1, 95% C.I. = 4.69, 12.02). These results are shown in Table 41. Since the measure was a new scale developed by the author, it was impossible to determine the extent to which this was due to a practice effect.

Table 41

Means, Standard Deviations (SDs) and Ranges of the CD Awareness Screen at T_1 and T_2

	LCD T_1	LCD T_2
N	27	27
Mean (SD)	34.93 (14.7)	43.29 (12.9)
Range	4-60	16-65

The first year of diagnosis with CD involves a great deal of new learning about the GFD and so this result was not unexpected, but the magnitude of change seemed modest, perhaps suggesting that key knowledge about CD and the GFD is acquired between the lead up to confirmation of diagnosis and the

first few weeks post-diagnosis, at the time of a limited series of dietetic sessions for many patients.

Affective Functioning

Minimal Change in Depressive Symptomatology at 1-Year Follow Up

Using a between and within-subject repeated measures ANOVA, there was an insignificant trend towards reduction in BDI-II depression in the CD group between T_1 and T_2 (F [1, 35] = 2.96, p = .094). Mean BDI-II scores for the two groups at T_1 and T_2 are shown in Table 42.

Table 42

Means, Standard Deviations (SDs) and Ranges for BDI-II Scores Across Groups

	CD		NC	
	T_1	T_2	T_1	T_2
N	27	27	10	10
BDI-II				
Mean (SD)	11.04 (6.4)	7.81 (6.2)	8.20 (4.5)	8.0 (3.9)
Range	0-25	0-21	1-14	0-13

Notwithstanding the lack of a significant mean decrease in BDI-II in the LCD group, there was a numerical decrease in BDI-II from T_1 to T_2 in 70.4%, or about seven in ten participants. The decrease equalled or exceeded 6 points in one third, as shown in Table 43. Of the eight LCD participants whose BDI-II score increased, the rise was limited to ≤ 3 points in all but one case.

Table 43

Magnitude of BDI-II Change in LCD Group Between T_1 and T_2

	Increase[1]	Decrease of 1-2	Decrease of 3-5	Decrease of 6-10
N	8	5	5	9
Percent	29.6%	18.5%	18.5%	33.3%

[1] of any magnitude (ranged from 1 to 6 points)

Although the BDI-II score decreased in seven out of ten LCD participants, only 29.6% of the sample

(eight participants) registered an actual shift in their depression rating, using the 4 range cut score scale (i.e., Minimal to Severe, outlined in Study 1 on p.131). For 22.2% (6 participants out of 27) a downward shift of one rating occurred, from Mild to Minimal in 5 cases, and Moderate to Mild in the remaining case. During interviewing, each of these LCD participants corroborated their improvement in mood at re-assessment, attributing the change at least in part to positive improvements in their general health and wellbeing as a result of proper diagnosis of their CD and adoption of the GFD. Four of these patients believed their improved mood state was entirely a result of diagnosis and GFD treatment. In two LCD participants, an upwards shift in depression from Mild-Moderate occurred. In one case, there were several ongoing GI symptoms and frustration was also expressed at the restrictions and pre-planning involved in following the GFD, while in the other, relationship difficulties were being experienced.

Somatic/ Affective – Cognitive Difference

Further analysis of the numerical decrease in mean BDI-II scores in the LCD group indicated that the changes was predominantly underpinned by a decrease in the Somatic/ Affective, as opposed to the Cognitive, dimension of self-reported depression, as shown in Table 44.

Table 44

Means, Standard Deviations (SDs) and Ranges of the BDI-II Somatic/ Affective and Cognitive Factor Scores Across the LCD Groups at T_1 and T_2

	LCD T_1	LCD T_2
N	27	27
Somatic (12 items)		
Mean (SD)	0.72 (0.43)	0.48 (0.41)
Range	0 – 1.50	0 – 1.42
Cognitive (9 items)		
Mean (SD)	0.26 (0.28)	0.23 (0.24)
Range	0 – 1.11	0 – 0.67

State and Trait Anxiety at Follow Up

Both state and trait anxiety, as measured by the STAI, decreased significantly between T_1 and T_2 in the LCD group. The change in state anxiety was greater ($t = 3.27$, $p = .003$, m.d. = 6.30, 95% C.I. = 2.34, 10.25), being significant in both male and female LCD participants after gender partitioning, where as the change in trait anger ($t = 2.41$, $p = .023$, m.d. = 3.00, 95% C.I. = .44, 5.56) was only significant across the full LCD group. Table 45 shows the mean scores at T_1 and T_2.

Table 45

Means, Standard Deviations (SDs) and Ranges of State and Trait STAI Scores at T_1 and T_2

	LCD T_1	LCD T_2
State Anxiety		
Mean (SD)	40.30 (12.7)	34.00 (10.2)
Range	24 – 69	20 – 55
Trait Anxiety		
Mean (SD)	41.78 (10.8)	38.78 (11.3)
Range	24 – 62	20 – 61

State and Trait Anger at Follow Up

Both state and trait anger were lower at T_2 compared to T_1 in the LCD group ($t = 2.08$, $p = .047$, m.d. = 1.37, 95% C.I. = .02, 2.72 and $t = 2.63$, $p = .014$, m.d. = 2.07, 95% C.I. = .45, 3.70). The results are shown in Table 46.

Table 46

Means, Standard Deviations (SDs) and Ranges of State and Trait STAXI Scores at T_1 and T_2

	LCD T_1	LCD T_2
State Anger		
Mean (SD)	13.19 (5.5)	11.81 (3.2)
Range	10 – 26	10 – 22
Trait Anger		
Mean (SD)	20. 37 (6.5)	18.3 (6.1)
Range	10 – 32	10 – 31

Other anger functions measured by the STAXI, namely Angry Temperament, Angry Reaction, Anger-In, -Out, -Control and Anger Expression were also re-assessed in the LCD group at T_2. No significant differences were found at T_2 compared to T_1, following application of a Bonferroni adjustment, setting alpha at .01, to compensate for the five STAXI sub-scores and corresponding tests.

Profile of Mood States

Scores on each of the six POMS scales, as well as a Total Mood Disturbance (TMD) score were computed, as exhibited in Table 47, with negative scores possible on TMD, as occurred.

Table 47

Means, Standard Deviations (SDs) and Ranges of POMS Scores in the LCD Group at T_1 and T_2

	LCD T_1	LCD T_2
N	27	27
Total Mood Disturbance (TMD)		
Mean (SD)	41.63 (34.3)	27.81 (35.54)
Range	-23 to 118	-19 to 132
Tension-Anxiety (T)		
Mean (SD)	11.03 (6.4)	7.81 (6.17)
Range	0-32	0-34
Depression-Dejection (D)		
Mean (SD)	11.03 (6.4)	7.81 (6.17)
Range	0-40	0-43
Anger-Hostility (A)		
Mean (SD)	11.03 (6.4)	7.81 (6.17)
Range	0-38	0-31
Vigor-Activity (V)		
Mean (SD)	11.03 (6.4)	7.81 (6.17)
Range	5-30	8-25
Fatigue-Inertia (F)		
Mean (SD)	11.03 (6.4)	7.81 (6.17)
Range	0-22	0-24
Confusion-Bewilderment (C)		
Mean (SD)	11.03 (6.4)	7.81 (6.17)
Range	2-23	2-21

There was a significant decrease in Total Mood Disturbance (TMD) score between T_1 and T_2 in the LCD group (t [26] = 3.31, p = .004; m.d. = 13.81, SD = 22.9, 95% C.I. = 4.76, 22.86. Caution was taken in interpreting this result, given its status as an experimental variable according to the POMS authors

and the size of the SD. Nonetheless, since TMD is an additive, composite score based on all mood scales, a significant decrease in general mood state was considered notable.

Prior to analysis of results in the six standard POMS scales, alpha level was adjusted to $p = .008$, decided on a Bonferroni basis by considering an overall .05 level for each score divided by the six scale scores. Notwithstanding this conservative approach, there was a significant change between T_1 and T_2 in three of the six scales, namely Anger-Hostility ($t = 2.90$, $p = .008$), Confusion-Bewilderment ($t = 3.14$, $p = .004$) and Fatigue-Inertia ($t = 3.59$, $p = .001$), the only scale in which the change held across gender.

There was not a significant change in Tension-Anxiety (T), Depression-Dejection (D) or, interestingly, Vigor-Activity (V), which may, in a sense, be considered the converse of Fatigue-Inertia. The lack of significant change in Depression-Dejection (D) corroborated the only other previous longitudinal findings involving depression levels after GFD implementation (Addolorato et al., 2001; Hallert & Åström, 1982; Hallert, Åström, & Walan, 1983).

Cognitive Functioning

The means, SDs and ranges of full scale, Verbal and Performance IQ at T_1 and T_2, in both the LCD and NC groups, are displayed in Table 48.

Table 48

Means, Standard Deviations (SDs) and Ranges of Full Scale, Verbal and Performance IQ Scores Across the LCD and NC Groups at T_1 and T_2

	LCD T_1	LCD T_2	NC T_1	NC T_2
N	27	27	10	10
WAIS-IQ (Full Scale)				
Mean (SD)	108.11 (15.5)	111.07 (16.2)	109.50 (11.0)	111.20 (11.7)
Range	75-145	77-143	86-125	87-126
Verbal-IQ				
Mean (SD)	106.30 (13.6)	108.19 (14.0)	109.40 (13.4)	110.00 (13.1)
Range	72-133	74-133	87-133	88-131
Performance-IQ				
Mean (SD)	109.33 (17.6)	112.11 (17.6)	108.50 (12.3)	110.90 (14.0)
Range	81-153	84-146	86-127	87-134

Using a paired comparison (dependent) t-test, there was a significant increase in WAIS-IQ between T_1 and T_2 in the LCD group (t = 2.80, p = .010; m.d. = 2.96, SD = 5.5, 95% C.I. = .78, 5.14), equating to 2.96 IQ points (SD = 5.5), but not in the NC group, in which the numerical increase in IQ was 1.7 points (SD = 3.1) and t = 1.76, p > .10). Importantly, the WAIS-IQ difference between T_1 and T_2 across the LCD and NC groups was not significant (t = .68, p = .499), demonstrating that the increase in mean IQ in the LCD, although statistically significant, was certainly not above a level that could be accounted for by a practice effect, assuming that this was the cause of change in the NC group.

