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Development of a Risk Score for Extraintestinal Manifestations of Coeliac Disease

Christine L. Chiu, PhD, Nerissa L. Hearn, B.Adv.Sc(Hons), and Joanne M. Lind, PhD

Abstract: The aim of this study was to identify indicators of coeliac disease (CD) in an Australian cohort, beyond the known gastrointestinal symptoms.

Individuals were recruited from the general population and at the 2014 Gluten Free Expo in Sydney and in Melbourne, Australia. Data on their current health status including medical history, diagnosis for CD, and family history were collected. Multivariable logistic regression was used to identify independent predictors of CD. A weighted risk score system was then generated for the independent predictors, and a risk score was calculated for each individual.

A total of 301 individuals were included in the study. We found an association between CD and having a family history of CD (odds ratio [OR] 7.6, 95%confidence interval [CI] 3.7–15.6), an autoimmune disorder (OR 2.1, 95%CI 1.1–4.1), anemia (OR 5.8, 95%CI 2.8–11.9), lactose intolerance (OR 4.5, 95%CI 1.2–17.7), and depression (OR 4.8, 95%CI 1.9–11.6). Risk score analysis found individuals in the medium (OR 4.8, 95%CI 2.5 to 9.3) and high-risk (OR 36.6, 95%CI 16.4 to 81.6) groups were significantly more likely to report having CD compared with those in the low-risk group.

This study identifies a set of factors more commonly observed in individuals with CD, beyond the traditional gastrointestinal complaints. These include a family history of CD, the presence of another autoimmune disorder, anemia, lactose intolerance, and depression. A risk score was developed (Coeliac Risk COMPARE) which scores individuals based on the presence or absence of these additional symptoms and provides an additional screening tool when assessing whether the patient requires follow-up testing for CD.

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Abbreviations: BMI = body mass index, CD = coeliac disease, CI = confidence interval, Coeliac Risk COMPARE = Coeliac Risk Computed at the Point of Care, DNA = deoxyribonucleic acid, FHx = Family history, HLA = human leukocyte antigen, IBS = irritable bowel syndrome, OR = odds ratio, ROC = receiver operator characteristic, SD = standard deviation.

INTRODUCTION

Coeliac disease (CD) is an autoimmune disease that is characterized by inflammation of the small intestine

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From the Western Sydney University, School of Medicine, Australia.

Correspondence: Joanne M. Lind, Locked Bag 1797, Penrith NSW, Australia (e-mail: j.lind@westernsydney.edu.au).

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mucosa, in response to dietary gluten, in genetically susceptible individuals. Population studies have shown that it is a relatively common disorder affecting ~1% of the population.^{1–5} In Australia, the prevalence of CD is 1 in 70, with more women (1 in 60) than men (1 in 80) affected.⁶ The symptoms associated with disease are variable and include gastrointestinal symptoms and malabsorption. The only proven treatment for CD is a lifelong gluten-free diet.⁷

The classical symptoms commonly associated with a patient's primary presentation of CD are gastrointestinal disturbances, for example, diarrhea, bloating, and/or abdominal pain. However, some CD patients remain asymptomatic or present with more generic symptoms such as fatigue⁸ or failure to thrive in children, which are not specific to CD. Additionally, CD symptoms overlap with those of irritable bowel syndrome (IBS)⁹ and can therefore delay the diagnosis of CD if it is not the first line of investigation.¹⁰ Once CD is suspected in a patient, a number of screening procedures are available to determine whether an intestinal biopsy is indicated in that patient (for example, serology for CD-specific antibodies or genetic testing for human leukocyte antigen [HLA] haplotype). However, in patients with nonclassical symptoms, this screening may not be implemented in the first instance. Therefore, the identification of other indicators of CD would be useful in determining whether CD screening should be initiated.

