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# Healthcare Resource Utilization and Costs in Celiac Disease: A US Claims Analysis

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**INTRODUCTION:** Celiac disease (CeD) is a lifelong immune-mediated enteropathy in which dietary gluten triggers an inflammatory reaction in the small intestine. This retrospective cohort study examines healthcare resource utilization (HRU) and costs between patients with CeD and matched controls.

**METHODS:** Patients with CeD (cases) with an endoscopic biopsy and ≥2 medical encounters with a CeD diagnosis between January 1, 2010, and October 1, 2015, were identified in the MarketScan databases. The date of the first claim with a CeD diagnosis on or after the endoscopic biopsy was the index date. Cases were matched 1:1 to patients without CeD (controls) on demographic characteristics and Deyo-Charlson Comorbidity Index score. Clinical characteristics, all-cause, and CeD-related HRU and costs (adjusted to 2017 US dollars) were compared between cases and controls during the 12 months before (baseline) and 24 months after (follow-up) the index date.

**RESULTS:** A total of 11,008 cases (mean age 40.6 years, 71.3% women) were matched to 11,008 controls. During the follow-up, a higher proportion of cases had all-cause and CeD-related HRU including inpatient admissions, emergency department visits, gastroenterologist visits, dietician visits, endoscopic biopsies, and gastroenterology imaging (all $P \leq 0.002$). Incremental all-cause and CeD-related costs were in the first ($7,921 and $2,894) and second ($3,777 and $935) year of follow-up, driven by outpatient services costs.

**DISCUSSION:** In this US national claims database analysis, there was evidence of an increase in both all-cause and CeD-related HRU and related costs in patients with CeD compared with matched patients without CeD, suggesting a significant economic burden associated with CeD.

## INTRODUCTION

Celiac disease (CeD) is a lifelong immune-mediated enteropathy in which dietary gluten triggers an inflammatory reaction in the small intestine in genetically predisposed individuals (1–3). Most patients diagnosed with CeD are women and are diagnosed in middle age, although onset can occur at any age (4). The prevalence of CeD has been estimated to range between 0.5% and 2% in different countries worldwide, although the true prevalence is difficult to ascertain because many people are undiagnosed (2,5). However, patients with other autoimmune disorders (such as autoimmune thyroiditis, autoimmune hepatitis, type 1 diabetes, dermatitis herpetiformis, Sjogren syndrome, and psoriasis) (6) or relatives of patients with CeD have a higher risk of developing CeD (7).

The only available treatment of CeD is lifelong strict adherence to a gluten-free diet, which can be challenging because of availability, cost, cross-contamination, and social pressure (8,9). If patients can maintain a strict gluten-free diet, then mucosal healing typically occurs within the first 1–2 years; however, some patients experience delayed mucosal healing (10). A 2008 study of 525 patients in the United States with CeD found that direct healthcare costs spiked by 41% in the year immediately after diagnosis and dropped to 8%–16% below the baseline in the subsequent 2 years (11). This suggests that the burden of CeD to the US healthcare system is only during the initial diagnosis and disease management stage; however, that study did not compare with controls, so it does not account for any CeD-related healthcare costs that existed before diagnosis and persisted after diagnosis.

Two studies have demonstrated that patients with CeD in the United States have higher healthcare costs than the controls (12,13). In Olmsted County, Minnesota, the 4-year cumulative direct medical costs, in 2008 US dollars (USD) of patients with CeD were $3,964 (2008 USD) higher than those of the controls (13), whereas the analysis of commercially insured patients from a nationally representative database reported that annual medical costs,

in 2013 USD, were $5,991 higher and the annual pharmacy costs were $1,293 higher for patients with CeD than the controls (12). Although these trends have been corroborated by studies in the United Kingdom and Israel (14,15), they lack procedure-level detail, enabling a more complete understanding of the burden of diagnosis, treatment, and management (16). To better understand the burden of illness, we carried out a large US claims analysis comparing all-cause and CeD-related healthcare resource utilization (HRU) and costs between patients with and without CeD.