Use of the standard between and within-subject repeated measures ANOVA of course yielded the identical insignificant result (F [1, 35] = .467, p = .499), but the relatively cumbersome, multiple-step alternative approach to the same problem, as outlined above, was undertaken simply to show that longitudinal changes may appear to be significant in the absence of a control group, but change may not be able to be attributed to effects specific to the group of interest, in this case the CD group. Clearly, a practice effect would seem to have contributed to the slight numerical increase in IQ observed in the LCD group. The mean scores, SDs and ranges of change in WAIS-IQ from T_1 to T_2 for both groups are shown in Table 49.

Table 49

Means, Standard Deviations (SDs) and Ranges of Change in WAIS-IQ Across Groups from T_1 to T_2

	LCD	NC
Mean Difference (SD)	2.96 (5.5)	1.7 (3.1)
Range	-10 to 13	-3 to 7

Furthermore, there was no correlation between dietary compliance and variation in WAIS-IQ. It therefore appeared that one year of the GFD, following CD diagnosis, had no impact on overall intellect.

Significant increases in performance in the CD group between T_1 and T_2 were observed in Verbal IQ (t [26] = 2.47, p =.020), Working Memory t [26] = 5.81, p =.000 and Processing Speed (t [26] = 2.47, p =.002). Further analyses were undertaken to determine if any of the mean changes in the WAIS-IQ Verbal, Performance or Index scores in the LCD group (ranging from .92 to 4.52 point increases)

differed significantly from the small increases observed in the NC group. Only one marginally significant difference was recorded in Working Memory, in which the LCD group change of 4.52 (SD = 4.0) differed from the NC group (t = 2.03, p = .050, m.d. = 2.92, 95% C.I. = .00, 5.84). Following a Bonferroni adjustment, however, this result was no longer considered significant.

Health Status and Life Quality One Year Post-GFD Implementation

In analysing any change in perceived health status between T_1 and T_2 it was evident that statistical comparisons concurrently involving the LCD and NC groups were not possible since health was being rated from different perspectives and this was complicated further by the longitudinal protocol. Therefore, a paired comparison t-test was used to compare the CD ratings between T_1 and T_2.

Using this approach, health status "since diagnosis" increased significantly from T_1 to T_2 (t [24] = 2.14, p = .043, m.d. = .48, 95% C.I. = .02, .94). From Table 50 it is also evident that the LCD group mean for retrospectively rated health status "prior to diagnosis" at T_1 and T_2 was identical. Notwithstanding the fact that a number of individual ratings changed slightly, the same result at T_1 and T_2 possibly validates the scale to a certain extent, given that the same time period was being evaluated, albeit from a different time point.

Table 50

Mean, Standard Deviations (SDs) and Ranges of Self-Assessed Health Status Prior to and Since Diagnosis in the LCD Groups at T_1 and T_2

	LCD T_1	LCD T_2
Health Status Prior to Diagnosis		
Mean (SD)	2.56 (1.5)	2.56 (1.5)
Range	1-6	1-6
Health Status Since Diagnosis		
Mean (SD)	4.04 (1.1)	4.51 (0.9)
Range	2-6	3-6

Using between and within-subject repeated measures ANOVA, there was not a significant change in QOL between T_1 and T_2 in the CD group (F [1, 35] = 3.757, p = .061), but a trend was evident.

Mean QOL increased numerically by an average of 6.15 points, which did not quite equate to a meaningful clinical increment within the slightly below average range in which the LCD QOL scores fell, on the basis of Evan and Cope's (1989) interpretative guidelines provided in the QOL Manual. There was no mean numerical change in QOL in the NC group. Total QOL scores in the LCD group at T_1 and T_2 are shown in table 51.

Table 51

Means, Standard Deviations (SDs) and Ranges of Quality of Life (QOL) in LCD Group (T_1 to T_2)

	LCD T_1	LCD T_2
QOL (Total score)		
N	27	27
Mean (SD)	94.48 (25.7)	100.63 (24.4)
Range	54-145	58-140

The number of LCD participants exhibiting high, medium or low QOL from T_1 to T_2 in the LCD was ascertained using T-scores, as shown in Table 52. Chi-square testing showed that the proportions of LCD participants in each of these ranges of QOL was not statistically different at T_1 and T_2, although it was noted that one-third of the longitudinal cohort still exhibited low life quality and less than one ten recorded high life quality on the QOL Questionnaire at one year follow-up.

Table 52

Number (and Percentage) of QOL Scores in the Low, Average and High Ranges for the LCD Subgroup at T_1 and T_2 Using T-Scores

	LCD T_1	LCD T_2
High QOL ($T \geq 61$)	1 (3.7%)	2 (7.4%)
Average QOL ($T = 41$ to 60)	15 (55.56%)	12 (44.4%)
Low QOL ($T \leq 40$)	11 (44.4%)	7 (33.3%)

In the five major domains of QOL there were no significant changes between T_1 to T_2 in the LCD group, with only trends towards an increase observed in General Well-Being and Leisure/ Recreation ($p = .075$ in both cases).

Multidimensional Health Locus of Control

A significant decrease occurred in Powerful Others HLOC between T_1 to T_2 in the LCD group ($t = 2.46$, $p = .023$, m.d. = 1.82, 95% C.I. = .28, 3.36). There was no change in either of the other two HLOC scales; Internal and Control.

Brief Case Reports

The recent history and pre-post results of three highly symptomatic LCD participants are succinctly reported, with their kind permission (but names changed), to illustrate the impact of the GFD where unequivocal improvement was observed. Coincidentally, each person had an initial BDI-II score of 15, placing them in the mild range of depression when first seen in Study 1.

Case 1. Jade, an 18 year old student living at home with her parents and younger brother, was the fifty-third CD participant in Study 1 and the fifth person followed up in Study 2. Her grandparents were all of Welsh lineage. When first assessed, she had been on the GFD for 63 days. At 168 cm and 52 kg, her BMI of 18.4 reflected her slightly underweight status, although this had already improved significantly from 44 kg at CD diagnosis 10 weeks earlier (BMI = 15.6), which Jade recognized as extremely underweight. Although quite slim her entire life, a three-day bout of food poisoning preceded a distinct 12 month symptomatic period pre-CD diagnosis, during which she was subsequently found to be anaemic. The development of GI symptoms, menstrual irregularities, anaemia and gradual weight loss lead to the investigation of CD, after many other medical conditions were ruled out.

Jade presented as shy, somewhat hesitant, and was interviewed while her father browsed for more than two hours in the foyer of the Victorian Coeliac Society Office. She reported feeling much better physically on the GFD, including far less irritable, "jittery" and "edgy", with all GI symptoms having subsided within a few weeks. However, her mild level of BDI-II depression was congruent with a

gloomy demeanour, with an equal endorsement of cognitive and somatic/ affective items. The only question on the BDI-II fully endorsed (Indecision) partly reflected Jade's uncertainty about what she would be doing the following year, as she was awaiting course offers, having just finished high school. Her FSIQ fell within the average range, although WM and PS were each low-average. Self-reported QOL was in the average range and her levels of state and trait anxiety and trait anger were elevated. She rated her health status as "fair" at assessment, compared to "poor" prior to diagnosis.

At one-year follow-up, there was a stark contrast in Jade's deportment; she appeared brighter, healthier-looking, and full of spirit. This was partially reflected in her BDI-II score, which had fallen to 9, placing her in the non-clinical range. Throughout interviewing, a new found sense of joy and humour was also evident which had been absent at the first meeting. Her weight had increased slightly to 56 kg, with no change in height (BMI = 19.8), although Jade expressed discontent with this minor increase. Given that her BMI placed her at the lower fringe of normality and she still appeared very slim, this was concerning. However, she now rated her health status as "very good" (up two increments from "fair") and retrospectively rated her health as "poor" prior to CD diagnosis, the same self-rating noted a year previously. Her trait anxiety score was almost unchanged, trait anger dropped marginally, but her state anxiety and anger scores were significantly lower, now placing her in the lowest percentile compared to normative data, a major shift. Her total POMS mood disturbance score had also halved in value. On the WAIS-III, FSIQ was identical at follow-up, WM had increased 2 points but was still in the low-average range and PS had increased 4 points, moving from the low-average to average range, with neither shift in excess of what may be able to be attributed to a practice effect.

Jade was studying in her chosen field and reported having the energy to work part-time and lead an active social life. She reported strict GFD adherence and felt well supported by her family. Jade said that two inadvertent transgressions had lead to a noticeable reaction within hours of gluten ingestion. This had consisted of abdominal cramping, with loose bowel motions on the first occasion and a headache on the second. Jade had received medical follow-up since CD diagnosis via her general practitioner. Her haematological parameters and menstrual cycle had normalised, but she had not been referred for a

DEXA scan to assess bone mineral density at or post-diagnosis.

Case 2. Len was a diminutive but sinewy 46 year old, self-employed wood carver, born in Scotland, who was married with two adult children. He lived rurally, but met with the author on several occasions while on weekend business trips to Melbourne. He had been on the GFD for 25 days when first seen, but stated that his weight had increased dramatically from 50 to 61 kg in just under one month, with his BMI rising from a gaunt 18.4 to 22.4 (within the recommended range). He had a history of moderate to severe, but unrecognised, CD-related symptoms spanning his entire life and had always been underweight until diagnosis. However, his GI symptoms had intensified in the preceding 12 months, during which he had experienced stress related to legal and financial problems. His was mildly depressed according to the BDI-II, but the elevation was limited to and therefore accentuated in the somatic dimension, with reflecting agitation, increased appetite, tiredness, reduced sexual interest, poor sleep and concentration strongly endorsed. Len also exhibited high scores on the STAI (state anxiety only) and STAXI (state and trait). His FSIQ and all Index scores were in the average range, except his Perceptual Organisation score, which placed him in the superior range.

His QOL score was "much below average", being about three standard deviations below the normative mean, while his POMS total mood disturbance score was highly elevated, being the fourth highest of the LCD group of 27. This seemed to truly reflect his level of distress across multiple psychological/ emotional domains, including Anger-Hostility, Fatigue-Inertia, Confusion-Bewilderment and Tension-Anxiety, in that descending order.

At one year follow-up, Len's appearance had changed noticeably; he had put on another 14 kg (BMI = 27.5), which was significant in the context of his previously lean frame. Like Jade, he expressed a concern regarding his now overweight status, which had the potential to introduce a range of new health problems, especially at his age. On all measures of mood, Len had scores placing him in the normal range compared to significant elevation on most measures a year earlier. There was minimal change in FSIQ and pronounced relative decrements in WM remained.

