2018

Disparities in follow-up adherence amongst pediatric patients with celiac disease

BOSTON UNIVERSITY

SCHOOL OF MEDICINE

Thesis

DISPARITIES IN FOLLOW-UP ADHERENCE AMONGST PEDIATRIC PATIENTS WITH CELIAC DISEASE

by

BRADLEY A. BLANSKY

B.S., University at Buffalo, 2015

Submitted in partial fulfillment of the

requirements for the degree of

Master of Sciences

2018

Approved by

First Reader

Margot Tang, M.D., M.P.H.
Instructor in Pediatrics

Second Reader

Jocelyn Silvester, M.D., Ph.D.
Attending Physician
Boston Children's Hospital

ACKNOWLEDGEMENTS

I first would like to thank my thesis advisor, Dr. Jocelyn Silvester, for her continual guidance and feedback throughout the process of formulating and completing this project. I would also like to acknowledge Dr. Margot Tang for her valuable insight during the writing process. Thank you as well to all of the faculty, fellows, and research assistants at both Boston Children's Hospital and Beth Israel Deaconess Medical Center for their kindness and support throughout my duration as a graduate research student. Lastly, to my family, who has supported and believed in me throughout this entire journey, none of this would have been possible without them.

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ABSTRACT

Introduction:

Celiac disease is a chronic immune disorder for which the only treatment is strict lifelong adherence to a gluten-free diet (GFD). Collaborative management through regular follow-up with a care team that includes physicians and dietitians may improve long-term outcomes. However, many individuals with celiac disease are lost to follow-up.

Objective:

This primary objective of this study was to identify factors associated with pediatric celiac disease patients being lost to follow-up. Secondary aims included identifying adherence to recommended care practices by both patients and providers.

Methods:

A chart review of 250 randomly selected children with biopsy-confirmed celiac disease diagnosed between 2010 and 2014 at Boston Children's Hospital (BCH) was conducted. Follow-up records were reviewed from diagnosis to 2017. Eligible children were diagnosed prior to age 18 and did not attend BCH solely for a second opinion. Demographics, medical history, visit information, and lab results were collected using an online database.

Results:

Of the 241 eligible subjects (64% female, 1-17 years, median 9.7 years) the median time until lost to follow-up was 2.8 years from diagnosis (IQR, 1.0-4.7 years) with 22 subjects (9%) not attending any follow-up visits with their pediatric gastroenterologist (GI) after diagnosis and an additional 37 subjects (14%) lost within the first year. A majority of subjects (83%) attended a GFD education visit with a registered dietitian, although this was not associated with follow-up adherence ($P>0.5$). Excluding those who had aged out of the clinical practice, children who were adherent to follow-up had a younger mean age of diagnosis (95% CI 0.5-3.1, $P<0.01$). Children who were insured under Medicaid/CHIP (N=20) were more likely to be lost within one year compared to those with private health insurance ($P<0.01$). Celiac serologies taken at time of last clinical visit were abnormal in 25% of the subjects with available results (N=141) and the median time since diagnosis in this positive serology subgroup was 20 months (IQR, 12-29 months).

Discussion:

The present study illustrates that children with celiac disease are not being followed-up adequately and that identifiable disparities exist in the pediatric celiac disease population. Within three years of diagnosis, 50% of the cohort was lost to follow-up with the majority of subjects lost within the first year of diagnosis. Children diagnosed at a younger age were more adherent to follow-up compared to those diagnosed during adolescence. Factors associated with decreased adherence included reliance on public medical insurance and older age at diagnosis. Improvement in long-term management of celiac disease may be achieved by increased outreach and education.

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LIST OF ABBREVIATIONS

BCH ..... Boston Children's Hospital

CD ..... Celiac disease

EMA ..... Endomysial antibody

EGD ..... Esophagogastroduodenoscopy

GFD ..... Gluten free diet

GI ..... Gastroenterology

HLA ..... Human leukocyte antigen

IgA ..... Immunoglobulin A

IgG ..... Immunoglobulin G

MHC ..... Major histocompatibility complex

RD ..... Registered dietitian

REDCap ..... Research Electronic Data Capture

tTG ..... Tissue Transglutaminase

INTRODUCTION

Celiac disease is a chronic gastrointestinal disorder that can present with a wide range of intestinal and extra-intestinal symptoms due to an immune reaction triggered by ingestion of gluten.[1] This disease affects approximately 1% of the global population with an increased prevalence among individuals with a family history of celiac disease and those with comorbidities such as trisomy 21, type I diabetes mellitus or other autoimmune disorders.[2,3] Females are slightly more likely to be diagnosed with celiac disease and most children are diagnosed between the ages of 7 and 10 years old.[4] The treatment of celiac disease requires strict lifelong adherence to a gluten-free diet, passing the onus of care from the healthcare provider to the patient.[1] Due to the communal role food plays in many cultures, individuals with celiac disease often report initial difficulty following a gluten-free diet and may have persisting symptoms due to non-adherence.[5] To help ease the treatment burden, as well as assure adequate mucosal recovery, national and international guidelines recommend that healthcare providers provide routine follow-up care to patients with celiac disease to monitor their health and assist with dietary management. [6–8] However, attendance follow-up visits is inconsistent, which may result in poor disease management along with decreased quality of life for these individuals.[9] The purpose of this study is to identify factors associated with non-adherence to follow-up in children with celiac disease.

Overview and Diagnosis of Celiac Disease

Celiac disease is an immune-mediated enteropathy that is activated by exposure to gluten. Gluten refers to both the specific plant storage protein found in wheat as well as an umbrella term for storage proteins in other cereal grains such as barley and rye. Gluten is composed of two main proteins, glutenin and gliadin, which are rich in proline and glutamine residues forming short, compact peptide chains that are difficult for digestive proteases to breakdown. Due to their proline rich nature, these proteins are also called prolamins.[10]

Gluten contains a wide variety of immunogenic epitopes, with the most common being contained within a 33-amino acid sequence in α-gliadin. The α-gliadin and other peptides are deamidated by the endogenous enzyme tissue transglutaminase (tTG), forming a negatively charged peptide. These modified gliadin peptides elicit an immune response due to an increased affinity to the major histocompatibility complex (MHC) II of antigen presenting cells encoded by the human leukocyte antigen (HLA) serotype DQ2 and DQ8, present in individuals with celiac disease.[11] Mucosal injury occurs as a result of the release of pro-inflammatory cytokines, such as interferon-γ and interleukin-21, and infiltration of cytotoxic T-cells in the intestinal epithelium and lamina propria. The autoimmune component of celiac disease is mediated by the humoral response and results in formation of high affinity anti-tTG and other autoantibodies, possibly stimulated by tissue injury. The accumulation of these autoantibodies in the intestinal mucosa and eventual overflow into systemic circulation may contribute to systemic manifestations of celiac disease.[1,12]