## METHODS

### Data source

This is a retrospective, observational study based on US administrative claims data captured in the IBM MarketScan Research Databases between January 1, 2009, and September 30, 2017 (study period). The MarketScan Commercial Claims and Encounters Database contains inpatient, outpatient, and outpatient prescription drug experience of approximately 137.6 million employees and their dependents covered under a variety of fee for service and managed healthcare plans, including exclusive provider organizations, preferred provider organizations, point of service plans, indemnity plans, and health maintenance organizations during 1995–2016, including 24.4 million lives in 2016. The MarketScan Medicare Supplemental and Coordination of Benefits Database contains the healthcare experience (both medical and pharmacy) of approximately 10.2 million retirees with Medicare supplemental insurance paid for by employers between 1995 and 2016, including 1.9 million lives in 2016. Both the Medicare-covered portion of payment (represented as Coordination of Benefits Amount) and the employer-paid portion are included in this database. The MarketScan Commercial and Medicare Databases provide detailed cost, use, and outcomes data for healthcare services performed in both inpatient and outpatient settings. The medical claims are linked to outpatient prescription drug claims and person-level enrollment data through the use of unique enrollee identifiers.

### Patient selection

Patients were included in the CeD cohort if they had ≥1 medical claim with a procedure code for endoscopic biopsy between January 1, 2010, and October 1, 2015, and ≥1 nondiagnostic medical claim with a diagnosis code for CeD on or after the date of the endoscopic biopsy. The date of the first eligible claim with a CeD diagnosis was defined as the *index date*. In addition, patients with CeD were required to have ≥1 nondiagnostic medical claim with a diagnosis code for CeD in the 12 months after the index date along with continuous enrollment in medical and pharmacy benefits for ≥12 months before the index date (baseline period) and ≥24 months after the index date (follow-up period).

The control population was sampled from patients in the MarketScan databases without any evidence of CeD between January 1, 2009, and September 30, 2017. Index dates were randomly assigned to match the distribution of index dates in the CeD cohort. Eligible patients were required to have continuous enrollment in medical and pharmacy benefits for ≥12 months before the index date (baseline period) and ≥24 months after the index date (follow-up period). Control patients were randomly selected and matched at a 1:1 ratio to patients in the CeD cohort using a direct matching algorithm. Patient characteristics used in the direct match included demographic characteristics: age, gender, geographic region of residence, primary payer (commercial or Medicare), index date, and Deyo-Charlson Comorbidity Index (DCI) score.

### Patient characteristics

Patient demographic characteristics were measured on the index date and included age, sex, geographic region, primary payer, plan type, and index year. DCI score and the presence of claims for select autoimmune and nonautoimmune comorbidities were measured during the baseline period. A full list of examined comorbid conditions can be found in Table (see Supplementary Digital Content 1, http://links.lww.com/AJG/B600).

### Outcome measures

All-cause and CeD-related healthcare utilization and costs were measured during the baseline period, the first year of the follow-up, and the second year of the follow-up. Claims which occur on the index date are included in the first year of follow-up, not the baseline period. Utilization and cost measures were itemized by the following categories: total healthcare, inpatient admissions, outpatient services (emergency department visits, office visits [nonspecialist, gastroenterologist, neurologist, orthopedist, and other specialist], laboratory services, radiology services, and other outpatient services) and outpatient pharmacy. Claims were defined as CeD-related if they met any of the following criteria: (i) inpatient medical claims with a diagnosis code for CeD in the primary position, (ii) outpatient medical claims with a diagnosis code for CeD in any diagnosis position, (iii) pharmacy or office claims for immunosuppressants (azathioprine, cyclophosphamide, cyclosporine, infliximab, mesalamine, methotrexate, and thioguanine), or (iv) inpatient or outpatient claims for the CeD-related treatment or healthcare encounters including dietician visits, endoscopic biopsies, gastroenterology (GI) imaging, partial bowel resections, and CeD-related blood testing (immunoglobulin testing or HLA typing). Claims for immunosuppressants or CeD-related treatment or healthcare encounters were considered CeD-related even if they were not accompanied by a CeD diagnosis on the same claim.

All healthcare costs were based on paid amounts of adjudicated claims, including insurer and health plan payments as well as patient cost-sharing in the form of copayment, deductible, and coinsurance. Costs for services provided under capitated arrangements were estimated using payment proxies that are computed based on paid claims at the procedure level using the MarketScan Commercial and Medicare databases. All costs are reported per-person per-year (PPPY) and were adjusted for inflation using the Consumer Price Index and standardized to 2017 USD.

### Analytics and statistics

Categorical variables were presented as the count and percentage of patients in each category; continuous variables were summarized by providing the mean and SD, and medians where appropriate. Statistical comparisons were made between the CeD cohort and the control cohort using 2 sample $t$-tests for continuous variables and $\chi^2$ tests for categorical variables. The alpha level for all statistical tests was 0.05. All data analyses were conducted using SAS version 9.4 (SAS Inc., Cary, NC).

