# Different dietary gluten restrictions and symptom expression in a large population of people with coeliac disease.

**MICHELLE STUART**

**Supervisors: Ms Kim Faulkner-Hogg**
**Dr Robert Loblay**
**Dr Warwick Selby**

**Allergy Consulting Rooms and the AW Morrow Gastroenterology and Liver Centre**

**Royal Prince Alfred Hospital**

## DECLARATION

1. I, **Michelle Stuart**, hereby declare that none of the work presented in this essay has been submitted to any other University or Institution for a higher degree and that to the best of my knowledge contains no material written or published by another person, except where due reference is made in the text.

2. The studies described in this essay were approved by the Central Sydney Area Health Service Medical Ethics Committee (RPAH Zone), and all subjects were anonymous.

Signature…… Monday 6th June, 1997.

## ABSTRACT

**The treatment for coeliac disease is a gluten free diet. Whether it is safe for coeliacs to ingest the minute amounts of gluten often found in gluten free diets is still controversial. The WHO/FAO Codex Alimentarius allows 0.3% protein from gluten containing grains in foods labelled as gluten free. This is thought to be the standard upon which gluten free diets are based in research studies and which is adopted as practice in many countries including Australia in the past. In March 1995 the Australian standard for gluten free food labelling changed from this WHO guideline. Currently a food cannot be labelled gluten free if it contains any detectable gluten. This study set out to examine the dietary patterns in a large population of subjects with coeliac disease and to relate any symptoms being experienced to the different levels of gluten restriction. This may help to determine if the dietary advice given to all coeliacs should now fall in line with the new Australian food standard for gluten free food labelling. Of the 1672 questionnaires sent to members of the Coeliac Society of NSW, 965 (58%) were returned. This questionnaire asked for a graded description of the severity and frequency of gastrointestinal symptoms commonly experienced by coeliacs, and other less commonly related symptoms. Food brand selection questions were asked so classification into one of three diet categories could be made. The categories were: overt gluten ingestion; trace gluten ingestion in accordance with the old Australian food standard and no detectable gluten ingestion as in the new Australian guidelines. Of the 71.9% of the respondents with trace gluten ingestion, 73% stated that they were not aware of ingesting gluten. After diagnosis and commencement of gluten restriction, a large proportion were still experiencing symptoms but generally found them to be less frequent and less severe. The frequency and severity of symptoms was greater at gluten intakes above that allowed in the old Australian gluten free diet. A comparison of symptom expression between the trace gluten and no detectable gluten diets revealed that only 2 of the 13 symptom categories were significantly different ($p<0.01$). Constipation was more severe( $p=0.0051$) in the trace gluten group, while diarrhoea occurred more frequently in those consuming no detectable gluten. The lack of differences in symptoms seen between the trace gluten and no detectable gluten diet categories would suggest that the less restrictive trace gluten diet may be appropriate for some coeliacs.**

## INTRODUCTION

Coeliac disease is a malabsorptive condition wherein the small intestinal mucosa is reversibly damaged by ingestion of gluten. Its prevalence varies geographically and it has been found to be as common as 1/300 in Scandinavia[1] and Ireland[2]. Individuals are genetically predisposed to this disorder[3]. Symptoms are highly variable such that no single group of symptoms can be regarded as characteristic[4]. Coeliac disease can affect many body systems but classically the gastrointestinal symptoms are recognised; nausea, vomiting, abdominal pain and cramping, diarrhoea, constipation, bloating and flatulence. Weakness, fatigue, weight loss, mouth ulcers, anaemia, muscle cramps, bone pain, headaches and dermatitis are some of the other symptoms that may occur[5], but are less readily recognised as coeliac disease. Although dermatitis herpetiformis can occur alone, it is the most common condition associated with coeliac disease and is treated similarly[6].

Blood testing for antigliadin antibody, anti-endomysial antibody and antireticulin antibody levels do not diagnose coeliac disease, but they are useful screening tests[7]. Currently coeliac disease can only be accurately diagnosed by the detection of small intestinal mucosal damage from a small bowel biopsy. After a period on a gluten free diet, a follow up biopsy should show a recovery of the villi. In some diagnostic cases a gluten challenge followed by a third biopsy, to show villous damage once again, is used[8].