Individuals with celiac disease may present with a wide range of symptoms, or no overt symptoms at all, which can make diagnosis difficult. Classical symptoms are most common in those diagnosed in early childhood, often coinciding with the introduction of gluten into the child's diet between ten and twenty-four months of age, and include chronic diarrhea, failure to thrive, and abdominal pain or distension.[1] In older children, diarrhea is less common and symptoms often present as consequences of chronic enteropathy and malabsorption, such as iron-deficiency anemia, aphthous stomatitis, and growth or pubertal delays.[13] Asymptomatic celiac disease is often more difficult to diagnose as individuals do not present with outward complaints and this group is most often diagnosed due to screening because of other risk factors.[13]

Diagnosis of celiac disease is often confirmed through a combination of blood tests and biopsies gathered through an esophagogastroduodenoscopy (EGD). If celiac disease is suspected due to either symptoms or secondary risk factors, initial screening often involves serological testing for autoantibodies such as anti-tTG immunoglobulin A (IgA), anti-endomysial antibodies (EMA) IgA and total IgA.[7] Individuals with celiac disease are more likely than the general population to be IgA deficient, thus current guidelines advise that in these scenarios immunoglobulin G (IgG) autoantibody testing should be used instead.[8] Results for these tests are positively correlated with likelihood of the person having celiac disease, and current guidelines of the European Society of Pediatric Gastroenterology, Hepatology, and Nutrition state that levels of anti-tTG antibodies over ten times the upper limit of normal along with positive anti-EMA antibodies and HLA genotyping indicative of celiac disease are often sufficient for a diagnosis in symptomatic

individuals.[6] However, the European guidelines recommend biopsy for patients with a tTG below ten times the upper limit of normal as well as those with an elevated tTG but a negative EMA. Diagnostic algorithms published by the British Society of Paediatric Gastroenterology, Hepatology and Nutrition and the North American Society of Pediatric Gastroenterology, Hepatology and Nutrition require intestinal biopsy to confirm a celiac disease diagnosis.[7,8] Thus, an overwhelming majority of children are often diagnosed with celiac disease on the basis of intestinal biopsy findings.

Biopsies gathered during EGD procedures are used to identify histological changes to the duodenal mucosa of people with celiac disease. Histological findings are graded on a six-level Marsh scoring system ranging from 0 to 3c, based on presence of intraepithelial lymphocytes, crypt hyperplasia, and villous atrophy.[7]

Treatment Through a Gluten-Free Diet: Challenges and Benefits

The only currently available treatment for celiac disease is a lifelong strict gluten-free diet (GFD). This diet requires avoiding foods that contain gluten, barley, and rye. In practice, strict avoidance of gluten can be difficult as food labels are often inadequate or unavailable, for example in restaurants or other social gatherings.[14] Obvious sources of gluten include breads, pastas, and other baked goods; however, gluten may also be present in food thickeners, fillers, or processed meats.[10] Oats are also controversial for those on a gluten-free diet because while they can be a good source of nutrients that many with celiac disease are deficient in, research is conflicting over whether avenin peptides in oats can cause an immune response in individuals with celiac disease.[15] Cross-contamination

during manufacturing and food preparation is also difficult to regulate and thus individuals with celiac disease must take extra precaution when buying pre-packaged meals.[16]

Due to the abundance of gluten-containing foods and frequent reliance on processed foods, the early stages of transitioning to a GFD may be especially difficult. Initial challenges to a GFD include proper identification of prohibited ingredients on food labels and an increase in grocery budget and meal preparation time.[5] This is especially true in the pediatric population, as children are often resistant to trying new foods, reliant on adult caretakers to provide food, and may be more susceptible to peer pressure.[16] Even after initiation of the diet, many adults and children report difficulty maintaining a GFD in less controlled environments outside of the household such as at restaurants and while traveling resulting in some families avoiding these activities altogether.[17]

Despite these challenges, those who follow a strict GFD generally report positive outcomes in regard to their celiac disease symptoms. In a survey of adults with celiac disease, over half of subjects who had abdominal pain and/or diarrhea at diagnosis had alleviation of symptoms after starting the diet.[18] The average time for alleviation of symptoms in this cohort was approximately four weeks. While improvement of symptoms is often an important, maintenance of a GFD also promotes recovery of intestinal damage that, if left untreated, could result in poor long-term outcomes such as increased risk for intestinal carcinomas, lymphoma, and osteoporosis.[19]

Complete restoration of intestinal villi does not happen simultaneously with alleviation of symptoms or normalization of serologies. A retrospective study of those who had a follow-up EGD two years after being diagnosed with celiac disease and

commencing a GFD showed that less than 50% had complete recovery of intestinal villi.[19] Factors that were associated with poor recovery from villous atrophy included increased age of diagnosis, lower educational attainment, and the male sex.

Persistent mucosal damage is often attributed to continual gluten exposure, either intentional or accidental. Deliberate non-adherence to a GFD is commonly underreported and compliance in children often coincides with parental attitudes towards the GFD.[20] Even individuals who report being on a strict GFD are often found to have persistent villous atrophy, indicating potential unintentional ingestion of gluten.[21] Self-reported adherence to a GFD is often overestimated due to lack of knowledge about sources of gluten in everyday food items.[22] Adequate education about the GFD has been shown to increase both dietary adherence and of intestinal recovery.[21]

Adherence to a GFD is important not only for long-term health, but also critical for children during the periods of growth and development. Persistent intestinal inflammation can have a significant impact on absorption of micronutrients such as vitamin D which is needed for proper bone growth and thus lack of dietary adherence can result in disruptions in bone metabolism.[23] In many children with celiac disease, low bone mineral density can be reversed and return to normal after commencing a strict gluten-free diet.[24] Adequate vitamin D and calcium intake is especially important in pediatric and adolescent populations due to the fact that maximum bone density is achieved between the ages of twenty and twenty-five years of age.[25] It is also recommended that children enrich their diet with calcium and vitamin D, either through foods abundant in these nutrients or through vitamin supplements.[26] Counseling with a registered dietitian can help properly

educate children and their caretakers to make sure that their individual diets contain adequate nutrients for proper growth during these critical times as well as monitoring of height, weight, and body mass index.[23]

Recent studies have also indicated that individuals with the HLA-DQ2 genotype are more likely to be nonresponsive to the hepatitis B vaccination, increasing their risk for acquiring this infection.[27] However, after commencement of a GFD, individuals with celiac disease are more likely to respond to a booster of the hepatitis B vaccine and titers should be obtained to assure adequate immunity to the virus.[28]

Role of Clinicians and Dietitians in Celiac Disease Management

While the primary role of treatment of celiac disease is often left to the child and their caregivers responsible for medical and dietary decisions, the involvement of clinicians and dietitians is also important. Long-term engagement between the patient and healthcare provider has been shown to improve long-term management of chronic illnesses.[29]