Research to date has shown that individuals with CD have a higher prevalence of other autoimmune disorders,¹¹ including type I diabetes, rheumatoid arthritis, and autoimmune thyroiditis.¹² In addition to autoimmune disorders, a number of other conditions, outside of the small intestine, have been associated with CD, including anemia, osteoporosis,¹³ and depression.¹⁴ Identifying which extra-intestinal comorbidities and/or symptoms are indicative of CD, compared with a healthy control population, would aid in the decision to screen for CD in the first line of investigation and reduce time to diagnosis.

The aim of this study was to identify indicators of CD in an Australian cohort by studying the association between CD and extraintestinal symptoms and comorbidities and to determine whether combinations of these factors could be used to aid in the identification of people with CD. A risk score can then be calculated based on these extraintestinal symptoms and comorbidities to determine the likelihood of CD in a patient presenting with nonclassical CD symptoms.

METHODS

Individuals were recruited from the general population, staff and students of Western Sydney University, and at the 2014 Gluten-Free Expos in Sydney and in Melbourne, Australia. Following informed consent, individuals were asked a series of questions about their current health status including medical history, any tests they have had to diagnose CD, family history, dental health, and alcohol and smoking status. DNA was collected using a combination of buccal swabs (Isohelix, Cell Projects, UK) and saliva (Oragene-DNA saliva collection kit

DNA Genotex, Canada). Informed consent was provided by each participant, and this study had approval from the Western Sydney University Human Research Ethics Committee (approval number H10513).

Genomic DNA was extracted from buccal swabs or saliva using the Qiagen DNA Mini Kit (Qiagen, Germany) as per the manufacturer’s recommendations. Genotyping for the HLA-DQ2 and HLA-DQ8 coeliac susceptibility haplotypes was performed using validated TaqMan SNP Genotyping assays as previously described.¹⁵

All the variables used in this study were derived from self-reported data. Only individuals who were 18 years or older at the time of recruitment, and did not have missing data for any of the variables studied, were included in the study.

Individuals were defined as having CD if they fulfilled all the following criteria: responded “Yes” to “Have you been diagnosed with coeliac disease?”; responded “Yes” to “Are you currently on a gluten free diet?”; reported being diagnosed via a small bowel biopsy; and carried at least 1 HLA-DQ2 or

HLA-DQ8 haplotype. Participants who responded “Yes” to “Have you been diagnosed with coeliac disease?”, but were not currently on a gluten-free diet, or had not been diagnosed via a small bowel biopsy, or did not carry an HLA-DQ2 or HLA-DQ8 allele, were excluded. Individuals were classified as healthy controls if they responded “No” to “Have you been diagnosed with coeliac disease?” and “No” to “Are you currently on a gluten-free diet?”. Individuals who responded “No” to “Have you been diagnosed with coeliac disease?” and “Yes” to “Are you currently on a gluten-free diet?” were excluded (Figure 1).

For ethnicity, individuals were classified as either Caucasian or non-Caucasian. The body mass index (BMI) was analyzed as a categorical variable (<25 healthy weight; 25–29 overweight; 30+ obese groups) according to World Health Organization guidelines.¹⁶

For autoimmune conditions, individuals were asked if they had been diagnosed with any of the following autoimmune conditions: autoimmune hepatitis; primary biliary cirrhosis; primary sclerosing cholangitis; type 1 diabetes mellitus;