Case 3. Full-time employed and living in a de facto relationship without children, Jocelyn presented as a

striking but worn-out looking 28 year old woman, with a placid temperament, when first assessed. She had been on the GFD for 25 days and had just returned to work following a three week rest after her CD diagnosis. This had been made following a continuous two year symptomatic period, marked by low iron levels, frequent headaches and self-reported depressive symptoms. Jocelyn indicated that her depression had "lifted" appreciably and her headaches had subsided in the last few weeks but she still felt "exhausted". Her BDI-II score placed her in the mild range of depression, with the somatic items preferentially endorsed, in particular those corresponding to reduced energy, sleep and concentration and increased tiredness. Her weight was 48 kg at diagnosis (BMI = 17.9) and had risen to 50 kg (BMI = 18.6) when first seen by the author. Jocelyn reported elevated mood disturbance, "poor" health status pre-diagnosis ("fair" at study enrolment) and average QOL. Anxiety levels were in the average range, while anger levels were very low. All WAIS-III scores were in the average range.

At one-year follow-up, Jocelyn, reminiscent of Jade, appeared in much better physical shape, rating her health status as "very good", compared with "very poor" pre-diagnosis (a decrease of one increment from her retrospective rating at study entry). Her full BDI-II score fell to just 3 and total QOL rose significantly to "above average". There were no changes in anxiety or anger levels (still average-low), but her total POMS mood disturbance score had fallen markedly. A small rise on FSIQ was of a magnitude attributable to a practice effect, but Jocelyn believed that her clarity of thought had improved greatly.

Each of the three cases presented as severely symptomatic prior to diagnosis, but only Len could be considered a classic CD case, in the sense he reported GI symptoms throughout his entire life. For two people, post-diagnosis weight gain was somewhat disconcerting, a common anecdotal finding observed by the author and often reported by dietitians and general practitioners. Extensive interviewing revealed that each person perceived their CD diagnosis as a relief and life changing event, providing them with the physical energy and motivation to be actively involved in life. However, there were other participants in the LCD cohort who felt that their lives had hardly altered, or who felt burdened by the GFD, or had become aware of new CD-related health problems. The overall impression was one of great individual variation in acceptance and adjustment to life post-CD diagnosis.

Discussion of Study 2: Key Results

Study 2 was a longitudinal analysis, at twelve month follow-up, of affective functioning, cognition and quality of life in a subset of the cross-sectional CD sample used in Study1. These participants had been diagnosed with CD and taking the GFD for less than nine weeks at T_1 (Study 1 entry) and for about one year at their second assessment (T_2). A small group ($\underline{n}$ = 10) of NC participants were also re-assessed twelve months after Study 1 enrolment, principally to monitor WAIS-III re-testing effects.

Affective Functioning and Mood States Profile at Follow-Up

There was a trend, but not a significant decrease in BDI-II depression between T_1 and T_2 in the LCD group, which supported previous findings (Addolorato et al., 2001; Hallert & Åström, 1982; Hallert, Åström, & Walan, 1983). Although a numerical decrease occurred in BDI-II from T_1 to T_2 in the majority of CD participants, which equalled or exceeded six points in one third, only 29.6% of the sample registered an actual shift in their clinical depression rating, using the standard four point cut score scale (i.e., Minimal to Severe) specified by Beck et al. (1996). For 22.2%, a downward shift of one rating occurred, from mild to minimal in five cases, and moderate to mild in the remaining participant. Further analysis of change in mean BDI-II scores indicated that it was underpinned by a decrease in the Somatic/ Affective, as opposed to the Cognitive, dimension of self-reported depression.

During interviewing, each of the LCD participants whose depression score fell subjectively believed that their mood had improved at re-assessment, invariably attributing increased well-being to proper diagnosis of their CD and adoption of the GFD. In two LCD participants, an upwards shift in depression from Mild-Moderate occurred. The restrictions and demands imposed by the GFD and lack of significant health improvements were cited as explanations for their higher level of depression.

Anxiety, as measured by the STAI, decreased significantly between T_1 and T_2 in the LCD group. The change in state anxiety was more pronounced, being significant in both male and female LCD participants after gender partitioning, whereas the change in trait anger was only significant across the full LCD group. Each of state and trait anger were lower at T_2 compared to T_1 in the LCD group, but no

significant differences were found at T_2 compared to T_1 in any of the other anger functions measured by the STAXI (i.e., Angry Temperament, Angry Reaction, Anger-In, -Out, Control and Anger Expression).

Using the Profile of Mood States (POMS) inventory, there was a significant decrease in Total Mood Disturbance (TMD) score between T_1 and T_2 in the LCD group. Caution was taken in interpreting this result, given its status as an experimental variable by the POMS authors. Nevertheless, given that it was an additive, composite score based on all mood scales, a significant decrease in general mood state was considered notable. There was a significant decrease between T_1 and T_2 in three of the six scales, namely Anger-Hostility, Confusion-Bewilderment and Fatigue-Inertia, the only scale in which the change held across gender. There was not a significant change in Tension-Anxiety (T), Depression-Dejection (D) or, interestingly, Vigor-Activity (V). The latter may be considered the converse of Fatigue-Inertia, in which the greatest change was observed.

Neuropsychological Re-Assessment

An increase in mean IQ in the LCD, although statistically significant, was certainly not above a level that could be accounted for by a practice effect, assuming that this was the cause of change in the NC group. Furthermore, as previously noted by Matarazzo et al. (1980), "Wechsler has consistently cautioned that a gain in IQ of about 5 points from test to retest generally should be considered a *practice* or *retest* effect rather than a clinically meaningful change in actual IQ" (p. 95; see also Kaufman, 1990, pp. 107-112, 204-206, and 297-299; Matarazzo, 1972, pp. 241-242; Wechsler, 1997, Technical Manual, pp. 56-61; Zimmerman & Woo-Sam, 1973, pp. 14-19).

There was also no correlation between dietary compliance and increase in FSIQ. It appears, then, that a diagnosis of CD and one year of the GFD, following CD diagnosis, had no impact on overall (i.e., global) intellectual ability. This result is consistent with, and extends, Study 1's results and Hallert and Åström's (1983) finding of "intact intellectual ability in adults after lifelong intestinal malabsorption due to CD" (p. 87) at diagnosis.

The index-specific weaknesses in WM and PS, compared to the NC group, observed in Study 1,

had not resolved at follow-up. These results mirror neurological findings in CD (Hadjivassiliou et al., 1998), in which relatively common neurophysiological manifestations of CD, such as idiopathic ataxia, "may be progressive" (p. 1582) and "reflect chronic irreversible damage to the cerebellum triggered by continuous ingestion of gluten in a gluten-sensitive individual" (p. 1585). On the other hand, those authors' noted that some patients with neurological signs "have shown improvement of ataxia and peripheral neuropathy on a GFD" (p. 1584; see Beversdorf, Moses, Reeves, & Dunn, 1996; Ward, Murphy, & Greenberg, 1985), while "some of our patients in whom the diagnosis of gluten ataxia was prompt have experienced complete resolution of their symptoms after strict adherence to a GFD" (p. 1585). In the present research, there were several LCD cases in which either the WM or PS Index scores, or both, improved significantly between T_1 and T_2, but a systematic increase across the LCD group in excess of a practice effect or relatively greater than the small increases in other Indexes was not observed. Individual scrutiny of the few cases in which significant increases in WM or PS occurred, against demographic or biomedical data and mood state, did not provide any clues as to why isolated increases occurred. They may be attributed to random processes associated with retesting such as a practice effect, chance variation and perhaps unidentified factors.

It may be suspected that in a number of the participants in Study 2, whose CD diagnosis was precipitated by an onset of symptoms soon before gastroenterological referral, adherence to the GFD may protect neural (and consequently neuropsychological) function in those susceptible to gluten-related neuropathic damage. Therefore, a holding of neuropsychological performance could be regarded as a satisfactory outcome.

These results highlight the essence of early detection of CD, even prior to the emergence of characteristic physical signs and symptoms. In this regard, neuropsychological assessment may play a role in cases where cryptic gluten sensitivity may be "an important cause of neurological illness" (Hadjivassiliou et al., 1998, p. 369). Those authors "showed that 57% of patients with neurological dysfunction of unknown cause had serological evidence of gluten sensitivity, compared with 12% of healthy blood donors" (Hadjivassiliou et al., 1996, p. 1582). If Study 1 and 2's results are replicated, it

is proposed that in instances where a neuropsychological test profile includes unexplained relative deficits in WM or PS combined with signs of malabsorption or inexplicable, chronic ill health, investigation of CD should be considered. Whereas in the small number of studies detailing neurodegenerative changes in CD, often the "neurological symptoms came before the diagnosis of gluten sensitivity and CD" (Hadjivassiliou et al., 1998, 1582), in the present thesis GI symptoms were the principal reason preceding referral for investigation of CD.

Health Status, Quality of Life (QOL), and Health Locus of Control

Perceived health status "since diagnosis" increased significantly from T_1 to T_2, while the LCD group mean for retrospectively rated health status "prior to diagnosis" at T_1 and T_2 was identical. Notwithstanding the fact that a number of individual ratings changed slightly, the same result at T_1 and T_2 possibly validates the scale to a certain extent, given that the same time period was being evaluated, although from a different time point.

Neither total QOL, nor the proportion of LCD participants in each of the three ranges of QOL (low, average, high), changed significantly between T_1 and T_2. In addition, one-third of the longitudinal cohort still exhibited low life quality and less than one in ten recorded high QOL at one year follow-up. In the five major domains of QOL there were no significant changes between T_1 and T_2 in CD patients.

The final chapter discusses key outcomes and clinical implications of Study 1 and 2 in relation to previous research, the strengths and limitations of the thesis, the interface with clinical and health psychology, future directions in CD research and suggestions for further study.

Chapter 6: General Discussion

In the past few decades, Italian, Swedish, Finnish and British investigators have traversed the brain-gut frontier in research on CD, with contributions from gastroenterology (see Fasano et al., 2000), and the perspective of the psyche, including psychiatry (e.g., Carta et al., 2002; Pynnönen et al., 2002), neurology (Alaedini et al., 2002; Cooke & Smith, 1966; Gobbi et al., 1998; Hadjivassiliou et al., 1996; Luostarinen, Collin, Peräaho, Mäki, & Pirttilä, 2001), functional neuropharmacology (e.g., Hallert & Sedvall, 1983; Hernanz, & Polanco, 1991), mood (Addolorato et al., 2001; Ciacci et al, 1998; Hallert et al., 1982), nutrition and orthomolecular medicine (e.g., Hallert, Åström, & Walan, 1983; Reinken, Zieglauer, & Berger, 1976), personality (Hallert and Åström, 1982), cognition (Hallert & Åström, 1983; Pavone et al., 1997), and psycho-social permutations, including quality of life (e.g., Hallert et al., 1998; Lohiniemi et al., 1998) and burden of illness (Hallert et al., 2002).