Continual evaluation of dietary compliance is critical to long-term care of this population due to increasing evidence that lack of compliance is correlated with long-term risk for gastrointestinal complications.[30] Celiac related autoantibodies tend to normalize within six to twelve months after commencing a gluten-free diet, which makes it less sensitive to intermittent exposure to gluten but a good overall indicator of gluten-free diet status.[8] Collection of additional intestinal biopsies to check for mucosal recovery after commencing a gluten-free diet has the disadvantages of being time consuming and

invasive for the individuals as well as requiring an expert pathologist to interpret results.[31] Use of dietary evaluation surveys can help identify sources of gluten in people's diet and are becoming a standardized method for assessing dietary adherence.[31,32] Methods to detect gluten immunogenic peptide biomarkers in stool and urine are currently being developed as a technique to identify recent gluten exposure.[33] The presence of gluten immunogenic peptides in the urine may be more sensitive means of detecting mucosal damage when serological results are negative.[34]

Follow-up care by physicians, nurses, and dietitians is important for the long-term success of individuals with celiac disease. Studies have shown that those who are adherent to follow-up visits have higher chances of normalized serologies, increased growth, and better psychological wellbeing, especially if these habits are started at a young age and continued through adulthood.[20,35] Regularly scheduled follow-up visits with a multidisciplinary team of healthcare providers helps children and caretakers stay informed with accurate information of maintaining a healthy GFD and can decrease the perceived treatment burden of celiac disease while increasing overall satisfaction.[36]

The Celiac Disease Program at Boston Children's Hospital (BCH) has established its own set of guidelines for treatment and monitoring of children with celiac disease.

The current recommended follow-up schedule for children with newly diagnosed celiac disease at BCH includes the following:

a) Attendance of "Going Gluten-Free" nutritional diet class with registered dietitian
b) Individual follow-up with dietitian 2 to 3 weeks after the class
c) Attendance of 3-month follow-up visit with physician

d) Attendance of 6-month follow-up visit with physician

e) Attendance of 12-month follow-up visit with physician

f) Annual follow-up visits with physician until transfer of care to an adult gastroenterologist

Aims of the Current Study

Previous unpublished studies using BCH Patient360 clinical data registry found that loss to follow-up of children with celiac disease is a significant problem, with a majority of patients being lost within five years of diagnosis. We hypothesized that patient level data would lead to identification of both modifiable and non-modifiable patient characteristics associated with follow-up adherence. Socioeconomic disparities in the presentation and management of celiac disease have been previously studied, including the underdiagnoses of children from low income homes along with the increased likelihood of persistence of symptoms.[37,38] Barriers to accessing clinical appointments due to travel constraints have been shown to disproportionally affect families with a lower socioeconomic status and we hypothesized that this would be true for our study.[39] Along with socioeconomic status, we also sought to evaluate the association between age of diagnosis, GFD adherence, and presence of comorbidities with adherence to follow-up with a pediatric gastroenterologist for long-term celiac disease management. This information may be useful for healthcare providers by indicating that children meeting these criteria may be more vulnerable to being lost to follow-up and thus facilitate early intervention to reduce the risk for these subpopulations.

METHODS

Study Design and Definitions

A retrospective chart review was conducted by examining the medical records of 250 children diagnosed with celiac disease at BCH between January 1st, 2010 and December 31st, 2014. Subjects were randomly selected from an existing database maintained within the Department of Gastroenterology and Nutrition at BCH, which includes children diagnosed with biopsy-confirmed celiac disease within the hospital network. Medical records from BCH were reviewed between January 1st, 2010 and December 31st, 2017. This time frame allowed for evaluation of follow-up visits for a minimum of three years following biopsy diagnosis. Subjects who had reached the age of 18 prior to diagnosis were excluded as well as those who came to BCH seeking a second opinion.

This study was approved by the Institutional Review Board at BCH.

For clinical results, low vitamin D was defined as levels below 30ng/mL and upper limit of normal for celiac antibody serologies was based on the specific assay used by the individual lab. BMI Z-scores were used to classify growth status, with -2.0 being defined as underweight, +1.0 as overweight, and +2.0 as obese.[40] Adherence to a GFD was determined based on persistence of symptoms, celiac serology, and clinician assessment at final follow-up visit. Subjects were then categorized as either adherent or non-adherent to the GFD.

"Lost to follow-up" was defined as subjects who did not return for a subsequent clinical gastroenterology visit with a physician or nurse practitioner, or a nutrition visit

with a registered dietitian, at either the main BCH campus or a network satellite clinic after being diagnosed with celiac disease. Time until lost to follow-up was calculated as the interval between the initial endoscopy and the last clinical gastroenterology visit attended. Subjects whose last visit was after the age of 18 were not considered lost as they were eligible to continue care with an adult gastroenterologist outside of the BCH network. However, individuals who continued to see their pediatric gastroenterologist beyond the age of 18 were not excluded if they continued to be adherent to follow-up.

A secondary analysis was performed to determine if the loss to follow-up was related to relocation. This was done by comparing the last celiac disease follow-up visit with visit dates with other providers within the BCH network. An attended visit with a network provider after the subject was defined as "lost to follow-up" to the gastroenterology and nutrition department was used to establish positive residency.

Adherence to follow-up was categorized based on the recommended follow-up schedule at BCH and previous studies[9]

1) Lost to GI follow-up after diagnosis
    a. Did not attend dietitian education
    b. Attended dietitian education
2) Lost within one year after attending at least one clinician follow-up
3) Lost to follow-up one year after diagnosis, attended at least one follow-up visit within first year

4) Non-adherent to recommended follow-up schedule as defined as first follow-up visit over one year after diagnosis and/or follow-up visits over 18 months apart
5) Adherent to recommended follow-up schedule
6) Lost to follow-up after age 18

Data Collection and Measurements

Study data was collected and managed on a case report form (Appendix 1) created using the Research Electronic Data Capture (REDCap) electronic data capture tool hosted by BCH. REDCap is a secure, web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources.[41]

Data abstracted from the departmental database included demographic data, diagnostic biopsy data, symptoms at time of diagnosis, family history, comorbidities, initial serology, and anthropometrics. Medical records compiled from PowerChart (Cerner, Kansas City, MO) were used to confirm demographic data accuracy with the internal database as well as to gather additional information regarding follow-up care.

Data abstracted from patient medical records included dates of all visits with gastroenterologists and registered dietitians were collected. Only the most recent visit date for providers in other departments at BCH were recorded. Active medical conditions, most recent medications on file, and anthropometric data from follow-up visits were

recorded. Additional family history gathered included the presence of absence of celiac disease in the immediate household, with attempts to distinguish between siblings and adults. Laboratory tests including celiac serologies, hepatitis B titers, hemoglobin, hematocrit and vitamin D levels. In depth visit information was collected for the most recent follow-up visit with GI and/or nutrition. This data included clinic location, clinician reported status of gluten free diet adherence, active symptoms at time of visit, and recommended follow-up interval. Most recent insurance provider on file was also recorded.

To facilitate analysis based on socioeconomic status, relevant census information was collected from the U.S. Census Bureau using the last zip code on file and year of last visit at any BCH department. Information inferred based on geographic location included median income, poverty rates, and percent of district with a high school or college degree. The exception to this was any individual who was seen in the year 2017, in which 2016 census data was used since at the time of this study the U.S. Census Bureau has not released 2017 data. Geographical distance between clinic sites and home zip code were determined using the haversine formula with corresponding latitude and longitude coordinates.