The recommended treatment of coeliac disease is a life long gluten free diet. Gluten comprises 80% of the total protein in wheat, but the term is also used collectively to describe the gut damaging prolamines of rye, barley and oats[9]. All these grains are generally excluded on a gluten free diet. Wheat gluten can be fractionated into four protein components; albumin, globulin, glutenin and alcohol soluble gliadin. Gliadin consists of four fragments; $\alpha$, $\beta$, $\gamma$ and $\omega$. The gliadins have been shown to contain the toxic element of the whole gluten molecule[10]. The wheat prolamin, gluten, is considered to be the most coeliac toxic, closely followed by the rye prolamine, secalin. The barley prolamine, horedin, is less so[11]. The toxicity of the oat prolamine, avenin, is somewhat controversial[12]. Grains and other cereals which are not noxious for coeliacs such as rice, corn, buckwheat, millet, potato, tapioca and soy are used as dietary substitutes for these damaging grains. The recent literature suggests that moderate amounts of oats may be consumed by less sensitive coeliacs without risk of villous damage[12].

Controversy persists worldwide over how much gluten, if any, should be allowed in a gluten free diet. International dietary practices vary greatly. The gluten free diet in Australia prior to 1995 followed the guidelines of the WHO/FAO Codex Alimentarius[13]. The Codex Alimentarius allows 0.3% protein from gluten containing grains in foods to be labelled as gluten free. This includes malt and wheat starch in the diet, and is thought to be the practice in most countries. They contain up to 0.022% of gluten[14]. In March 1995 the Australian food standard for the labelling of gluten free foods changed. Commercial foods can no longer be labelled gluten free if they contain detectable gluten[15]. The ELISA monoclonal antibody test used detects

gluten in foods to the level of 0.003%[16] so ingredients such as malt and wheat starch are not suitable for use. There are also some who believe that although the gluten may not currently be detected in some foods manufactured from gluten containing grains, extreme caution is necessary, and all such products should be avoided.

Many studies [17, 18, 19, 20, 21] are suggestive of individual differences in gastrointestinal and symptomatic response to gluten. The aim of this study is to document the diets being consumed by a large proportion of coeliacs, and compare these with the frequency and severity of a range of common symptoms.

## METHODS

*STUDY POPULATION*

In April 1995, approximately one month after the NFA food standard regarding gluten changed, current members of the Coeliac Society of NSW were sent a questionnaire package. Non coeliac, medically interested members did not receive this. Of the 1672 questionnaires sent, 1384 recipients were adults with Coeliac Disease, 153 were parents of Coeliac children, 38 had been diagnosed with dermatitis herpetiformis, 37 had both dermatitis herpetiformis and Coeliac Disease and 60 were following a gluten free diet but were as yet undiagnosed.

The questionnaire package consisted of two sections. One was devised by the Coeliac Society of Australia and was designed to obtain a description of its membership. The second questionnaire compiled by the Allergy Clinic and AW Morrow Gastroenterology and Liver Centre at Royal Prince Alfred Hospital, was designed to describe the symptoms of this group of coeliacs before and after diagnosis and to document the level of gluten avoidance in their overall diet.

*DIET AND SYMPTOM QUESTIONNAIRE*

This was sent state wide to all members of the Coeliac Society of NSW and was anonymous but number coded with the questionnaire from the Coeliac Society of Australia. Ethics permission was obtained in February 1995 from the Ethics Review Committee of the Central Sydney Area Health Service (RPAH Zone) for its distribution.

*Symptom Report*

To assess the effect of the instigation of a gluten free diet after diagnosis, recipients were asked to record both their current and pre-diagnostic symptoms. A list of commonly described symptoms was provided. *(Appendix 1)* Those generally accepted to be associated with bowel problems were diarrhoea, constipation, nausea, vomiting, bloating, stomach pain, cramps and excessive flatulence. Dermatitis herpetiformis was included due to its close relationship to Coeliac Disease. Mouth ulcers, headaches and fatigue were three other non-bowel related problems listed. The final category 'other' gave the opportunity to list less common complaints. Recipients were asked to indicate the presence or absence of the symptom and to judge the frequency and severity of the problem. *(Appendix 1)*

*i) Severity:* Recipients were asked to record the severity of their symptom according to these guidelines:

MILD- you are aware of the symptom but it is easily tolerated.

MODERATE- this symptom is enough to cause interference with daily life or usual activity.

SEVERE- this is incapacitating with inability to work or take part in your usual activities.

ii) *Frequency:* Recipients were asked to record if their symptoms occurred less than once a month, monthly, weekly or daily.