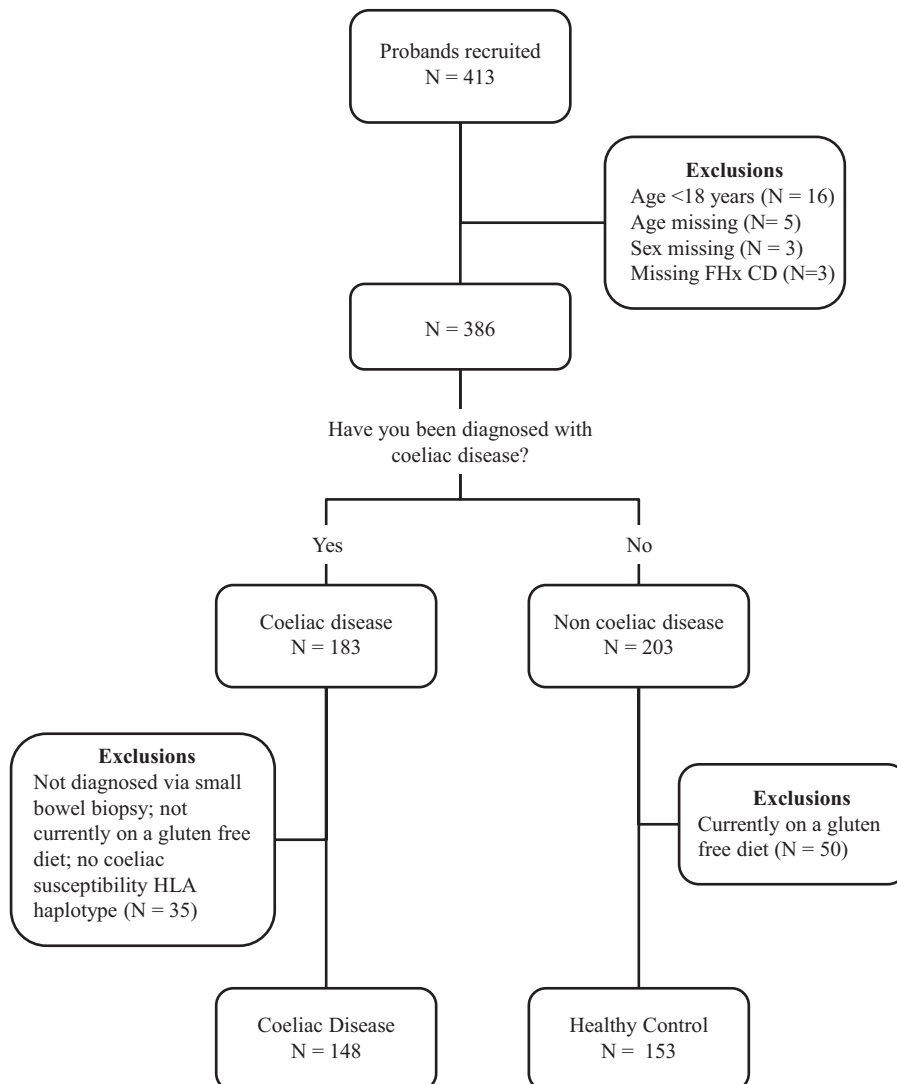


FIGURE 1. Participants included in the study. CD = coeliac disease; FHx = family history; HLA = human leukocyte antigen.

autoimmune thyroid disease; Addison’s disease; rheumatoid arthritis; Sjogren’s disease; Lupus; dermatitis herpetiformis; psoriasis. Data from these variables were combined to generate the variable “autoimmune condition” as the prevalence of each individual condition was low and no one condition was significantly associated with having CD. Individuals who reported “Yes” to any of the above conditions were classified as having an autoimmune condition. Individuals were also asked if they had ever been diagnosed with asthma, anemia, depression, lactose intolerance, osteoporosis/low bone mineral density, or recurrent mouth ulcers.

Generalized linear models were run to determine if there were significant differences in demographic and lifestyle factors between the CD cohort and controls, with each factor as the dependent variable, adjusted for all other variables. A linear regression model was performed for age, whereas binary logistic regression was performed for all other demographic and lifestyle factors. Any differences identified between the cohorts were subsequently adjusted for in the prediction of CD.