Data Analysis

Statistical analysis was performed using R[42] version 3.2.1 using RStudio[43] version 1.1.383. Pearson's correlation was used to find associations between continuous variables such as age at diagnosis, median income, and time until lost to follow-up. Paired t-tests (or Wilcoxon signed rank sum for non-parametric populations) were used to find associations between continuous and categorial variables, such as age at diagnosis and defined

follow-up adherence categories. Other tests used included one-way ANOVA (or Kruskal Wallis for non-parametric populations) and Chi-squared tests. The Kaplan-Meier method was used to determine rate of loss to follow-up in this cohort. Survival curves were censored to remove the subject when they reached age 18 or attended a visit after June 1st, 2016 to account for this study's time period ending in 2017. Two-sided P-values <0.05 were considered statistically significant.

RESULTS

Characterization of Cohort

Of the 250 subjects included, 9 attended BCH for the sole purpose of obtaining a second opinion and thus were excluded from the analysis as per exclusion criteria. Of the remaining 241 subjects, 64% were female, median age of diagnosis was 9.70 years, and median age at last clinical visit was 12.75 years (Table 1) No subjects were reported as deceased during the observation period. Race was unknown or not reported for 37 subjects, and, of the 204 reported, only 11 (5%) were non-Caucasian. Data on household composition was available for a majority of the subjects (N=224), indicating that 195 (87%) subjects had at least two adults in the household. Sibling data was available for 228 subjects, 114 (50%) had only one sibling and 18 (8%) were an only child. This cohort included 4 pairs of siblings. There were only 14 (6%) subjects who had an out of state zip code; 8 from New Hampshire, 3 from Rhode Island and 1 each from Connecticut, New Jersey, and New York. However, the median distance from the main hospital was 12.3 miles. A median of 95% of adults in the census designated regions had a high school diploma or higher, compared to the 2017 national average of 87%.[44]

Table 1: Demographic Information (N=241)

Female [N (%)]	154 (64%)	Single-parent household (N=225)	28 (12%)
Non-Caucasian (N=205)	11 (5%)	Median Income Above $100,000 [N (%)]	105 (43%)
Median Age at Diagnosis [IQR]	9.70 [6.23,13.33]	Median Percent Adults with HS Diploma	95%
Median Age at Last Visit [IQR]	12.75 [9.27, 16.23]	Median Distance to Hospital (mi) [IQR]	12.3 [6.9, 22.5]
		Medicaid/CHIP as Primary Insurance (N=237)	20 (8%)

Only one subject had a Marsh score of 1 at diagnosis, with the rest of the cohort having a Marsh score of 3. Most subjects had at least one other medical condition in addition to celiac disease. Only 33% (N=80) subjects had no other medical conditions listed. The most frequent coexisting conditions as well as those related to celiac disease are listed in Table 2.

Table 2: Coexisting Medical Diagnosis by System (N=241)

Gastrointestinal		**Endocrine**	
Chronic Constipation	32 (13%)	Type I Diabetes Mellitus	21 (9%)
Gastroesophageal Reflux Disease	12 (5%)	Thyroid Disease	9 (4%)
Eosinophilic Esophagitis	10 (4%)	Short Stature	7 (3%)
Inflammatory Bowel Disease	2 (1%)	Osteopenia	4 (2%)
Irritable Bowel Syndrome	5 (2%)	**Psychiatric**	
Nutrition		ADD/ADHD	21 (9%)
Growth concerns	6 (2%)	Anxiety	9 (4%)
Eating Disorder	5 (2%)	Depression	4 (2%)
Obesity	4 (2%)	**Other**	
Nutritional Deficiency	2 (1%)	Asthma	19 (8%)
Gynecologic		Scoliosis	9 (4%)
Endometriosis	4 (2%)	Trisomy 21	4 (2%)
Irregular menses	2 (1%)	Iron-Deficiency Anemia	3 (1%)

Family history of celiac disease was present in 81 (36%) subjects[1], with 11 (14% of subpopulation) of these individuals having both a parent and sibling with celiac disease. History of a first degree relative having celiac disease resulted in 34 referrals to the Celiac Disease Program after screening for autoantibodies was positive.

At diagnosis, abdominal pain (57%), constipation (34%), weight loss (24%), and vomiting or nausea (24%) were the most frequent symptoms (Figure 1) Other symptoms included hematochezia, hair loss, and either fecal or urine incontinence. At time of last

[1] Family history of celiac disease unknown or not reported in 17 subjects

visit, over half of the subjects (61%) had resolution of their original complaint of abdominal pain and 30% of the total cohort reported being asymptomatic compared to only 6% at presentation. Resolution of symptoms for subjects who did not return for a visit after diagnosis is unknown and was not considered.