Few research projects concerning the mental aspects of CD have involved the concurrent study of diverse facets of psychological functioning – across affective, cognitive and behavioural domains. The primary goal of this thesis was to assess these distinct, albeit connected, features of psychological life among adults with CD and tentatively calibrate any results against those to be expected in either people with or without a chronic illness involving some parallels (e.g., self-management of diet). A review of the cross-sectional and longitudinal assessment and analysis of these factors, as assessed in Study 1 and 2, is discussed in the current chapter in reference to previous research and implications for future study.

Major Outcomes of Study 1 and 2

The CD sample in Study 1 was heterogenous in terms of clinical severity at diagnosis, with 37 patients best described as oligosymptomatic (one or no symptoms at diagnosis) and 73 designated multisymptomatic (two or more distinct CD-related symptoms). Mean age at diagnosis was 36.9 years (range 1-84, SD = 15.4), occurring after the age of 19 years in 87% of cases, and the mean duration of dietetic restriction was 4.2 years; SD = 7.9 years). The estimated total duration of CD symptoms before

diagnosis averaged 56 months (SD = 78), with no significant gender differences. Symptomless periods were excluded in this calculation, as described in Chapter 4. Most CD participants were decidedly compliant with the GFD. The sample was 99% Caucasian, and, using weightings based on family lineage, 30% English, 20% Irish, 18% Scottish, 16% European (7% German, 4% Italian), 8% unspecified British and 7% Welsh. There was a high lifetime prevalence of comorbid health problems in the CD sample, compared to the NC group, including headache, migraine (37% of CD sample, leading directly to eventual CD diagnosis in two cases), hay fever (47%), asthma (34%), reduced bone mineral density (32% overall, but 58% of those actually tested) and dental enamel hypoplasia (28%). Previous observations that depressive symptomatology is more prevalent in CD were generally supported – if oligosymptomatic cases were omitted – than in people without a chronic illness, even after diagnosis and implementation of the GFD. Overall depression, using the BDI-II (but not the POMS), was higher in the proportion of the CD group clinically multisymptomatic pre-diagnosis, with statistical significance attributed to the contribution of somatic, rather than cognitive, factors.

A trend towards reduced BDI-II depression was observed at one year follow-up in the group tracked in Study 2, with change underpinned by a lowering of the Somatic/ Affective, as opposed to the Cognitive, dimension of self-reported depression. This result, although statistically weak and clinically marginal, may be partly considered in the context of two distinct (but perhaps additive) explanations; the recession of symptoms of physical illness post-diagnosis and the universal observation in depression that "physical symptoms become more prominent as depression becomes more severe" (Glenmullen, 2000, p. 271), but also tend to ebb prior to the resolution of underlying psychological symptoms.

Using the STAXI, state, but not trait, anger was higher in the multisymptomatic CD subgroup compared to the NC group. State anxiety (on the STAI) was higher in the multisymptomatic CD sub-group in Study 1 than in both the DM and NC comparison groups, but significantly decreased within the longitudinal cohort after one year of GFD intervention. Trait anxiety was significantly higher in the CD group compared to the healthy (but not the chronic illness) comparison group. At one year follow-up, a decrease occurred in the longitudinal cohort in fatigue-inertia (which held across gender),

confusion-bewilderment and anger-hostility. A total mood disturbance score, based on the summation of all six POMS subscales, was also found to significantly decrease after one year on the GFD.

At study entry, life quality was significantly reduced in multisymptomatic CD patients compared to the NC (but not the DM) group. Retrospectively self-reported health status was markedly lower prior to diagnosis in relation to each comparison group, across the full CD sample. Unlike participants with DM, whose self-rated health status declined slightly pre-to post-diagnosis, a significant increase in subjective health status was reported in the CD group following diagnosis.

In Study 2, perceived health status increased at one year follow-up (compared to Study 1 entry), verifying the similar retrospective finding in Study 1. However, the multisymptomatic subgroup in Study 1 still rated their health status following diagnosis (i.e., at study enrolment) as below healthy control levels. Upon gender partitioning, statistical significance only held for females. The lack of perceived health improvement in the DM comparison group pre- to post-diagnosis was attributed to the almost inevitable, eventual deterioration of health associated with DM, compared to the remission of health problems generally observed in CD following consistent GFD adherence.

Quality of life scores did not rise appreciably at follow up in the LCD group and one third still exhibited low QOL. Given the somewhat above-average socioeconomic status (SES) of the CD group as a whole, this would appear especially disconcerting if extrapolated to less well resourced patients.

A full intellectual assessment of the CD group, whose mean IQ was in the above-average range, leads to new observations about relative cognitive strengths and weaknesses in CD compared to normative expectations. Reduced working memory and processing speed index scores were observed in the CD group compared to the NC group at neuropsychological assessment, regardless of SES, total IQ, age at study entry, age or number of symptoms at CD diagnosis, time on or compliance with the GFD and mood state. The processing speed deficit was greater in male, compared to female, participants with CD. A mean 3-point improvement in full IQ, not above a level that could be accounted for by a practice effect, occurred within the longitudinal CD group, with residual index-specific weaknesses in working memory and processing speed compared to normal controls.

Discriminant function analysis, using a three and four factor hypothetical damage quotient, was used to establish whether readily obtainable clinical data had utility in distinguishing depressed from non-depressed CD patients. This process correctly predicted group membership of three quarters of the CD group, each classified prior to analysis as either non-depressed or above the minimum cut-score conferring BDI-II depression at enrolment into Study 1. Seven out of ten non-depressed CD participants were correctly classified, with identification of more than eight out of ten who were depressed. The high sensitivity and reasonable specificity of this straightforward procedure may be of major clinical relevance. Since only easily procurable clinical information was utilised and false positives could be screened via psychometric assessment or clinical interviewing, this rapid, inexpensive approach may be applicable in mental health interventions in the care of CD patients.

Relation of Study 1 and 2 Results to Previous CD Research: Clinical Issues

A considerable occurrence of associated health conditions – as found in the CD sample – was not unexpected, but direct comparisons with other cohorts of CD patients was not undertaken due to differences in disease definitional criteria and participant sampling methods. In the present thesis, determination of the existence of most recorded general health conditions was by marking categories (via self-report). Inclusion criteria were broad or open-ended, in all probability inflating cited prevalence figures, which were tabulated for completeness, rather than specific study. Nevertheless, the high prevalence of headache and/ or migraine (just over one in three) was comparable to figures pertaining to a similarly sized, randomly selected Spanish CD sample (Roche Herrero et al., 2001).

The high incidence of bronchial conditions (hay fever and asthma) in the present study must be additionally considered in the context of sharply rising worldwide rates, especially in Australia, as noted almost a decade earlier (Peat et al., 1994). In relation to health-related behaviours, cigarette smoking was reduced by about half in the CD sample compared to Australian community averages, with only 13% CD participants (18% of males; 9% of females) being current smokers and 60% having never smoked (61% of both genders). These results agreed with several recent studies (e.g., Austin,

Logan, Thomason, & Holmes, 2002). Alcohol consumption and vitamin-mineral supplement use in the CD group was unremarkable compared to both the comparison groups and community levels.

Almost one in three participants who were multisymptomatic at CD diagnosis reported at least mild depressive symptomatology at Study 1 entry, an almost identical finding to that reported by Ciacci et al. (1998). Depending on the criteria and cut points used to define depression, a figure of about one in three also appears congruent with other previous reports (see Hallert, 1997, for a review). In relation to Goldberg's (1970) series, Hallert and Åström (1982) reported that the "demonstration of depressive traits in 42% seemed high" (p. 23), but a third of that sample did not follow a strict GFD, in contrast to the group studied in the present research. At one-year follow-up, almost one-quarter of the longitudinal cohort remained at least mildly depressed. These results support the generally held view of an increased prevalence of depression in CD, compared to expected community levels, but are markedly lower than the 57% figure reported by Addolorato et al. (2001) in a newly diagnosed group at diagnosis and at one-year follow-up.

In the present thesis, the mean level of depression and proportion of depressed patients was comparable to the DM group, in contrast to Ciacci et al.'s (1998) findings of 1 in 10 hepatitis C virus-related chronic persistent hepatitis patients experiencing depressive symptoms. This disparity between studies underlines the impact of one's choice of a chronic illness comparison group in CD research, as much as the apparent commonality of levels of depressive symptomatology. Ciacci et al. (1998) concluded "that symptoms are better related to the characteristics of CD than to a general chronic illness condition" (p. 249), in direct response to a statistically higher mean score in their CD group on the Zung Self-Rating Depression Scale (31.8 versus 28.7 in chronic persistent hepatitis patients), and a greater proportion of depressed CD patients. Alternatively, the current research found no evidence for increased depression, other than that which may be attributed to having a chronic illness. Of course, it has also been established that there is a high prevalence of depression in DM (Gavard et al., 1993), with an occurrence at least three times higher than in the general population (Lustman, Clouse, Alrakawi, et al., 1997) and major depression affecting one in five DM patients (Lustman, Clouse,

Griffith, et al., 1997). It may be that some of the mechanisms leading to depression in CD are different than those in DM, but that the end result is a comparably high level of depression in each illness.

That the elevated level of depressive symptomatology observed in the CD group was able to be attributed to the contribution of somatic-affective, rather than cognitive, factors was also contrary to Ciacci et al.'s interpretation that psychological, rather than biologic, mechanisms were "probably...in our sample, predominant" (p. 250). As in Addolorato et al.'s (2001) group of newly diagnosed CD patients, the level of depression, as measured by both the BDI-II and the POMS, did not markedly decrease at one year follow-up in the group tracked in Study 2. Minimal changes were underpinned by a lowering of the Somatic/ Affective, as opposed to the Cognitive, dimension of self-reported depression. The distinction between somatic-affective and cognitive factors, in relation to CD and the findings of the present thesis, has several clinical implications.