Multivariable logistic regression was used to identify independent predictors of CD. A weighted risk score system was generated for the independent predictors, by dividing the β -coefficients of each variable by the smallest β -coefficient in the model, multiplying by 2 and rounding to the nearest integer.^{17,18} This risk score was called the “Coeliac Risk Computed at the Point of Care” (or Coeliac Risk COMPARE). A Coeliac Risk COMPARE score was then calculated for all individuals. The total score was then categorized into 3 groups where the lowest group consisted of individuals with no CD risk factors (<2). The remaining individuals were stratified as medium risk (2–6) or high risk (7+) using the median score (between 6 and 7) as the cut point. This categorical variable was then used as the single independent variable in a logistic regression model with CD as the dependent variable. The amount of variability in CD explained by the Coeliac Risk COMPARE score was analyzed using the c-statistic, defined as the area under the receiver operator characteristic (ROC) curve. All statistical tests were 2-sided, using a significance level of $P < 0.05$.

RESULTS

A total of 301 individuals were included in the study (Figure 1). Of these, 148 reported having been diagnosed with CD via an intestinal biopsy, were currently on a gluten-free diet, and carried at least 1 HLA-DQ2 or DQ8 haplotype, and 153 individuals responded no to having been diagnosed with CD and no to being on a gluten-free diet. Demographic and lifestyle characteristics of individuals with CD compared to healthy control individuals are outlined in Table 1. Individuals with CD were older compared to individuals without CD, and significantly more women reported having been diagnosed with CD compared to men. Ethnicity, current BMI, smoking status, and alcohol consumption were not significantly different between the CD cohort and controls. HLA typing for CD risk haplotypes was carried out in both CD and control groups. After exclusions, all individuals within the coeliac group had at least 1 HLA risk haplotype, whereas 57.1% of the control group were found to carry at least 1 risk haplotype.

Multivariable logistic regression was used to identify variables that were independently associated with CD. A family history of CD, the presence of an autoimmune condition other than CD, and having been diagnosed with anemia, lactose intolerance, or depression were found to be independent predictors of CD, adjusting for age at recruitment and sex (Table 2). Asthma, osteoporosis and/or low bone mineral density, and recurrent mouth ulcers were not associated with CD. The adjusted β -coefficients from significantly associated variables were used to generate a weighted risk score named the Coeliac Risk COMPARE. This score was then calculated for each individual by adding together the points corresponding to their risk factors. This Coeliac Risk COMPARE score showed good discrimination for CD, with a c-statistic of 0.85 (95%CI 0.8–0.9), and a specificity of 91.5% and sensitivity of 57.4% at the cut-off risk score between 6 and 7. Individuals in both the medium and high-risk group were significantly more likely to report having CD compared with those in the low-risk group. Table 3 summarizes the odds ratios for CD in each risk group.

TABLE 1. Demographic and Lifestyle Factors Associated With CD

Characteristics		CD n = 148 (%)	Control n = 153 (%)	Odds Ratio [†] (95% CI)
Age (years)	Mean ± SD	45.0 ± 15.1	35.9 ± 14.1	0.05 (0.03–0.07); $P < 0.001^*$
Sex	Male	21 (14.2)	59 (38.6)	1.0
	Female	127 (85.8)	94 (61.4)	4.6 (2.4–8.6); $P < 0.001$
Ethnicity	Caucasian	129 (87.2)	120 (78.4)	1.0
	Other	19 (12.8)	33 (21.6)	0.6 (0.3–1.2); $P = 0.14$
BMI	<25	71 (48.0)	85 (55.6)	1.0
	25 to 29	36 (24.3)	43 (28.1)	1.0 (0.5–1.9); $P = 0.96$
	30+	41 (27.7)	25 (16.3)	1.4 (0.7–2.9); $P = 0.30$
Smoking status	Never	107 (72.3)	112 (74.7)	1.0
	Quit	36 (24.3)	28 (18.7)	1.0 (0.5–1.9); $P = 0.95$
Alcohol consumption	Current	5 (3.4)	10 (6.7)	0.6 (0.2–2.1); $P = 0.42$
	0/week	60 (40.5)	50 (32.7)	1.0
	1 to 5	66 (44.6)	74 (48.4)	0.7 (0.4–1.3); $P = 0.24$
	6 to 10	13 (8.8)	14 (9.2)	0.7 (0.25–1.8); $P = 0.41$
	11+	9 (6.1)	15 (9.8)	0.4 (0.1–1.3); $P = 0.12$

BMI = body mass index; CI = confidence interval; OR = odds ratio; SD = standard deviation.