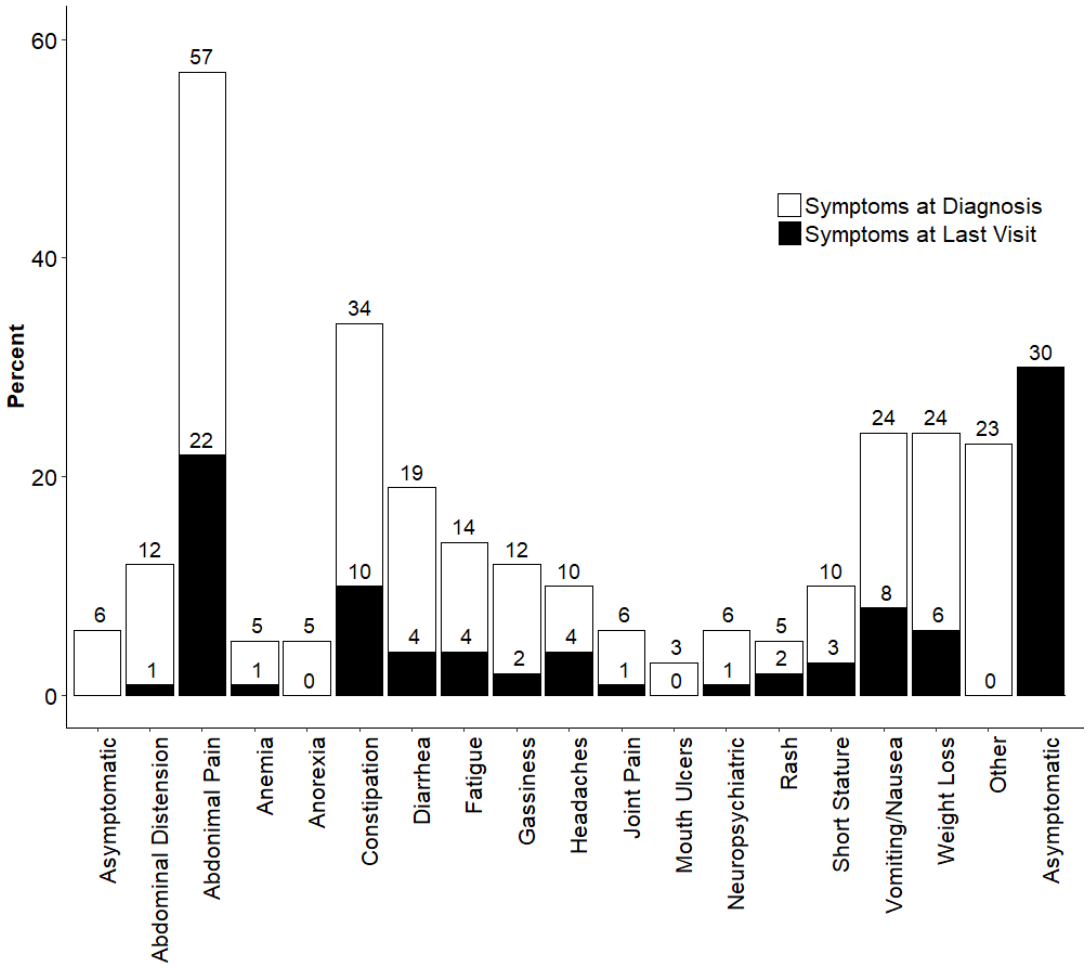

Figure 1: Percentage of cohort with symptoms at time of presentation and alleviation of symptoms at time of last clinical visit. Includes subjects presenting with multiple symptoms. N= 241

Visit Information

The median time between the initial celiac consultation and biopsy date was 23 [13, 32] days and median time to first follow-up visit was 59 [20, 109] days.

Most subjects (83%) attended at least one visit with a dietitian in either a classroom setting or an individual visit (Table 3). Visiting with a dietitian was not associated with a significant difference on assessed dietary adherence at the last clinical visit attended (P>0.26). Family history of celiac disease was also not associated with attending a dietitian visit (P=0.13) or assessed dietary adherence at last visit (P=0.17).

Table 3: Utilization of Dietitian Services

GFD Adherence at Time of Last Clinical Visit	**Attended nutrition class and individual visit (N=74)**	**Attended nutrition class only (N=51)**	**Attended individual visit only (N=76)**	**No RD Visits (N=40)**
Adherent	62 (84%)	41 (80%)	53 (70%)	27 (68%)
Non-Adherent	8 (11%)	4 (8%)	11 (14%)	4 (10%)
Unknown	0	2 (4%)	6 (8%)	1 (2%)
Lost After Biopsy	4 (5%)	4 (8%)	6 (8%)	8 (20%)

Almost half of subjects were on dietary supplements after diagnosis, with higher rates in those with vitamin deficiencies. Of the 179 subjects who had vitamin D levels available, 119 (66%) had at least one result indicating vitamin D deficiency. The number of subjects who had a low vitamin D level at time of their last documented blood draw was reduced to 68 (38%), or 60% of the original subjects identified as vitamin D deficient. These individuals had increased usage of vitamin D supplements (P=0.03). However, multivitamin usage did not differ significantly (P=0.19). Attendance of a visit with a dietitian was not associated with use of a multivitamin or supplement or presence or absence of vitamin D deficiency.

Table 4: Utilization of Multivitamin and Vitamin D Supplements

Supplement Use	Entire Cohort (N = 241)	Vitamin D Deficient (N = 68)
Multivitamin	117 (49%)	30 (44%)
Vitamin D	45 (19%)	22 (32%)
Multivitamin & Vitamin D	26 (11%)	12 (18%)

At least one anthropometric measurement was available for the entire cohort. At diagnosis, 16 (7%) subjects were underweight, 29 (12%) were overweight, and 4 (2%) were obese. For those who attended at least one follow-up visit with the GI and Nutrition Department and had measurements available (N=227), 6 (3%) were underweight, 22 (15%) were overweight, and 4 (2%) were obese at time of last follow-up visit. Of those who were underweight at time of diagnosis, only 2 were also classified as underweight at time of last follow-up visit, with both visits greater than one year after initial diagnosis. Over half of the subjects (62%) who were overweight or obese at time of diagnosis were also overweight or obese at time of last follow-up visit. The median time since diagnosis for individuals who were overweight or obese at last follow-up visit was 34.2 months [21.0, 53.4]. Across the entire cohort, height and weight steadily increased compared to baseline measurements taken at diagnosis (Figure 2) with the most significant growth occurring at least 2 years after diagnosis.