*Dietary Assessment*

In order to assess each respondent's dietary practice, relevant questions were asked regarding the use of gluten free substitutes for breads, breakfast cereals, flours, biscuits, cakes, confectionery, alcoholic beverages, sauces and thickeners used in cooking. Information was obtained regarding the company name and precise product name. When a company manufactured a range of similar products, details of the exact one used by the respondent were requested. Details of home cooking practices, medications and use of vitamin and mineral supplements were asked for as well as choices made when dining out or for take away meals. During assessment when there was uncertainty as to the ingredients of any food, pharmaceutical or vitamin and mineral product the relevant company was contacted. They were also asked to indicate how strictly they perceived their adherence to the gluten free diet according to the categories below:

STRICTLY- no known gluten intake.

MOSTLY STRICT- sometimes eat small amounts of wheat, barley, rye, oats, malt.

NOT VERY STRICT- having wheat products at least once a week.

NOT AT ALL- eat a normal diet.

Details of any dietary change within the last three months were requested. The questionnaire *(Appendix 1)* was intentionally sent out at the time of the change in the food standard, so that there would be respondents with varying levels of gluten in their diet.

To study these dietary differences and their subsequent symptom outcome, respondent's eating habits were classified under the following headings:

Gluten Containing Diet- this classification was made for diets where any overtly gluten containing foods were eaten; eg. ice cream cones, communion wafers, bread/pasta made from wheat flour etc.

Trace Gluten Diet- this diet was in accordance with the old NFA food standard based on the Codex Alimentarius which allows up to 0.3% protein from gluten containing grains in foods classified as "gluten free". This diet can include foods containing malt or wheat starch. Oats were not permitted.

No Detectable Gluten Diet- this is the new gluten free diet according to the revised NFA food standard which allows a food to be labelled as "gluten free" only if it contains no detectable gluten using the ELISA monoclonal antibody test. This diet does not contain malt or wheat starch, and oats were again not permitted. Although the following: glucose syrup, maltodextrin, dextrins, dextrose, 1400 series thickeners; may sometimes be derived from gluten containing grains, current technology has not detected its presence hence they were permitted in this diet.

*Statistical Database*

A computer database was set up in order to efficiently analyse the large volume of data. Responses were coded numerically and entered into the Minitab 9 statistical program. As well as descriptive statistics, Minitab was used to perform one sample Student t-tests to compare severity and frequency for each symptom in the diet

categories. To compare the symptoms between the trace gluten and gluten free diet groups, the two sample Student t-test was used.

*COELIAC SOCIETY of AUSTRALIA QUESTIONNAIRE*

The Coeliac Society of Australia prepared and distributed their questionnaire nationally. This questionnaire *(Appendix 2)* detailed symptoms, diagnostic events, limited diet and medication information, concurrent and related illnesses, family history, age, sex and anthropometry. The answers from these respondents had been entered into a computer database by a representative of the Coeliac Society of Australia.

Since the two questionnaires were code matched, it was possible to use the information from the two questionnaires cojointly. It was not possible to match up the two questionnaire groups exactly since not exactly the same group returned each questionnaire, however details of current age, sex, age of diagnosis and BMI were obtained for the majority of respondents to the state wide questionnaire from the Allergy Clinic.

## RESULTS

*Description of Group*

Of the 1672 questionnaires sent, 965 were returned. This was a 58% questionnaire response rate. There were figures from the national questionnaire that corresponded to 823 (85%) of our respondent subjects. Of this group, 72% were females and 28% were males. 6% were children. The average age was 50 ranging from 4-88. The average BMI of the female adults was 23.4 and ranged between 16.4 and 44.6. The average BMI of the male adults was 24 and ranged between 16.9-34. The children's average age was 10 and ranged from 4-17. The median age of diagnosis for the total group was 39 ranging from 8 months to 83 years.

Of the 965 respondents to the diet and symptom questionnaire, 18.2% were classified as following a no detectable gluten diet, 71.9% were following a trace gluten diet, 5.9% were following a gluten containing diet and 4% were unable to be classified *(Figure 1).* Five percent of respondents stated they had made a change to their own diet in the previous 3 months in accordance with the March 1995 NFA food law change. 73% of respondents believed they were following their diet strictly, 23.4% believed they were mostly strict, 3.2% believed they were not very strict and 0.4% believed they were not strict at all *(Figure 2).* Of the 71.9% of respondents following the trace gluten diet, 73% did believe they were following a strict gluten free diet.