% is the percentage of individuals within that group, either CD or Control.

*Linear variable, therefore beta value and 95% CI reported.

†Adjusted for age, sex, ethnicity, BMI, smoking status, and alcohol consumption.

TABLE 2. Adjusted Odds Ratios for CD Using Logistic Regression and the Coeliac Risk Computed at the Point of Care (Coeliac Risk COMPARE) Score

	n = 301 (%)	OR (95% CI); P Value	β	Score
Family history CD	91 (30.2)	7.6 (3.7–15.6); P < 0.001	1.02	6
Autoimmune condition	100 (33.2)	2.1 (1.1–4.1); P = 0.03	0.74	2
Anemia	88 (29.2)	5.8 (2.8–11.9); P < 0.001	1.76	5
Depression	52 (17.3)	4.8 (1.9–11.6); P = 0.001	1.56	4
Lactose intolerance	29 (9.6)	4.5 (1.2–17.7); P = 0.03	1.51	4

CI = confidence interval, OR = odds ratio.

Analysis adjusted for age at recruitment and sex. Score for each risk factor was calculated by dividing the β-coefficient of each variable by 0.74 (the lowest β value corresponding to autoimmune condition), multiplied by 2 and rounded to the nearest integer.

DISCUSSION

This study investigated the association between CD and extraintestinal symptoms and comorbidities. Age and sex were significantly different between the CD cohort and controls, with a greater proportion of women in the CD cohort, and individuals with CD were more likely to be older. Although studies have reported a higher prevalence of CD in women compared to men (1:80 vs 1:60),⁶ the age and sex differences in this study are likely the result of recruitment bias. The majority of our CD recruitment occurred at Gluten-Free Expos, where the bulk of attendees were middle-aged females, whereas our control cohort was primarily recruited within a university environment. This is reflected in our study cohort as there are ~3 times more women, and the difference in mean age between the cohorts is 10 years. As a result, these variables were adjusted for in the remainder of the modeling.

A number of extraintestinal symptoms and comorbidities were significantly associated with having CD. These included: a family history of CD; having another autoimmune condition; anemia; depression; and lactose intolerance. These associations remained after adjusting for age at recruitment and sex.

Genetic factors play an important role in CD and individuals with a family history of CD are at an increased risk of disease.¹⁹ This was highlighted in our study where a family history of CD was found to be an independent predictor of CD, with CD individuals 6.8 (95%CI 3.4–13.8) times more likely to have a family history of CD, compared with controls. The HLA class II molecules are the largest genetic risk factor in CD, with CD individuals having at least 1 HLA-DQ2 or HLA-DQ8 haplotype.²⁰ However, as these haplotypes are also commonly found in the general population, the presence of HLA-DQ2 or HLA-DQ8 alone cannot predict the presence of disease.

Autoimmune conditions occur more frequently in individuals with CD than in the general population.²¹ We studied a

subset of autoimmune conditions that had been previously associated with CD. We found that individuals with CD had a 2.1 (95%CI 1.1–4.1) times higher likelihood of having another autoimmune condition, compared with individuals who did not have CD. Our results are in agreement with previously published studies where the prevalence of autoimmune conditions was significantly higher in individuals with CD compared with healthy controls.^{12,21,22} Therefore, the presence of an autoimmune condition could signal further investigation for a diagnosis of CD in presenting patients.