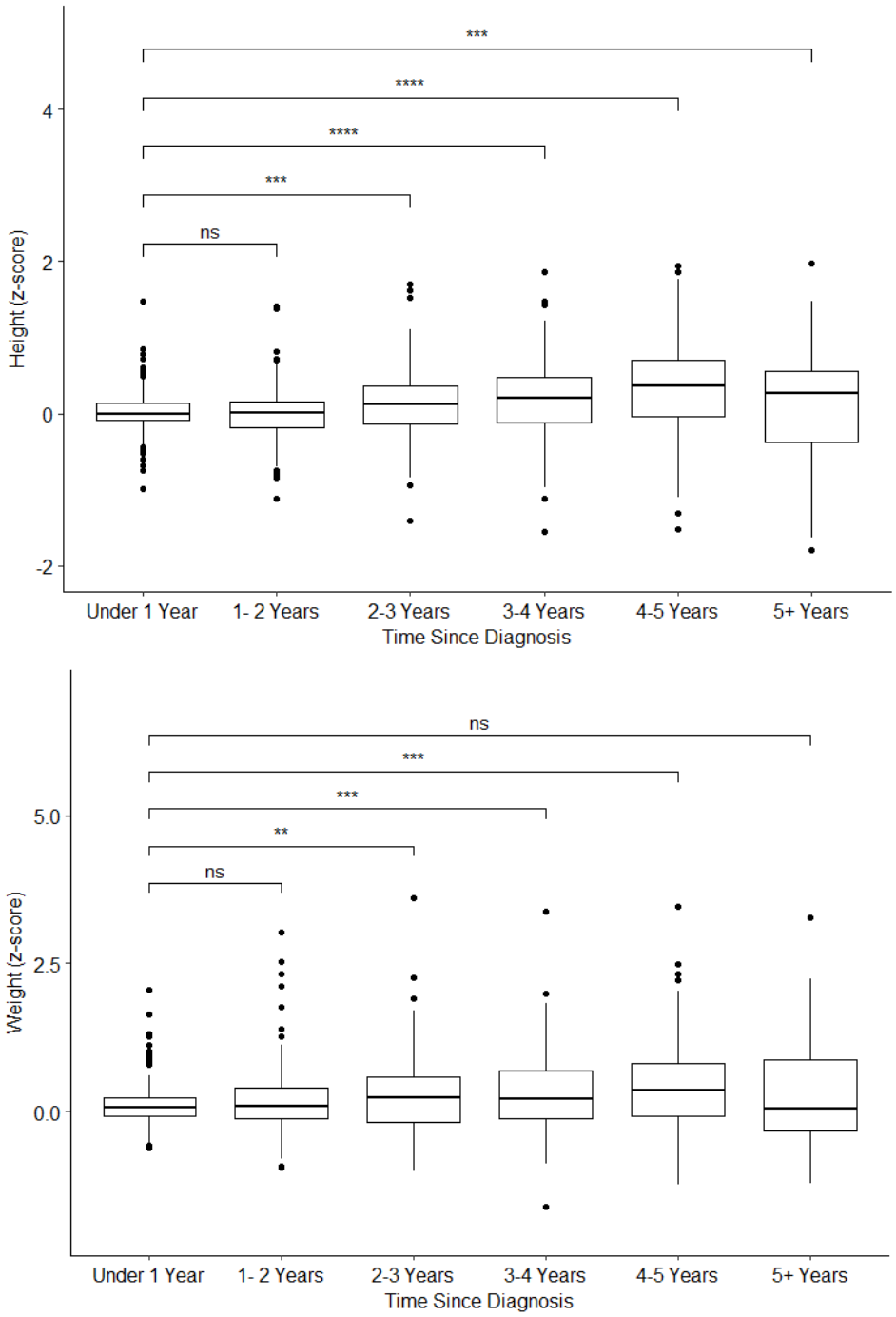

Figure 2: Top) Changes in Z-score of height measurements compared to Z-score of height at diagnosis. Total of 932 measurements compared over 7 years. N = 228. Bottom) Changes in Z-score of weight measurements compared to Z-score of weight at diagnosis. Total of 932 measurements compared over 7 years. N = 232.
ns (p>0.05), ** (p<0.01), * (p<0.001), **** (p<0.0001)**

Final celiac antibody serologies were available for 141 (59%) subjects, with one quarter of this subgroup (N=35) having an tTG IgA titer above the upper limit of normal with a median time since diagnosis of 20 months [12.4, 28.6]. Subjects who continued to follow-up with GI until the end of the study period were significantly more likely to have normalized serology levels regardless of how strict this adherence to follow-up visits were (Figure 3). After being lost to GI, 10 (4%) subjects continued to have celiac serologies ordered by other department providers, with 2 having an abnormal tTG IgA over 3 years after initial diagnosis. These two individuals were lost to GI within one year.

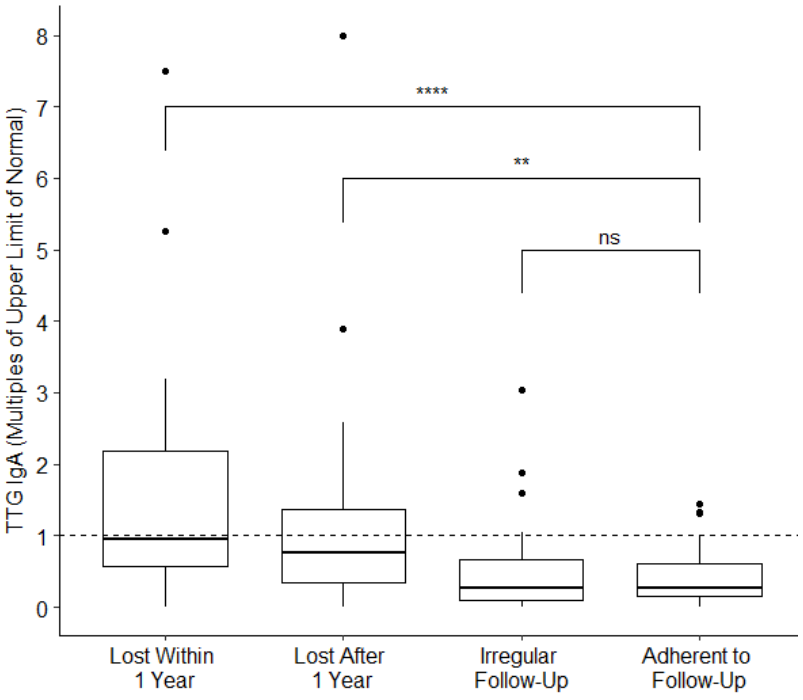

Figure 3: Results of tTG IgA serologies at last clinical GI visit based on adherence to follow-up. Dotted line represents upper limit of normal. N = 146. ns (p>0.05), ** (p<0.01), ** (p<0.0001)**

Hepatitis B titers were ordered for 106 (44%) subjects seen for follow-up, and of these individuals, 87 (82%) were not immune to the virus. Of this subgroup of non-

immune subjects, 40 (46%) had repeat titers documented with 30 being immune and 10 remaining negative for the hepatitis B surface antibody. There were no hepatitis B antibody titers ordered prior to August 2013.

Adherence to Follow-Up Analysis

Overall, 50% of subjects were lost to follow-up within 39 months of diagnosis with the largest decrease occurring during the first 12 months (Figure <<>>). By 5 years post-diagnosis, almost 75% of subjects were no longer attending follow-up visits. There were 22 (9%) subjects who did not attend a clinical GI visit after diagnostic endoscopy, 14 (64%) of whom attended at least one visit with a dietitian after diagnosis (Table 5). An additional 37 (15%) subjects were lost within the first year after diagnosis, with more than half lost within the first six months (N=20). Individuals who were eligible to transfer care to an adult gastroenterologist comprised 14% (N=34) of the entire cohort population. Half of these individuals did not return for follow-up while the other half continued to see their pediatric gastroenterologist until the end of the observation period. Those who continued to be seen by their pediatric celiac care provider after the age of 18 were more likely to have been diagnosed at an earlier age compared to those who left BCH care after turning 18 ($P<0.01$).

Table 5: Categorization of Subject Adherence to Recommended Follow-Up

Category	N (%)
1a: Lost after biopsy, did not attend education with dietitian	**8 (3)**
1b: Lost after biopsy, attended education with dietitian	**14 (6)**
2: Lost within first year, attended at least one follow-up visit	**37 (15)**
3: Lost after first year, attended at least one visit within and after first year	**61 (25)**
4: Following up, non-adherent to recommended follow-up schedule (first visit after 12 months and/or follow-up visits over 16 months apart)	**63 (26)**
5: Following up, adherent to recommended schedule	**41 (17)**
6: Lost to follow-up after age 18	**17 (7)**