Figure 1: Proportion of subjects on each diet

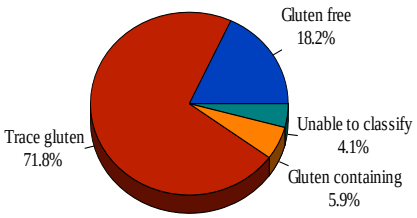
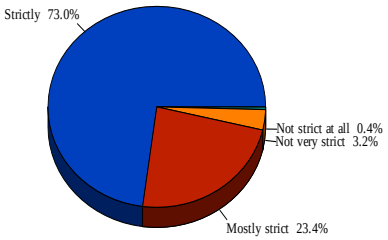



Figure 2: Personal perceptions of dietary adherence



*Symptoms*

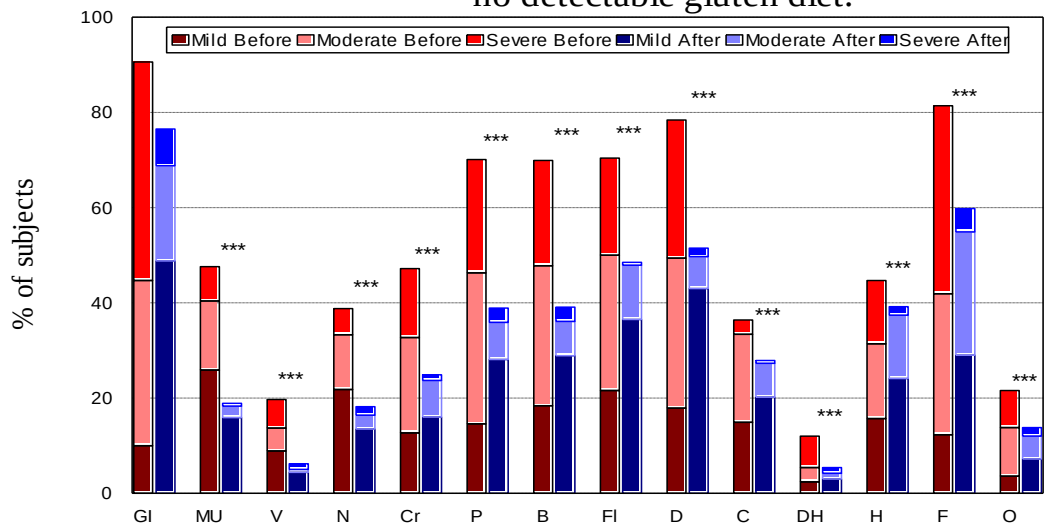
In the total group of respondents, there is a significant decrease ($p<0.005$) in both the severity and frequency of all symptoms after beginning any diet with some level of gluten restriction. The gastrointestinal symptom changes can be seen in Table 1.

Table 1. Comparison of gastrointestinal symptoms experienced before and after diagnosis and commencement of any degree of dietary gluten restriction.

| | | Before Diagnosis (%) | After Diagnosis and Dietary Gluten Restriction (%) |
|---|---|---|---|
| Severity of symptoms | none | 12 | 31 |
| | mild | 8 | 39 |
| | moderate | 28 | 20 |
| | severe | 52 | 10 |
| Frequency of symptoms | never | 16 | 32 |
| | <1/month | 3 | 18 |
| | monthly | 3 | 13 |
| | weekly | 13 | 19 |
| | daily | 65 | 18 |

In the no detectable gluten diet category, the decrease in symptoms in terms of severity and frequency is significant (p<0.005) for all symptoms *(Figures 3a & b)*.

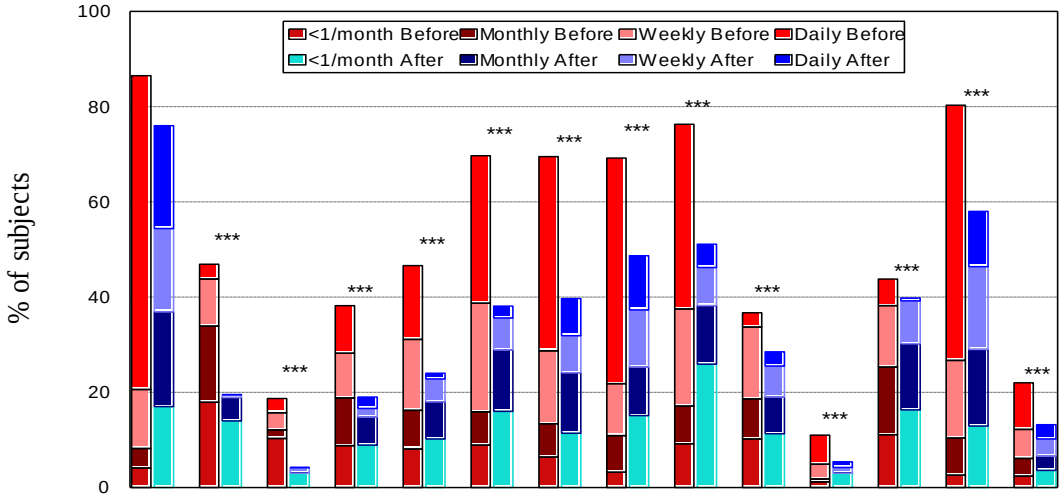
Figure 3a: Severity of symptoms before diagnosis and after treatment no detectable gluten diet.