Anemia and lactose intolerance were also significantly associated with CD. Individuals with CD were 5.9 (95%CI 2.9–12.0) and 4.3 (95%CI 1.1–16.5) times more likely to have reported having these conditions, respectively. These results are in line with previous studies that have reported higher frequencies of iron-deficient anemia and lactose intolerance in individuals with CD.^{23–25} Vitamin and mineral deficiencies are frequently observed in untreated individuals with CD due to malabsorption caused by intestinal damage.^{23,26} Reduced iron absorption and a loss of lactase during intestinal villi flattening results in anemia and secondary lactose intolerance in individuals with CD.²⁷ In the majority of individuals, commencement of a gluten-free diet and subsequent resolution of intestinal damage has been shown to improve these conditions. No information regarding whether anemia and lactose intolerance resolved after the commencement of a gluten-free diet in the CD individuals was available in our study.

Neurological and psychiatric disorders have been reported in association with CD.^{28,29} We found individuals with CD were more likely to report having depression. Population-based studies have found that individuals with CD are at an 80% increased risk of depression compared to controls.^{28,30} Longitudinal studies have shown depressive symptoms can improve following a gluten-free diet³¹; however, lifetime depressive

TABLE 3. Odds Ratios for CD Stratified by the Coeliac Risk COMPARE Score

Risk Group	CD n (%)	Control n (%)	OR (95% CI); P Value
Low (<2)	15 (15.2)	84 (84.8)	1.0 (reference)
Medium (2–6)	48 (46.2)	56 (53.8)	4.8 (2.5 to 9.3); P < 0.001
High (7–17)	85 (86.7)	13 (13.3)	36.6 (16.4 to 81.6); P < 0.001

CD = coeliac disease, CI = confidence interval, OR = odds ratio.

symptoms may remain in up to one-third of the CD patients who adhere to a gluten-free diet.³² Mechanisms to explain the increase in depressive symptoms may include reduced well-being from malabsorption and nutritional deficiencies before diagnosis. Following diagnosis, the stress of adhering to a gluten-free diet and compromised social relationships may also contribute to depression.³²

As mentioned above, a family history of CD, presence of another autoimmune condition, anemia, depression, and lactose intolerance were all identified as independent variables associated with CD in this study. We used these 5 variables to generate a new risk score (Coeliac Risk COMPARE) that was able to stratify an individual's risk of having CD based on the presence of combinations of these risk factors. Using this scoring system we were able to classify individuals into low, medium, and high risk of CD, with relatively high specificity, particular for the high-risk group (specificity 91.5%). Sex and age were adjusted for in the model, but not included when calculating final risk scores due to the identified recruitment bias. These variables could therefore be used in the primary clinic setting, at the point of care, to ascertain whether a presenting patient is at low, medium, or high risk of having CD based on extraintestinal symptoms and comorbidities. Individuals at high risk for CD, based on the Coeliac Risk COMPARE score, have a 36.6 (95%CI 16.4–81.6) times increased likelihood of having CD, compared with a healthy control population. Identifying this high-risk group would result in early investigations of CD and could reduce the time to diagnosis, and expedite the initiation of a gluten-free diet. This would help reduce the long-term complications that can be associated with untreated CD, such as cancer of the small intestine.³³

A limitation of this study was that we used self-reported data, which can be subject to recall bias. Many autoimmune conditions require regular follow-up with a medical professional, and as a result the probability of a false positive classification is low. Self-reporting of CD status may have also led to a false-positive CD classification; however, as we restricted our CD cohort to only those who had been diagnosed via an intestinal biopsy by a specialist, misclassification due to self-reporting is less likely. False-negative CD classification is also possible. Due to the prevalence of CD of 1 in 70, it is possible that ~2 individuals in our control cohort were asymptomatic individuals with undiagnosed CD or would develop CD later in their lifetime.

In conclusion, we have identified that a family history of CD, presence of an autoimmune condition, a history of anemia, lactose intolerance, and a history of depression are associated with CD. Combining these variables, we developed the Coeliac Risk COMPARE score that was able to significantly stratify individuals into low, medium, or high CD risk. Validation of our scoring system in an independent cohort is required; however, these results highlight the importance of factors outside the intestine in CD and has the potential to improve the time to diagnosis.

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