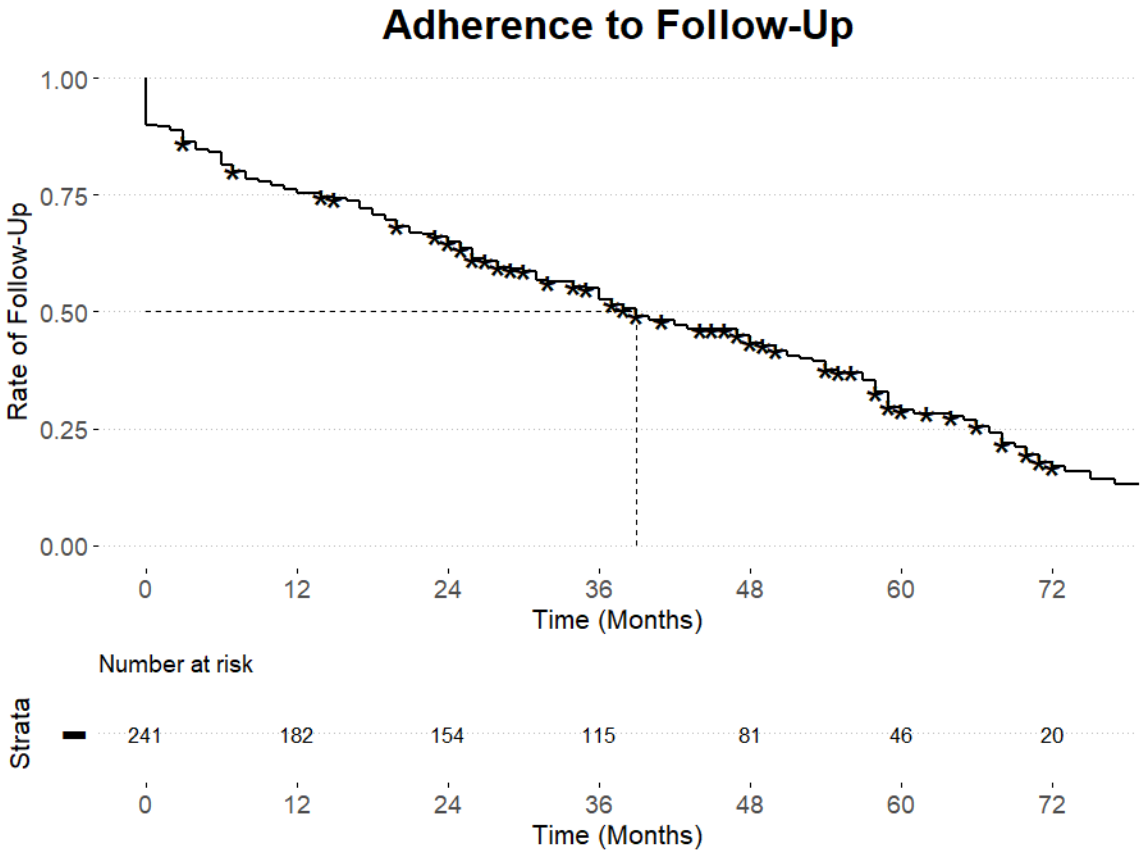

Figure 4: Kaplan-Meier estimator analysis curve of 241 subjects from diagnosis until lost to follow-up. * indicates censor when subject turned 18 years of age or end of study time period.

Almost half of the cohort (N=105, 43%) had a zip code in a census designated region in which the median income was over $100,000. Of those lost within the first year after diagnosis, including those lost after biopsy, less than one quarter were from this high-income subgroup (24%). One in three subjects (N=45) from the lower income group (N=136) were lost within this time frame. Subjects with Medicaid listed as their last insurance provider on file (N=20) had a shorter median duration of follow-up adherence compared to those who used private insurance providers (P=<0.01), with 50% of this subgroup being lost to follow-up within one year.

Subjects who were lost to follow-up within one year had a median age of diagnosis of 11.4 years compared to age of diagnosis, 8.7 years, of those who were adherent to follow-up for at least one year (P=0.03). Having a sibling with celiac disease resulted in a shorter duration of follow-up adherence compared to those who did not have a sibling with celiac disease, even when controlling for other family members with celiac disease (P=0.01). Of the 4 pairs of siblings in this cohort, only 1 sibling pair was considered adherent to follow-up; 1 was lost after diagnosis, 1 within the first year, and the final pair was lost to follow-up after 26 months. Individuals who were asymptomatic at last visit also had decreased adherence to follow-up compared to those who continued to have celiac disease symptoms (P=0.02).

Almost three quarters (73%) of subjects had at least one visit with a non-GI provider within the BCH network. Attending visits with non-GI providers within the BCH network was not associated with adherence to GI follow-up (P=0.77). Over 20% of the entire cohort attended a visit with a non-GI provider after being lost to GI, thus

confirming that these individuals were not lost due to relocation. Of those lost within one year after diagnosis, including those lost immediately after biopsy, 26 (44%) met the criteria for confirmation of residency and thus relocation was not the reason for not attending follow-up.

DISCUSSION

In this retrospective cohort study of children with a biopsy-confirmed diagnosis of celiac disease, the principal finding was that most were non-adherent to recommended follow-up care with 50% of individuals being lost to both gastroenterology and nutrition follow-up within 3 years of diagnosis. The sharpest drop in follow-up adherence occurred during the first year after diagnosis, with 25% of subjects being lost to follow-up within this time frame. Children diagnosed at a younger age were more adherent to follow-up compared to those diagnosed during adolescence. However, those who had siblings with celiac disease were less adherent to follow-up compared to those who had no family history or remote family history of celiac disease. Socioeconomic disparities also existed between those with public and private health insurance, with individuals on Medicaid having decreased follow-up adherence.

These numbers are disconcerting because successful treatment of celiac disease is dependent on adequate patient knowledge and implementation of dietary and lifestyle modifications. A 2015 study demonstrated that continual follow-up and dietary education is associated with increased adherence to a gluten-free diet as well as better quality of life. Counseling by a dietitian was shown to result in better understanding of the gluten-free diet in recently diagnosed individuals compared to those who did not attend a visit with a dietitian.[45] Thus, in this current study, with 40 (17%) subjects failing to attend a visit with a registered dietitian, it is questionable whether this subpopulation was properly

educated on accurate information regarding a gluten-free diet, especially the 8 subjects who did not meet with either a dietitian or GI clinician after diagnosis.

Over 20% of subjects who had an abnormal celiac antibody level did not return for repeat serologies. In addition, over half of these individuals were diagnosed over 18 months prior to the drawn labs. Results above the upper limit of normal after the first 18 months of diagnosis may be indicative of poor intestinal recovery and/or continual gluten exposure.[46] Ergo, it's uncertain if the potential source of gluten exposure was identified in these individuals because they did not have a subsequent visit with GI or nutrition.

Less than half of this cohort had a documented hepatitis B serology. Individuals who were lost to follow-up before this test was routinely ordered are at risk due to the fact that their immunization status is unknown. If their status reflects the subpopulation of subjects whose status was checked, then most of these individuals are most likely not immune to hepatitis B. Lack of adherence to follow-up results in individuals being at risk for hepatitis B infection.

Continued follow-up care and adherence to the gluten-free diet resulted in a majority of these subjects having an increase in height and weight percentiles. Over 75% of those who were underweight at time of diagnosis had their growth increase and normalize after diagnosis and follow-up. However, 15% of the cohort was considered overweight or obese at the time of their last follow-up. This is consistent with findings in other studies regarding the tendency of the GFD to cause excessive weight gain as well as the importance of follow-up to evaluate nutritional status.[47,48] Besides assuring adequate growth after commencing a GFD, continual dietitian guidance along with clinician monitoring

can help children form healthy dietary habits that will benefit their long-term wellness. Studies have shown that children with chronic illnesses that focus restricting food intake have an increased risk for developing an eating disorder and higher incidences of psychological problems such as anxiety and depression.[49,50] This is consistent with the current study as 2% of the cohort had an eating disorder, 4% had anxiety, and 2% had depression. Services offered by BCH to help families adjust to the lifestyle and dietary changes required after diagnosis include trained celiac social workers, psychological services, and family support groups. Regular follow-up visits with the celiac care team can help children and family members identify problems early and provide appropriate care for children who have difficulties adapting to the GFD after diagnosis.