The spectrum of mood disorders described in the DSM-IV and ICD-10 include a number of categories potentially applicable to the depressive features observed in CD. Hallert and Derefeldt's (1982) observation that 19% of CD patients attended a psychiatric clinic in the decade prior to CD diagnosis and that "depression was the principal diagnosis and neurotic disorders as a whole...the commonest reason for the granting of a disability pension in the entire celiac series" (Hallert, 1984, p. 98-99), proves that "psychiatric illness may be severe in undiagnosed [CD]" (Hallert & Derefeldt, 1982, p. 17). Findings of refractory depression in CD post-diagnosis (Addolorato et al., 2001; Hallert & Åström, 1982) were also confirmed in the present research, albeit to a lesser degree in a sample of comparatively greater than average SES.

With individual exceptions, the general clinical impression garnered by the specific results obtained at interview in both Study 1 and 2 were of a group of features in the CD group that, at study entry, most often resembled Neurasthenia (ICD-10; WHO, 1993), Dysthymic Disorder (DSM-IV; APA, 1994) or the DSM-IV research criteria for minor depressive disorder (p. 719), recurrent brief depressive disorder (p. 721) or mixed anxiety-depressive disorder (p. 723). The criteria for these proposed categories of psychiatric disorder are tentatively based on thresholds and durations of

symptoms that do not quite reach requisite criteria for MDD, or which do meet the requirements for Anxiety Disorder Not Otherwise Specified. In the case of mixed anxiety-depressive disorder, the dysphoric mood symptoms in this thesis' CD group that most frequently presented – from the pool of 10 (see list on p. 724-725) – were the first four, namely: (1) difficulty concentrating or mind going blank, (2) sleep disturbance, (3) fatigue or low energy, and (4) irritability. These observations were verified by the individual BDI-II item results discussed in Chapter 4. It was noted that all four symptoms were somatic in nature. Exclusionary criteria for the three research disorders included the symptoms not being due "to the direct physiological effects...of a general medical condition" (DSM-IV, p. 725) and criteria "never" having been met for MDD, Dysthymic Disorder, Panic Disorder, or Generalized Anxiety disorder, nor "currently...for any other Anxiety or Mood Disorder" (p. 725).

The case of a medical condition disqualifying the mixed anxiety-depression criteria needs consideration in light of Carta et al.'s (2002) implication of subclinical thyroid disease as a "significant risk factor" (p. 789) for psychiatric disorders in CD, as well as the unresolved question of whether CD itself may qualify as a medical illness directly responsible for depression, via the range of possible mechanisms outlined in Chapter 2. Although associations between CD and thyroid dysfunction are believed to have immunological underpinnings, selenium deficiency is not uncommon in CD pre- and post-diagnosis (Cortigiani et al., 1989; Hinks et al., 1984; Kalita et al., 2002; Ward et al., 1984), so its role in thyroid function (Sher, 2001) in CD should not be overlooked. This is an example of the breadth of subtle consequences of CD that may ultimately manifest in mood disturbance, with the effect of another single nutrient – pyridoxine – on depression in CD previously proven (Hallert, Åström, & Walan, 1983).

As noted in Chapter 2, Carta et al. (2002) found an increased prevalence of Major Depressive Disorder, Dysthymic Disorder, Panic Disorder and Adjustment Disorder, using DSM-IV criteria and the Italian version of the composite international diagnostic interview. In the present thesis, sufficient criteria for current Major Depressive Disorder (MDD; DSM-IV) was lacking in most cases at Study 1 entry. However, based on background information gathered at interview, a case for

retrospective lifetime diagnoses of either MDD or Dysthymia could be made in about four out of ten CD participants across the full sample. One CD patient had a prior diagnosis of Bipolar Disorder (DSM-IV). The question of whether the DSM-IV category "Mood Disorder Due to a General Medical Condition" was applicable to CD was considered, given the increased prevalence of depression in certain neurological, metabolic, endocrine and autoimmune conditions, as well as CD, which may involve multi-systemic degeneration if untreated. However, evidence suggesting the utility of that category was not compelling, primarily due to lack of clarity of a "direct physiological effect", especially in retrospective attempts at diagnosis.

Clinical levels of current BDI-II depression were identified in 21.8% of the CD group (i.e., about one in five people). This figure increased to 22 out of 73 (i.e., 30%) of CD participants when the multisymptomatic subgroup was isolated. Their BDI-II scores ranged from 14 to 34. Of great concern, 47% of those severely symptomatic at diagnosis were clinically depressed. No evidence existed that the Somatic/ Affective dimension of depression was more prominent than the Cognitive dimension in the CD patients whose total scores placed them above the minimum BDI-II cut score, with both or either dimension equally likely to be elevated. However, as noted earlier, the Somatic/ Affective dimension of depression was more prominent than the Cognitive dimension across the CD group as a whole.

Correlational and discriminant function analysis clearly demonstrated that depression in the CD group was strongly associated with static diagnostic factors, especially the number and duration of CD symptoms pre-diagnosis. Although Hallert (1984) noted that in a previous study of psychic disturbances in adult CD (Hallert & Åström, 1982) the "depressive attitudes were not explained by the somatic complaints" (p. 99) a significant correlation was identified between MMPI depression and daily fat excretion ($r_s = .66$) by those authors. Similarly, Lohiniemi et al. (2000) found that "poorer psychological well-being was associated with abdominal symptoms in coeliac patients" (p. 947). In the present thesis, it was clearly evident that both a greater severity and duration of (untreated) illness is associated with a poorer psychological outcome, to the extent that the likelihood of depressive symptomatology post-diagnosis could be predicted in more than eight of ten CD patients (identified as depressed at study

entry), using the aforementioned variables in conjunction with time since diagnosis.

The significantly high level of state anxiety observed in multisymptomatic CD patients in Study 1 (compared to both comparison groups), which decreased within the CD group at one year follow-up, supported the findings of Addolorato et al. (2001). However, it was notable that significance disappeared if the full CD group was used in Study 1 (i.e., if oligosymptomatic CD patients were included). The dissipation of significance upon addition of minimal symptomatic cases may merely reflect sample selection differences, in that it is realistic to expect that the CD patients who volunteered to participate in the present thesis were, overall, less likely to be severely ill as a group, on average, than a series of successive CD patients presenting at a gastroenterology clinic, even if only due to the passage of time since diagnosis.

As reported, trait anxiety was significantly higher in the CD group compared to the healthy (but not the chronic illness) comparison group in Study 1, with the result less pronounced than for state anxiety, again supporting Addolorato et al.'s observations. Overall, 8% of both the CD and DM groups, compared to 4% of the NC group, were using psychotropic (anxiolytic or antidepressant) medication at study entry. Lifetime use was similar across the three groups, varying from 23% for participants with CD, 19% for the DM group and 18% for the NC group. Across the full CD sample, on the basis of clinical interviewing, retrospective lifetime diagnoses of an anxiety disorder sufficient to meet DSM-IV criteria could be made in just over two out of ten CD participants across the full sample, with 14% of the sample retrospectively meeting DSM-IV criteria for a panic attack within the preceding two years. The decrease in fatigue-inertia (significant regardless of gender), confusion-bewilderment and anger-hostility within the CD group at one year follow-up, was reflected in the decreased total mood disturbance score. This result was consistent with anecdotal decreases in irritability and apathy, and increases in energy, reported after GFD treatment.

Neuropsychological findings observed in this thesis partially agreed with limited previous research, in that there were no differences between groups regarding overall intellectual ability (Hallert & Åström, 1983). The comparable level of perceptual organisation ability in the CD and NC groups

contrasted with Pavone et al.'s (1997) and Incorpa et al.'s (1997) findings of reduced visual discrimination ability, a key component, with abstract reasoning, of the WAIS-3 Perceptual Organisation Index. Verbal Comprehension was not significantly different across the three groups of people comprising Study 1. No evidence was found that GFD compliance significantly affected overall intellectual functioning or specific Index performance. The lack of decrements in the PO Index in DM compared to NCs was also consistent with previous studies in DM (e.g., Ryan & Geckle, 2000).

An unexpected result was a reduction of working memory and processing speed (PS) in CD, compared to NC's and normative expectations, but not DM, in which a similar pattern, but less salient deficits were also identified. The CD result was congruent with Pavone et al.'s (1997) and Incorpa et al.'s (1997) conditional findings of relatively lowered short-term memory in children with CD (1997), based on patients non-compliant with the GFD and small sample sizes. A concomitant reduction in PS seen in the CD group in this thesis has been found previously in other degenerative or neuropsychiatric disorders (Wechsler, 1997), but was not noticeable in Hallert and Åström's (1982) consecutive series of 19 CD patients in two tests of reaction time. No other studies were available for comparison.

The PS result was accentuated in male, compared to female CD patients. This result was in agreement with others' general observations of neurological impairment in both CD (Ciclitira, 2001; Hadjivassiliou et al., 1998) and temporal lobe epilepsy (Briellmann, Berkovic, & Jackson, 2000). Frodl et al. (2002) found that hippocampal changes in patients with a first episode of major depression were "more pronounced in male patients" (p. 1112), further noting that "a substantial number of brain disease seem to affect male patients more severely than female patients" (p. 1115). Potential explanations of these gender differences include the finding that "estrogen protects while testosterone exacerbates" neurotoxic processes (Nishino et al., 1998, p. 303).

Although the results pertaining to working memory may have neurological underpinnings related to a subtle degradation in hippocampal structure in DM (Hershey et al., 1997), connecting the neuropsychological findings of reduced immediate memory and psychomotor slowing in CD to brain structure is not straightforward. Federico et al. (1997) reviewed the neuropathological picture in CD.

Those authors described "a cerebellar syndrome characterized by ataxia, marked by speech impairment (associated in some cases with memory loss), myoclonus, fibrillation and hypoareflexia" (p. 266), with "the most consistent neuropathologic changes...in the cerebellum, deep-grey and brain-stem nuclei, and spinal cord" (p. 266). A contrast with the pattern observed in alcoholic and nutritional cerebellar degeneration was noted. They pinpointed the "focal neuronal loss and/ or gliosis in deep-grey and brain stem nuclei" as "mainly involving [the] thalamus, caudate nucleus, globus pallidus, putamen, amygdala, anterior hypothalamic nuclei, periaqueductal grey, corpora quadrigemina, substantia nigra, red nuclei , and motor and sensory cranial nerve nuclei..." and "demyelination of posterior columns" (p. 266). These brain structures are all involved, to a greater or lesser degree, in memory, emotional tone and fine motor movement (Kolb & Whishaw, 1990).