GI=Gastrointestinal symptoms (grouped).
MU=Mouth ulcers
V=Vomiting
N=Nausea
Cr=Cramps
P=Stomach pain
B=Bloating
Fl=Flatulence
D=Diarrhoea
C=Constipation
DH=Dermatitis Herpetiformis
H=Headaches
F=Fatigue
O=Other symptoms

Statistical significance of the difference in heights for each individual symptom: *=p<0.05 **=p<0.01 ***=p<0.005

Figure 3b: Frequency of symptoms before diagnosis and after treatmer no detectable gluten diet.

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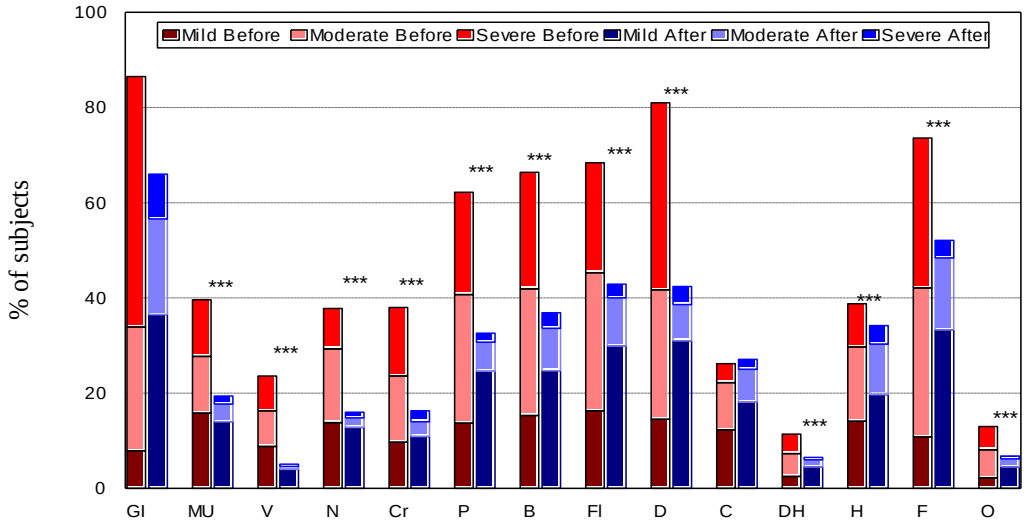
Refer to Appendix 3 for tabular summary of the figures used for these graphs

In the trace gluten diet category, the decrease in symptoms in terms of severity and frequency is significant ($p<0.005$) for all symptoms other than constipation which had p-values of 0.073 for severity and 0.053 for frequency *(Figure 4a &b)*. Constipation had increased in both these categories.

Figure 4a: Severity of symptoms before diagnosis and after commenc treatment with a trace gluten diet.

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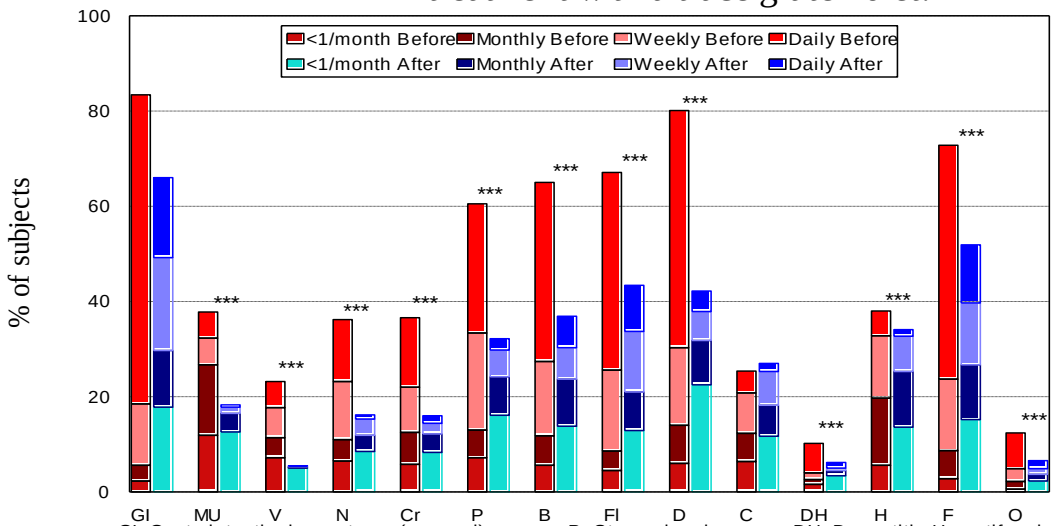
Statistical significance of the differences in heights for each individual symptom: *=p<0.05 **=p<0.01 ***=p<0.005