One of the aims of this study was to identify factors that may be associated with nonadherence to follow-up. Subjects who were asymptomatic were less likely to attend a subsequent follow-up visits compared to those who continued to have celiac symptoms. As well as the high rates of dropout within the first year after diagnosis, the second largest decrease in follow-up was between the second and third year after diagnosis. This group would have returned for at least one annual visit and met with a dietitian. After this time, subjects and their caregivers may feel that they have fully adjusted to their celiac disease diagnosis and transition to a gluten-free diet, thus preferring to self-manage their condition.

Children diagnosed at a younger age were more likely to be adherent to recommended follow-up compared to those who were diagnosed in adolescence. The decrease in follow-up adherence in older children has been demonstrated in prior studies, as well

as the association between lack of GFD adherence in children lost to follow-up.[51] Continual follow-up throughout childhood is important, especially throughout different stages of development. A recent study, also conducted at BCH, surveyed children with celiac disease, and their caretakers, and aimed to evaluate self-management competencies across multiple age groups. Key findings included that, as children progress through adolescence, new situations arose that required additional skills and understanding of how to maintain a gluten-free diet.[52] Another similar study indicated that adolescents and young adults face challenges maintaining a GFD when relying on school cafeterias and dining services for the majority of their meals.[53] By neglecting to continue with regular follow-up visits with their celiac provider, children with celiac disease and their families are thus unable to receive adequate and updated information about navigating the intricacies of a GFD in these new situations.

In this study, subjects who had turned 18 made up of a unique subpopulation, as discontinuing follow-up at BCH was not classified as being lost. Subjects who had turned 18 had a 50% chance of continuing care with their pediatric provider. While one would like to believe that the other 50% successfully transferred their care to an adult gastroenterologist, prior studies on individuals with chronic illnesses diagnosed during childhood have shown that this transition is not always successfully made.[54] In this cohort, subjects who were diagnosed at a younger age were more likely to continue care with their pediatric GI past the age of 18. This may be due to comfort and familiarity with their provider developed over the years.

Socioeconomic circumstances were also associated with decreased adherence to follow-up. Prior studies have identified socioeconomic disparities in individuals with celiac disease. In those with a lower socioeconomic status, celiac disease is often underdiagnosed, although these individuals often report more severe symptoms which take longer to resolve compared to the rest of the celiac disease population.[37] The increase in food costs associated with a GFD is often cited as a barrier to treatment and can be especially pronounced in populations who already have difficulties securing meals.[5]

A 2012 study that focused on follow-up adherence in children with congenital heart disease also found that increased cancelled visits and lower median income were associated nonadherence to follow-up. This study was conducted in Canada, a country with access to universal healthcare, indicated that median income is not only attributed to access to health insurance but also factors such as caregiver ability to take time off of work to attend visits during business hours as well as associated transportation costs.[55]

Children with siblings with celiac disease were less likely to be adherent to follow-up compared to those who either had no family history or had distant family history of celiac disease. The increased time commitment by caregivers to attend additional visits for these children may influence their adherence to clinical follow-up or may feel that they understand the complexities of the GFD.

Limitations of this study include a homogenous sample size limited to children with means of access to a tertiary care center. Missing information from medical records due to conversion of paper charts to electronic versions resulted in some data gaps in subject records, but this was mostly concentrated to encounters in early 2010. Other missing

information included serological results or other data not being entered into the BCH medical records from offices outside of the network. The cohort of subjects sampled for this project included only children with a diagnosis of celiac disease confirmed through intestinal biopsy. It is possible that children diagnosed without biopsy would have different patterns of adherence to follow-up, although the number of individuals diagnosed without biopsy confirmation at Boston Children's Hospital during this time period is limited.

Future directions include increasing the population size and expanding to multiple centers or settings to increase diversity of the cohort. The sample in this study were mostly from more affluent areas of Massachusetts with abundant access to medical facilities. At least one subject was noted to be transferring their care to a primary care provider outside of the network. While it is recommended that individuals with celiac disease be followed by a gastroenterologist, expanding the study to more underserved areas, where access to pediatric gastroenterologists and dietitians is less feasible, could allow for a differing investigation of follow-up adherence.

Taking a more interactive approach to determining reasons as to why individuals are lost to follow-up could be introduced by contacting these children and their families and investigating specific reasons for not returning for follow-up. The limitations of this approach however would be the fact that many of the contact information in the medical records of these individuals may be outdated.

In conclusion, the present study illustrates that children with celiac disease are not being followed-up adequately. Identifiable disparities in follow-up adherence exist in the

pediatric celiac disease population. Factors associated with non-adherence include Medicaid as the primary health insurer, older age at diagnosis, and siblings with celiac disease. Future studies should be focused on emphasizing the importance of continuity of follow-up care to both providers and patients as well as exploring proactive measures to increase adherence in children with identified risk factors.

LIST OF JOURNAL ABBREVIATIONS

Arch Dis Child	Archives of Disease in Childhood
Aliment Pharmacol Ther	Alimentary Pharmacology and Therapeutics
Am J Clin Nutr	American Journal of Clinical Nutrition
Am J Gastroenterol	The American Journal of Gastroenterology
Best Pract Res Clin Gastroenterol	Best Practices and Research: Clinical Gastroenterology
BMC Pediatrics	BioMed Central Pediatrics
Br Med J	British Medical Journal
Cardiol Young	Cardiology in the Young
Clin Gastroenterol Hepatol	Clinical Gastroenterology and Hepatology
Clin Nutr	Clinical Nutrition
Clin Pediatr	Clinical Pediatrics
Eur J Clin Nutr	European Journal of Clinical Nutrition
Indian J Gastroenterol	Indian Journal of Gastroenterology
Int J Eat Disord	International Journal of Eating Disorders
Int Sch Res Not	International Scholarly Research Notices
J Biomed Inform	Journal of Biomedical Informatics
J Community Health	Journal of Community Health
J Gastroenterol Hepatol	Journal of Gastroenterology an Hepatology
J Multidiscip Healthc	Journal of Multidisciplinary Healthcare
J Pediatr Gasteoenterol Nutr	Journal of Pediatric Gastroenterology and Nutrition

J Pediatrics	Journal of Pediatrics
Paediatr Child Health	Pediatrics and Child Health
Public Health Rep	Public Health Reports
Rev Endocr Metab Disord	Reviews in Endocrine and Metabolic Disorders
Semin Immunopathol	Seminars in Immunopathology
World J Gastroenterol	World Journal of Gastroenterology

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