A multi-faceted model of neuroaxonal degeneration in psuedoglutaric aciduria II (see Federico et al., 1997, p. 268-269), inclusive of concepts of nutrient malabsorption, as well as immunological abnormalities, toxins, environmental stress and genetic background, may have utility in discerning the pathologic mechanism in CD-related neurological and neuropsychological impairment. It is feasible that each mechanism may play a role in isolation or in coalition, with "immunologically mediated neural damage" (Hadjivassiliou et al., 1998, p. 1584) perhaps most pertinent – but other factors additive – to the final manifestation. Diffuse, mild damage to multiple sites has been implicated in psychomotor slowing in a number of other disease processes (Kolb & Whishaw, 1990; Lezac, 1983) and the Digit-Symbol subtest of the WAIS-III, on which the CD patients performed especially poorly, is sensitive to subtle, generalized deficits (Crowe et al., 1999). More research is needed in this area.

A plausible alternative explanation for the pattern of neuropsychological results observed in the CD and DM, compared to the NC group, is that higher levels of depression or anxiety, each known to be related to psychomotor slowing, distractibility and reduced output under time pressure (Kaufman, 1990), may have caused or contributed to the observed results. When the effect of depression and state anxiety were independently controlled via covariate analysis, the neuropsychological deficits diminished slightly, but a significant difference in performance between the CD and NC groups remained.

Strengths and Limitations of Thesis

Considered in its entirety, the present study of psychological sequelae in CD is unique regarding cross-sectional sample size, Study 1's use of two comparison groups, 1-year follow-up of a longitudinal cohort and the range of assessments undertaken in both studies. Few studies of neuropsychiatric functioning CD have utilised sample sizes of beyond two dozen cases. Only one of comparable size in this regard also used two comparison groups (Ciacci et al., 1998). Prospective studies are also scarce, with only Addolorato et al. (2001) using an equivalent number of CD patients. The present cross-sectional study's use of large sample sizes, and close matching across demographic variables, permitted the use of parametric statistical procedures, using a similar protocol to Ciacci et al. (1998).

Employment of two comparison groups in Study 1, that is people with DM and people without a definitive chronic illness, was a distinguishing feature of the thesis. The selection of DM patients was motivated on similar grounds to Hallert et al. (2002), although those authors used exclusively type-2 patients. Ciacci et al. (1998) utilised hepatitis C virus-related chronic persistent hepatitis patients as their chronic control condition. Close matching with the CD group across age, gender, education, SES and IQ was achieved in both comparison groups in the present thesis. The CD group was heterogeneous in relation to age at and time since diagnosis, as well as the duration and intensity of CD symptomatology pre-diagnosis, permitting a wide range of intra-group comparisons based on these distinctions. Recruiting a sufficient number or proportion of males has been an issue in previous CD research, but a reasonable gender balance was achieved in the present thesis, with 40% of the sample male, compared to 24% in Ciacci et al.'s sample. Finally, a large number and diversity of psychometric psychological measures were used in each participant's assessment, resulting in a carefully defined and extensively studied CD sample.

Limitations of the present thesis are also acknowledged. A primary consideration is the middle-upper SES of the CD groups in both Study 1 and 2 and, as a consequence of close matching, similar demographics in each comparison group. Unlike Ciacci et al.'s (1998) sample, in which 42% and 11% of patients were of low and high SES respectively, the opposite demographic trend was observed in the

present research, with 11% and 30% the corresponding proportions. The moderately elevated SES of the CD group as a whole was, not surprisingly, accompanied by a somewhat above-average mean IQ score (= 112), which may have been expected to be closer to 100 in truly unselected community samples, notwithstanding the unavailability of Australian norms for the current version of the Wechsler Adult Intelligence Scale. However, it must also be noted that, unlike the U.S. normative sample, the group of patients comprising the CD sample in present thesis was 99% Caucasian and English was the first or predominant language used in all cases. It was presumed that the demographic aspects of the CD group, including slightly above-average mean intelligence (equating to about three-quarters of a SD above the U.S. normative mean of 100), also reflected the method by which the sample was drawn.

Self-selection into Study 1, largely via advertisements in the national Coeliac Society magazine, invitations to participate at a local conference and direct phone solicitation of newly diagnosed CD patients, was neither a systematic, nor necessarily representative process. Unlike other studies which have used consecutive series of CD patients presenting at university or hospital-based gastroenterology clinics (e.g., Ciacci et al., 1998; Hallert and Åström, 1982), selection of CD patients in the present research was comparatively varied and expansive. This was necessary to generate a large sample size within planned timelines and also enabled the development of a relatively heterogeneous group. There was a strong bias towards selection of current Coeliac Society members, who may be assumed to be more conscientious regarding dietary adherence (and health in general) than non-members.

By virtue of volunteering to be involved in the study, the Coeliac Society members who participated may be further hypothesised to have formed an especially conscientious subgroup compared to members who declined. These biases perhaps underpinned several of the aforementioned demographic patterns. Although tight inclusion and exclusion criteria were applied in order to ensure the integrity of the CD and comparison groups, it is possible that, as a result of the recruitment methodology utilised, the CD group is not as representative of CD patients in the local community as may otherwise have been the case if successive patients from a large gastroenterology clinic had been used. The higher than average mean IQ score may provide an indication of this.

Realistically, it is uncertain what effect the selection biases and ultimate composition of this study's CD group (in relation to IQ, SES, etc.) had on key outcome variables such as the proportion of the group who were clinically depressed. It may be speculated that if a greater proportion of low SES participants (as in Ciacci et al.'s 1998 sample) had been included, the frequency or severity of depression may have been greater across the full CD group. However, selection factors unique to this thesis may have had this effect. For instance, people who are more troubled by CD or psychological difficulties, including depression, may have been more likely to volunteer to participate in response to advertisements mentioning "coping" and "quality of life", which were phrases used. Certainly, it was anecdotally observed that the less symptomatic Coeliac Society Members did not appear to avail themselves as often for study participation when directly invited. Ultimately, though, these intangible effects are unquantifiable unless people declining participation are also thoroughly assessed.

What constitutes an appropriate chronic illness comparison group in CD research – or for that matter studies involving many multifactorial illnesses – remains open to debate. A non-GI illness with as many other similarities to CD was preferred. The use of DM patients in the present study was considered a suitable choice based on several commonalities, such as the degree of responsibility on the patient's part in treatment management and the fundamental role of dietary awareness and restrictions. However, DM may certainly be considered "a more serious condition" than CD (Hallert et al., 2002, p. 41). For this reason, people in the early to moderate stages of DM were recruited, with very poorly managed cases or those involving end-state complications deliberately screened out.

The admixture of type-1 and type-2 DM patients in the chronic illness comparison group, although based on both clinical and pragmatic grounds, may also be considered a contentious matter by some observers. Although the reasons underlying this decision have been outlined in earlier chapters, it is conceded that, in spite of clinical similarities and significant overlap across each entity, type-1 and type-2 DM could be viewed as separate disease processes with somewhat different medical, practical and psychological implications. In the present research, though, there were minimal apparent differences between the type-1 and -2 subgroups on the psychological measures employed.

In the end, this justified their combination into one group, enabling parametric statistical comparisons with the CD and NC groups.

An acknowledged flaw is the use of different testing venues (e.g., home versus office), for convenience, in participant assessment. However, minimal biases were identified across groups in this regard, with equivalent proportions of participants from each group assessed at either type of venue. Only one examiner, the author, was involved in recruiting, as well as assessing and interviewing all participants, and was therefore not blind to participants' disease (or health) status.

Finally, it is also acknowledged that neither the DM nor the NC participants were systematically medically screened for CD – or the CD patients for DM – at or following study enrolment. An increased prevalence of CD in DM and vice versa raises the possibility that a very small number of participants with either CD or DM may have been undiagnosed with the other illness, as was discovered in the case of a person subsequently excluded from statistical analysis. Nevertheless, it should be remembered that participants with existing symptoms of the alternate illness were excluded prior to study entry. Also, a significant proportion had been subject to medical investigations of DM or CD as part of their previous treatment, conceivably reducing the likelihood of any participants having both diseases to a very low level.

Implications for Interface with Clinical/ Health Psychology

Hadjivassiliou et al. (1999) portrayed the spectrum of gluten sensitivity as a "many headed hydra" (p. 1710), while Greco (1997) remarked that new cases of CD are increasingly "found by obstetricians, neurologists, psychiatrists, dental surgeons, dermatologists, rheumatologists and endocrinologists" (p. 13). Similar observations were made in previous decades, initially by Barry, Baker, and Read (1974), as cited by Hallert (1984), who noted initial hospital enquiries or admissions by undetected CD sufferers were often in departments other than Gastroenterology or Medicine. These included Neurology, Ear, Nose and Throat or Dentistry, Orthopaedics, Gynaecology, Psychiatry and Dermatology in the Swedish experience. Clearly, adult patients may present for CD-related illnesses in a variety of medical/ health settings and at almost any hospital department, with "psychiatric morbidity a leading cause of disability

among adult coeliacs" (Hallert, 1987, p. 127).

Clinical and health psychologists are therefore likely to directly encounter untreated, newly or distantly detected CD patients in private practice, public hospitals and community health settings, or incidentally in population based research and health promotion campaigns. Behavioural medicine approaches to CD have been proposed by Manikam (2000), who conceptualised the illness as a biopsychosocial disorder, a justifiably all-encompassing description applied in treatment models pertaining to other multifactorial conditions, such as DM (Jacobson, 1996; Jenkins, 1995), GI illnesses in general (Drossman, 1998) and irritable bowel syndrome in particular (Camilleri, 2001).

Increased CD awareness among mental health care professionals would assist the case-finding process, greatly reducing unnecessary and seemingly inexplicable suffering in individual instances, given that mood changes, including depression, appear to be common even in screening-detected, otherwise asymptomatic patients (Catassi, 1997). Since these screening studies demonstrate that CD is considerably under-diagnosed, and disabling psychiatric illness may antedate recognition by years or decades (Hallert, 1984), psychologists should be cognizant that untreated cases may masquerade as apparently refractory depression, anxiety or other psychological conditions during different life stages. Given the latency of CD in many cases, previous exclusion of CD early in life should not preclude re-testing, given that serious complications of CD, such as osteoporosis, have emerged after the disease was "wrongly excluded in childhood" (Barnes & Catto-Smith, 2002, p. 983).

An undiagnosed CD sufferer who is depressed may not improve upon psychiatric or psychological intervention, regardless of the therapy undertaken, if the depressive disturbance is underpinned by gluten sensitivity. Lack of responsiveness to antidepressant medication or, for that matter, other drug resistant psychiatric or neurological conditions (e.g., intractable epilepsy) should prompt investigations of CD as a key element of further enquiry (see Corvaglia, Catamo, Pepe, Lazzari, & Corvaglia, 1999).