Figure 4b: Frequency of symptoms before diagnosis and after comme treatment with a trace gluten diet.

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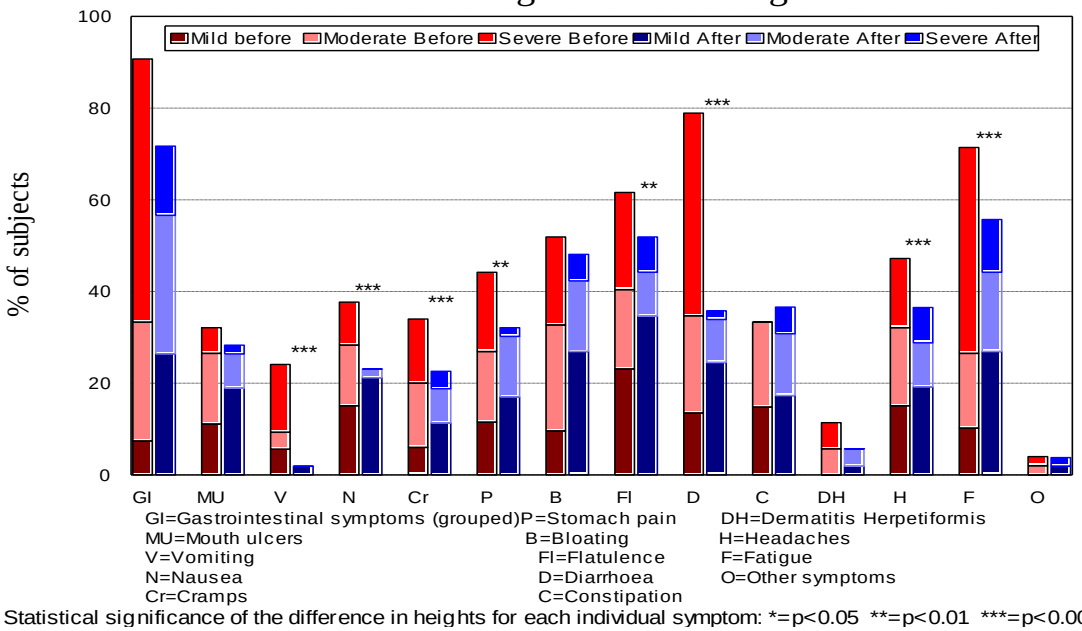
Statistical significance of the difference in heights for each individual symptom: *=p<0.05 **=p<0.01 ***=p<0.005

Refer to Appendix 3 for a tabular summary of the figures used for these graphs.

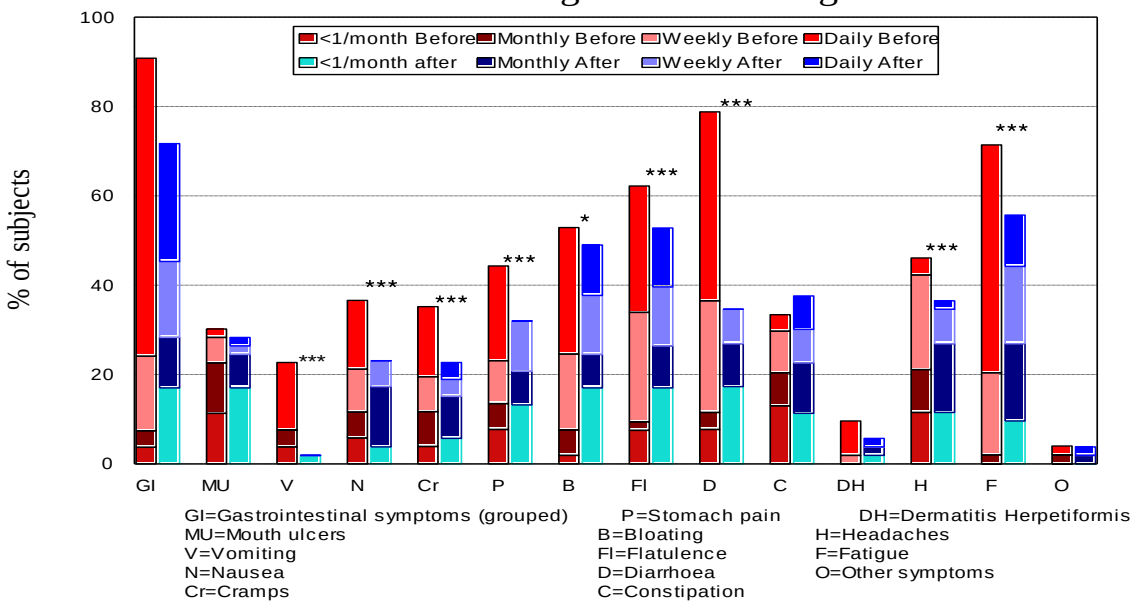
In the gluten containing diet category, at the level of $p<0.005$ few symptoms were significantly different after diagnosis. However when $p<0.05$, the decrease in severity of symptoms was significant for diarrhoea, nausea, vomiting, stomach pain, cramps, flatulence, mouth ulcers, headaches and fatigue. It is not significantly decreased for constipation, bloating, dermatitis herpetiformis and the other symptom category. In terms of frequency, the decrease in symptoms is significant for diarrhoea, nausea, vomiting, bloating, stomach pain, cramps, flatulence, headaches and fatigue. It is not significantly decreased for constipation, mouth ulcers, dermatitis herpetiformis and the other symptom category *(Figure 5a & b)*.

Figure 5a: Severity of symptoms before diagnosis and after treatmer gluten containing diet.




Statistical significance of the difference in heights for each individual symptom: *=p<0.05 **=p<0.01 ***=p<0.005

Figure 5b: Frequency of symptoms before diagnosis and after treatm gluten containing diet.




Statistical significance of the difference in heights for each individual symptom: *=p<0.05 **=p<0.01 ***=p<0.005

Refer to Appendix 3 for a tabular summary of the figures used for these graphs.

When the symptoms were compared between the trace gluten diet category and the gluten free diet category there was found to be no significant difference ($p>0.01$) in the severity of any symptom other than constipation ($p=0.0051$), which was more severe for the subjects following a trace gluten diet. There was no significant difference ($p>0.01$) between the two groups for the frequency of any symptom except for diarrhoea ($p=0.0032$) which was more frequent for the subjects following the no detectable gluten diet.

## DISCUSSION

To better understand if the dietary advice given to all patients needs to correspond with the new food standard, this study set out to examine the dietary patterns in a large population of coeliacs at the time of the NFA food standard change, and to document any current symptoms experienced at these different levels of gluten restriction. In doing so we have shown that a large proportion of coeliacs still have continuing symptoms despite this gluten restriction.

Across all diet categories, it was clear that a reduction in the gluten content of the diet resulted in a decrease in the number of people experiencing each symptom. Those who still experienced symptoms generally found them to be less often and less severe. All severities and frequencies significantly decreased in the no detectable gluten group after beginning the diet. This was mirrored in the trace gluten diet group for all symptoms except constipation. There were fewer significant decreases in symptoms as the level of gluten rose above this as seen in the gluten containing diet category, suggesting a dose dependent trend for symptom expression and gluten ingestion. Catassi et. al.[22] found a similar graded effect of gluten on villous morphology.

A number of criticisms can be made of the methodology in this study. While the sample size is very large the questionnaire response rate was only 58%. The respondent population is of an average age of 50, in the majority female and all are members of the Coeliac Society of NSW. It is unknown if this sample is representative of the Australian population diagnosed with coeliac disease. The questionnaire is based only on the subject's self reporting. There was no medical documentation to support claims, since some of the symptoms reported may due to a

separate condition. Difficulty could have been encountered when respondents were allocating a single number rating each to the severity and the frequency of symptoms they have experienced. In some cases considerable time had passed since diagnosis, making recollection of symptoms during this period difficult. There was no allowance made in this number rating system for variations in the severity or frequency of symptoms experienced by each individual on different occasions. Dietary grouping was often difficult. Limited questions were asked regarding the frequency and quantity of consumption of some key food groups, thus the distinction for some subjects between the particular diet classifications was sometimes ambiguous. While many relevant food types were included and the food names and brands given were thoroughly checked, we must still question whether or not all sources of gluten were recorded by the questionnaire respondent. Cooking contamination may occur when cooking appliances and ingredients are shared with other non-coeliacs. Ingredients listed on food labels can be misleading and advice given in take away food shops can be incorrect thus gluten ingestion may occur unknowingly. These points will be taken into account when a similar survey is performed in the future to determine whether coeliacs have adopted the food standard, and if symptoms have responded. It was apparent from this study that when it was done, few coeliacs were aware of the food standard changes, or that malt and wheat starch can contain gluten.