Serotonin, a key neurotransmitter long known to be implicated in depressive illness (Åsberg & Bertilsson, 1979), is synthesised in a series of steps that are heavily dependent on micronutrient precursors supplied in the diet (Wurtman, 1979). In untreated CD patients, depression may be secondary

to a reduced neuronal production of monoamines (serotonin, dopamine and noradrenalin), related to the characteristic malabsorption of nutrients essential to neurotransmitter regulation (Addolorato et al., 2001; Challacombe & Wheeler, 1987; Hallert, Åström, & Sedval, 1982; see also Hallert, Mårtensson, & Allgén, 1982; Hallert & Sedvall, 1983). In these circumstances, appropriate treatment obviously hinges on awareness of the nature and possibility of underlying physical illness. On the other hand, the languor and apathy characteristic of CD pre-diagnosis may resemble depressive symptomatology, but psychiatric/ psychological interventions will not correct the somatogenic causes of impaired general health and diminished sense of psychophysical well-being (see Marziani & Pianaroli, 2000).

In either case, suspicion of CD should lead straight to serologic testing by a general practitioner, followed by biopsy in the case of suggestive results. Strong suspicion on clinical grounds, regardless of serology, also necessitates specialist referral, via a general practitioner, for endoscopic, duodenal biopsy (Fasano & Catassi, 2001). Hallert (1997) "recommended that adults seeking care for depression who give a history of unexplained nutritional deficiencies should be routinely screened" for CD (p. 216).

Detection of CD and treatment with the GFD usually improves physical health – often remarkably – if gluten is strictly excluded, as highlighted by the significant increase in health status from pre to post diagnosis noted in Study 1. However, acceptance of and compliance with the dietary restrictions, or even the diagnosis of CD itself, may be difficult for children and require primary parental supervision (Anson, Weizman, & Zeevi, 1990). Parents' understanding of CD, the GFD and young patients' need for follow-up may be enhanced by psychological, as well as medical and dietetic, intervention (Bardella et al., 1990; Jackson, Glasgow, & Thorn, 1985).

Primary difficulties stemming from a reluctance to accept a child's CD diagnosis among parents should not be underestimated, given the "disconcerting finding" raised by Hill et al (2000) that half of the parents in their epidemiological study whose children were identified with a positive serologic result "were unwilling to allow their children to undergo intestinal biopsy" (p. 89). Those authors acknowledged that a general lack of awareness of CD, and, in many cases, symptoms, may have influenced the pervasive disinclination to "accept the concept of a GFD" (p. 89), yet embracing the

GFD is difficult even for very unwell patients in high CD-awareness nations.

In adolescents, and adults as well, such self-regulated regimes are difficult to implement, and adhere to lifelong, without considerable psychologic resources and interpersonal support, as observed or surmised in CD (Barr et al., 1993; Ciacci et al., 1998; Kokkonen, Viitanen, & Simila, 1989), other illnesses (e.g., DM; Hanson et al., 1996) and general medical conditions (e.g., hypertension; Richardson, Simons-Morton, & Annegers, 1993). Peer group pressure is a strong force in adolescence (Barr et al., 1993) and "socialisation may expose the coeliac patient to many potential sources of gluten" (Ryan, 2000, p. 837), with beer consumption in teenage CD patients "often denied" but a common example of either unknowing or "deliberate inattention to dietary guidelines" (p. 837). Unfortunately, beer, pasta and pizza are typically favourite – and socially endorsed – former choices, as noted by Lohiniemi (2001). Ciacci et al. (1998) speculated that the "main psychopathologic dimension of depression (that is, the 'reactiveness') could be related to a restricted lifestyle" (p. 250), which may well sustain depression in CD post-treatment, but does not explain its initial existence.

The GFD may also be especially difficult to subjectively justify and maintain if CD has been identified via screening, rather than on clinical grounds (Fabiani et al., 2000). An absence, mildness or delay of physical symptoms in following an unrestricted or partially GFD is certainly not conducive to adolescent or even adult GFD compliance (Kumar et al., 1988; Mayer, Greco, Troncone, Auricchio, & Marsh, 1991), which depends most strongly on the perceived utility of dietary restriction (Buckfield, 1997). This may partially underlie the reduced retention of new Australian Coeliac members detected via family screening or incidental detection – one year after joining – compared to an increased rate of overall, annual membership renewal (G. Price, personal communication, July 9, 2002).

An interesting result in the present thesis was the unsubstantiated hypothesis that a lower GFD compliance would be associated with greater depression (or, equally, that depressed patients would be less compliant). This was expected to be one of the key damage quotient variables, but its contribution to variance in the prediction of depression was negligible. Although there were numerous *individual* cases in which poor dietary adherence and lowered mood were observed, there were almost

as many cases in which the opposite trend was observed (i.e., high compliance comorbid with significant depression). A close, case-by-case, perusal of the database suggested that the frequency of the latter coupling (i.e., high GFD compliance + elevated depression) statistically negated any systematic association in the expected direction, based on hypothesised underlying relationships (i.e., high compliance => lower depression, and vice versa). Given that there was a strong inverse association between perceived health status and depression in this study, it is not inconceivable that people who were mildly to moderately depressed were more conscientious about following the GFD in an effort to improve their health. Depression not infrequently involves ruminative and obsessional qualities, with the possibility in some patients of increased vigilance in relation to avoiding gluten and strict dietary adherence. Indeed, there were individual cases in which poor health and/ or elevated depression appeared to be channelled towards an almost fanatical adherence to the GFD.

Clearly, the level and type of depressive symptomatology must be individually evaluated. Health care professionals must differentiate between a lack of – or lapses – in motivation, in relation to GFD adherence, versus excessively strict compliance, in terms of a potentially distressing tendency of some patients to be hypervigilant. A fixation with dietary restrictions in the GFD may be disadvantageous in regard to social integration and interaction, leading to or exacerbating social avoidance. Fortunately, the restrictions characteristic of CD may be not be as detrimental to social functioning in adolescence as the effects observed in IBD and chronic liver diseases (Calsbeek et al., 2002).

It would seem constructive to be able to declare, unequivocally, that greater dietary compliance in CD automatically lowers the risk of depression, or that lowering depression in CD results in greater GFD compliance, leading to better health outcomes. However, the results of this thesis suggest that the relationship between depression and GFD compliance is a complex one, perhaps most appropriately assessed and managed clinically on a case-by-case basis.

Depression and other psychological disorders in CD often persist in spite of dietary intervention, for many reasons. These may include later feelings of inferiority and increased vulnerability stemming from early events of undiagnosed CD (Hallert, 1982) and secondary psychological reactions to the

dietary and social restrictions peculiar to the illness (Ciacci & De Rosa, 1996), as distinct from the consequence of having a chronic illness per se (Addolorato et al., 2001). Gasbarrini and Addolorato (1997) speculated that the elevated ('reactive' type) state anxiety and depression found in a very small central Italian CD series compared to healthy controls – at levels indistinguishable from irritable bowel patients – could indeed be secondary "to the emotional reaction to the symptoms of disease" (p. 353), additional to reduced neurotransmitter activity.

Residual nutritional deficiencies in CD (Hallert, Åström, & Walan, 1983), possible nutritional inadequacies of the GFD itself (Hallert, Lilliecreutz, et al., 1999), apprehension of irretrievable loss of physical health, and risk or fear of complications, which increase with age at diagnosis and duration of gluten exposure (Lanzarotto et al., 2000), may all contribute to psychological morbidity after diagnosis. Depression "left unrecognised may complicate the clinical course and contribute to persistent feelings of ill-health despite [GFD] adherence" (Hallert, 1997, p. 216).

Conversely, unintentional gluten ingestion is an important consideration in cases of enduring mental as well as physical ill-health in those apparently adhering to the GFD (Fasano & Catassi, 2001), with even the trace amounts detectable in "gluten-free" diets defined traditionally by the World Health Organisation's Codex Alimentarius standard possibly responsible for the continuing symptoms seen in some CD patients (Faulkner-Hogg, Selby, & Loblay, 1999).

Resentment or bitterness at not being diagnosed earlier in life (e.g., in short stature men), or simply being different, plus the perceived burden of illness, can be other explanations for reduced subjective health and life quality in CD, perhaps especially so in young children (Kolsterman, Koopman, Schalekamp, & Mearin, 2001) and female, compared to male, CD patients, with social context especially germane (Hallert et al., 2002). Simply feeling different was recently found to be positively correlated with a cluster of negative emotions (sadness, anger and fear) in Italian CD patients (Ciacci et al., 2002). Another gender- and GFD compliance-related issue worthy of exploration following dietary treatment, intestinal restitution and restored absorptive function, is greater than desired weight

gain (Barr et al., 1993), especially in female CD patients, and different aspects of body image, which may be pertinent in both males and females.

An irrepressible appetite or the capacity to consume unlimited portions of food, but an inability to put on weight, may be replaced pre-post diagnosis by an unintended, rapid or unmanageable increase in body mass index (BMI) and novel GI symptoms (e.g., constipation). Reckless abandon regarding caloric intake may be superseded by hypervigilance regarding the presence of gluten. Thus, some preconditions conducive to the development of eating disorders, which, like CD, are under-diagnosed (Jones, Lawson, Daneman, Olmsted, & Rodin, 2000) may exist. Indeed, the "cycle of weight loss at disease onset and subsequent weight gain" with treatment and "trend towards a higher BMI, and dietary restraints" (Snoek & Skinner, 2002, p. 266), seen in DM, is also applicable to CD. At present, though, the coexistence of eating disorders and CD is a relatively unexplored area of research.

In the present thesis, mean BMI was comparable across the three groups of participants, at 23.5 for the CD group, 24.5 for the NCs, and, not surprisingly, slightly higher at 26.3 for the DM patients. In the CD group, BMI had increased just over one point from the time of diagnosis, so the average change was minimal. This is reflective of the contemporary rarity of severe weight loss as a symptom of CD pre-diagnosis, especially in adult-detected CD patients, unlike "in the early days", when emaciation was a "cardinal sign" (Hallert, 1984, p. 92).

Bulimia was one of the "main neuropsychiatric complaints taken into consideration" by Bottaro et al. (1997, p. 353), in a retrospective clinical study of all 550 paediatric CD patients (aged 7 months to 17 years at diagnosis; mode around second year), detected in their department from 1985-94. However, it was a primary or associated "psychic complaint" (p. 354) in only two and five cases respectively, among all patients in that series. Furthermore, it was unclear whether the neuropsychiatric complaints were considered only at the time of diagnosis and also how the assessment was undertaken.