A higher incidence of constipation was seen in those subjects following the trace gluten and gluten containing diets which was not seen for those following the no detectable gluten diet. This may suggest that exquisite attention to gluten removal has a positive effect on constipation. Lack of dietary fibre has generally been thought

responsible for constipation because the gluten free diet restricts the choice of grains, minimising the range of high fibre foods available.

It is interesting to note that when the symptom frequency and severity profiles for the trace gluten category were compared with the more restrictive diet category, there was no significant differences seen between the groups for gut symptoms other than diarrhoea and constipation, or for headaches, fatigue, mouth ulcers, dermatitis herpetiformis and the other category. This appears to show that the symptoms experienced by the trace gluten and gluten free diet groups of coeliac subjects are almost the same. However it is important to note that this is a group trend and it may not be true for each individual. Several studies [12, 18, 20] suggest that some individuals with coeliac disease are more sensitive to gluten than others. We have not been able to show if our subjects with the gluten free diet classification would have had more severe and frequent symptoms if malt and wheaten starch were eaten. The greater frequency of diarrhoea seen in those eating no detectable gluten may indicate them to be a more sensitive group. Diarrhoea showed the most dramatic fall after restricting gluten in the diet. The percentage of people experiencing it daily, fell from between 39-50% to between 0-5% over all three diet types. It may be simplistic to assume that the diet followed is the only one known of by the coeliac or their medical care team. The reduction or removal of diarrhoea alone may be a main goal for the individual, and thus influence the diet each coeliac follows.

Reducing this and other symptoms to a tolerable level may be only one of several influencing factors behind each individual's chosen level of gluten restriction. Some may find the restrictions too difficult to cope with socially, so choose to be gluten free

only at their convenience. Since some forms of cancer, particularly the bowel lymphoma[23] have been linked with non compliance to a gluten free diet[19], it may be possible that this is why some coeliacs choose to be strict with their diet independent of symptom presence.

Holmes et. al.[24] found that a gluten free diet may be important in preventing or decreasing risk of later complications such as bowel lymphoma and other gastrointestinal malignancies. While that study did not define the level of gluten in the diet of its subjects, it is likely that the Codex Alimentarius was the gluten free diet guide. Therefore it may be unnecessary for some patients to follow a completely gluten free diet if they appear to be symptom free on a diet containing trace amounts of gluten. We are currently unaware of any knowledge linking people on a gluten free diet with persistent abnormal biopsies, as being more likely to have future malignant complications. Due to this unknown factor, these people may again choose a more restrictive diet in the hope of obtaining a normal biopsy.

This controversy concerning a 'safe' level of gluten for coeliacs continues due to varying results from studies performed to investigate the effect of low gluten diets on both symptom occurrence and morphological changes of the villi in coeliac subjects. Ciclitira et. al.[18] found that there was a variety of symptomatic responses in coeliacs consuming bread containing wheat starch. Some patients experienced one or more gastrointestinal symptoms whereas others experienced none. Our study has shown similar findings in all three of our gluten restricted diets. Other studies have shown that symptoms can be present in some patients without morphological damage [18, 20, 21] and that small amounts of gluten do not always cause villi destruction [17, 18, 19]. This

tends to indicate little need for the coeliac with tolerable symptoms and a normal biopsy to follow the no detectable gluten diet.

We have concluded from this study that for many coeliacs, after beginning a gluten free diet, the severity and frequency of symptoms experienced, while milder, may still be present. The group data suggests that the less restrictive trace gluten diet may be followed in some coeliacs with similar benefit to the no detectable gluten diet. However some studies above show that symptomatic benefit may be gained in some individuals by the removal of trace gluten, and in the short term, no villous damage occurs after its ingestion. Management of this disease may therefore be better approached if continuous assessment of current biopsy results, symptom frequency and severity, together with lifestyle and family history of cancer, are taken into account when determining the level of dietary gluten restriction for each individual coeliac.

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