References in the CD literature to anorexia (said by Bottaro et al. to be present in 50% of CD cases) typically relate to unintentional weight loss due to malabsorption in untreated CD, and perhaps occasionally apathy, rather than deliberate food restriction in the sense of anorexia nervosa (AN).

However, CD diagnoses prior to and following the onset of AN have been reported in Italian women (Ricca, Mannucci, Calabro, Bernardo, Cabras, & Rotella, 2000). Those authors discussed two case studies illustrating the "complex relationships" between CD and AN, proposing that "the onset of CD could have exacerbated the clinical symptoms of AN" where CD was identified after AN onset and that "the dietary restriction could act as trigger for the eating disorder" in the patient in which AN was identified after CD diagnosis (p. 119). Heightened susceptibility to the development of eating disorders in CD cannot be ruled out in the absence of epidemiological research. Several circumstances certainly appear ripe for the evolution of underlying emotional factors associated with an obsessive concern with food consumption and one's weight, which is subject to various dynamics pre-post diagnosis.

Recent reports of a marginally increased incidence of cosmetic surgery in CD patients pre-diagnosis versus controls (Ciacci et al., 2001), which those authors related to an "impaired psychological profile" (p. 2206), perhaps also point to the possibility of disturbed body image in CD. It may be hypothesised that in men with CD, underweight status prior to diagnosis may lead to a disturbed body image, whereas in women, problems are more likely to emerge following diagnosis as a result of increased weight or overweight status, because of enhanced caloric retention.

Ideally, psychologists should be alert to different types of psychological complications which may be attributable to underlying physical conditions such as CD, even after diagnosis, and mindful of the importance of timely specialist medical intervention and management if doubt exists about the source of a particular health-related problem. Evidence is accumulating that having CD may activate disordered adjustment to life stressors, potentiating reactive processes in depression or anxiety stemming from unrelated causes or events, over and above the changes expected in people without a chronic illness, and possibly specific to the pattern of psychological sequelae in CD (Carta et al., 2002; Gasbarrini & Addolorato, 1998). Making these distinctions in treating a depressed patient, who also happens to have CD, or vice versa, should be contingent on the evaluation of clinical, histological, dietary and nutritional parameters, as well as psychosocial, cognitive-behavioural or psychodynamic considerations.

Future Directions

The prevalence and impact of CD on the physical and mental health of Australians needs systematic investigation. In Italy, a high CD-awareness nation, the cost of long-term complications of CD and malignancies clearly exceed diagnostic expenditure (Greco & Percopo, 1996). A recent study (Sandler et al., 2002) highlighted the cost burden of GI and hepatic illness in the United States, with the direct estimated cost of all digestive disease in that nation equal to a fifth of the Australian gross domestic product. It was concluded that establishing the prevalence of these diseases was a key task. Fasano (2003) recently reiterated that the CD prevalence is approaching 1% in general populations worldwide. He argued a strong case for screening Europeans and North Americans for CD, based on CD meeting all five WHO mass screening recommendations. These criteria include the target disease being common and causing significant morbidity, early clinical detection difficulties, the existence of highly specific/ sensitive screening tests, available treatment (i.e., GFD), and lack of recognition resulting in severe, difficult to manage complications (e.g., osteoporosis, lymphoma). In 1996, Australia's federal government, in consultation with each State, identified national health priorities (Wall, Wood, & Holman, 1999). These were determined on the basis of the major existing and projected medical and public health problems. The inclusion criteria included morbidity, mortality and the cost, at different levels, to the Australian community. The original list of five was:

(1) Cardiovascular Health

(2) Cancer Control

(3) Injury Prevention and Control

(4) Mental Health

(5) Diabetes Mellitus

After intense lobbying by many community groups for the inclusion of a number of other disease entities or systemic health problems, Asthma/ Respiratory Health and Arthritis/ Musculo-skeletal Disease were recently added. Stated goals of the National Health Priority Initiative are "reducing the burden of illness", focussing on "common health determinants" (Wall, Wood, & Holman, 1999, p. 47) and supporting "early detection" (p. 48).

With these goals in mind, a quick inspection of the dynamic priority list (of seven categories) is of great relevance in connection with CD. A strong case can be made that, in four out of seven disease entities, the prevalence of CD is significantly increased, the exceptions possibly being Injury Prevention/ Control, Asthma/ Respiratory Health and Cardio-Vascular Disease, notwithstanding Hallert et al.'s (1999/ 2002) observations of increased blood homocysteine in CD, a major risk factor for cardiovascular disease, an increased risk for CD in end-state heart failure (Prati et al., 2002) and the author's observations of one third of the CD group in Study 1 having a lifetime history of asthmatic symptoms.

As discussed in Chapter 1, where CD is undetected and consequently untreated with the GFD – or not optimally managed – the prevalence of the four other associated health problems increase further. The risk of CD in association with the seven disease entities identified in the ongoing National Health Priority Initiative is displayed in Table 53.

Table 53

Risk of CD in Relation to Health Priority Areas and Documented Association

Risk	Priority	CD Association
X	(1) Cardiovascular & Stroke	Raised homocysteine (Hallert et al., 1999/ 2001)
XX	(2) Cancer Control	Upper GI lymphoma risk increased
XX	(3) Diabetes Mellitus	Proven association (Holmes, 2002)
X	(4) Asthma/ Respiratory Disease	History in 34% of CD patients in Study 1
XX	(5) Mental Health	Depression/ anxiety elevated; Life quality lower
-	(6) Injury Prevention & Control	Nil
XXX	(7) Arthritis/ Musculoskeletal	Osteopaenia present in most new CD diagnoses

XXX Strong Association

XX Increased Prevalence

X Weak, Hypothetical or Unconfirmed Association

It should also be recalled from Chapter 1 that CD is frequently implicated in occult cases of neurological impairment, as well as gynaecological and obstetric disorders, including unexplained infertility, which collectively impact on the quality of life of hundreds of thousands of Australians.

Conclusion

The present thesis is unique in CD research in its concurrent use of a very wide range of psychological assessments, a large, well-defined and gender balanced adult CD sample, the utilisation of two comparison groups and a combination of cross-sectional and longitudinal protocols. For each of these reasons, a number of important results were calculable and firm conclusions were able to be drawn. Having established that the prevalence of depression in this thesis' CD sample was only greater than in healthy controls when CD cases physically oligosymptomatic pre-diagnosis were omitted, four disease correlates were identified that were hypothesised to collectively form a quartet of factors expected to impinge on a CD patient's trajectory to depression post-diagnosis.

A damage quotient model was tested in a series of discriminant function analyses. The most successful function was able to identify more than eight out of ten CD patients who were depressed at study entry, regardless of whether a clinical or sub-threshold level of depression was set as the independent variable, based on three readily procurable items of information. These were the severity of illness, duration of CD symptomatology pre-diagnosis and, to a lesser degree, time since diagnosis. This actuarial approach to detecting the risk of depression in CD would appear to be highly relevant at the time of diagnosis, in conjunction with other standard interventions. The timely diagnosis and treatment of depression requires the expertise of a mental health professional, whose involvement may be ideally considered close to the time of diagnosis.

Detection of subtle, but systematic, neuropsychological deficits in working memory and processing speed in CD highlighted the need for highly sensitive assessment tools in clinical practice and sufficient sample sizes to ensure adequate power in quantitative research, in identifying these deficits. A similar pattern of relative neuropsychological decrements were also found in DM, with different mechanisms (e.g., chronic hyperglycaemia and acute hypoglycaemic episodes) possibly involved. In both the CD and DM groups, a higher level of each of depressive and CD or DM-related symptomatology, while not changing the significance of these results if factored out, exacerbated the extent of psychomotor slowing and impaired verbal memory.

Each of these deficits, whilst often mild from a clinical perspective, were acutely felt by individuals, with complaints about memory the most commonly expressed misgiving during neuropsychological testing in the CD group. It must be remembered that the CD group utilised was of above average intellect and SES, factors which may, in the present thesis – and previous studies – have served to mask rather than accentuate findings of specific neuropsychological deficits, including the distinct pattern found identified in Study 1. Each study detailed in this thesis highlighted that the psychological sequelae observed in CD are typically juxtaposed with markers of clinical severity at diagnosis and physical symptomatology post-diagnosis. For the majority – but not all – of those newly diagnosed, mood state ameliorates in concert with recession of physical symptoms in response to a strict GFD sustained over the passage of time. However, the specific neuropsychological weaknesses – once established – may be relatively refractory to dietary change.

Increased symptomatic duration prior to diagnosis significantly impacted on the degree of impairment, underlining the essence of early detection. In Study 1, there was typically a lag of many years from patients' recollections of initial CD-related symptoms to the time of diagnosis. Furthermore, self-reported depression affected about one third of multisymptomatic CD participants at study enrolment and remained elevated in almost one-quarter of all newly diagnosed CD study entrants at one year follow-up. Finally, multisymptomatic members of this longitudinal group did not quite attain, on average, the same quality of life as healthy comparison participants, with a significantly greater proportion reporting low life quality. These results reinforce the earlier proposition that psychological intervention should be considered following CD diagnosis, in conjunction with ongoing specialist medical advice and expert dietary assistance.

If epidemiological considerations of CD are illuminated by conceptualisations of an iceberg model, awareness of general well-being, including the psychological sequelae, may be likened to the notion of an undiagnosed patient floating on their back in ocean waves, obscured by spray. The spine would be submerged and situated at the deepest point, perhaps symbolic of reduced bone density, one of the most common but regularly undetected, underlying physical problems at

diagnosis. In cases of moderately severe illness, the distended gut is likely to be visible from the water surface, even through the haze. The face may lie at the same level as the body, but appear pallid, and is susceptible to descending below the water's surface and out of view without constant arm movement, just as psychological concerns often go unnoticed. In rougher seas, some patients must paddle with their legs and flail their arms to avoid total submersion, yet even their spirited activity is often unseen from above and their desperate calls for help frequently unheard. When depression is the major sign of ill health in CD, the potential for health care practitioners to overlook the underlying physical cause of illness is ever present. Even after diagnosis, clinically noticeable depression often remains an obstinate problem. The modest, but consistent, pattern of neuropsychological test performance decrements identified in this thesis requires further exploration, whilst the quality of life of patients is of great importance in considerations of their immediate and long term well-being. For the entire person to remain buoyant and thrive, catching sight of, recognising and attending to parallel aspects of health – the physical and the psychological – is indispensable in CD.

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