### Ethics approvals

This study used anonymized, deidentified retrospective claims data from MarketScan databases, and no patient identifiable data
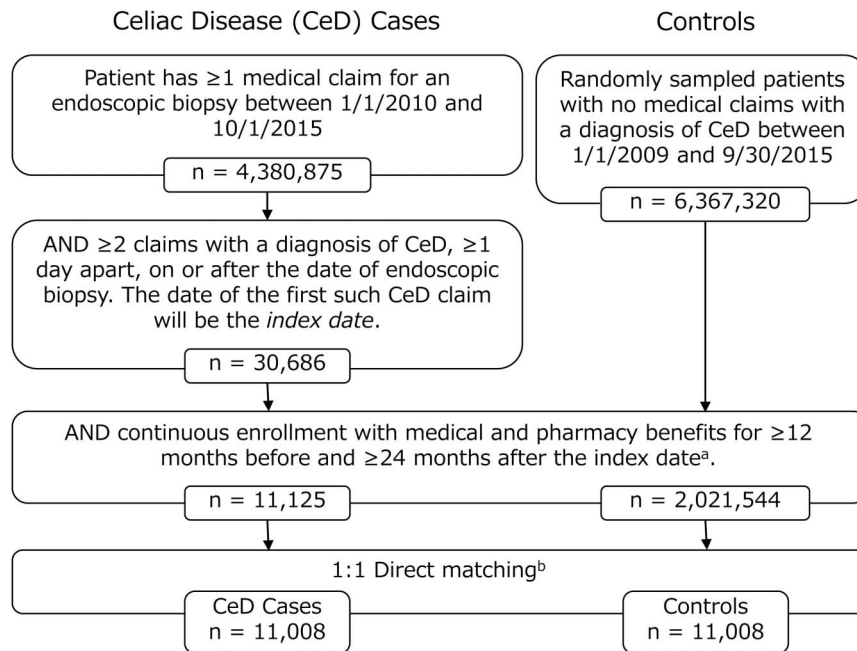
**Figure 1.** Patient selection: [a]Index dates were randomly assigned to match the distribution of index dates in the CeD cohort. [b]Variables included in direct matching were age, gender, geographic region of residence, primary payer, index date, and Deyo-Charlson Comorbidity Index. CeD, celiac disease.

were used. Data were analyzed and reported on a group level, and Institutional Review Board approval was not required.

All study data were accessed with protocols compliant with US patient confidentiality requirements, including the HIPAA of 1996 regulations. Because all database used in the study are fully deidentified and compliant with the HIPAA, this study was exempted from Institutional Review Board approval.

## RESULTS

During the enrollment period, there were 30,686 patients with at least 1 claim for endoscopic biopsy and at least 2 qualifying claims indicati

ng a diagnosis of CeD (Figure 1). Of these, 11,125 had sufficient continuous enrollment to be included in this study, and 11,008 could be directly matched to patients eligible for inclusion in the non-CeD control cohort. The mean age of patients included in the CeD cohort was 40.6 years, and 71.3% were women (Table 1).

At the baseline, 31.9% of patients had a DCI score of at least 1, and the mean DCI score among all patients with CeD was 0.52 ± 1.04 (Table 1). At the baseline, the most common autoimmune comorbidities among patients with CeD were thyroid disease (16.8%), type I diabetes (4.4%), rheumatoid arthritis (1.9%), and Crohn's disease (1.9%) (See Table, Supplementary Digital Content 2, http://links.lww.com/AJG/B601, which presents additional baseline comorbidity data). Thyroid disease (16.8% vs 9.7%), type I diabetes (4.4% vs 2.4%), and Crohn's disease (1.6% vs 0.6%) were more common in the CeD cohort than in the control cohort but similar prevalence of rheumatoid arthritis at the baseline (1.9% vs 1.6%).

Among the other comorbidities examined at baseline, the most common among patients with CeD were hypertension (18.5%), chronic obstructive pulmonary disease/asthma (12.0%), depression (11.2%), other heart disease (10.9%), and anxiety (10.9%). Hypertension was more common among control patients (23.4%),

whereas anxiety and other heart diseases were less common (8.8% and 9.3%, respectively). The prevalence of chronic obstructive pulmonary disease/asthma and depression were similar between the CeD and control cohorts (relative difference < 10%).

### HRU among patients with CeD and controls

During the baseline period, patients with CeD were less likely than the controls to have an all-cause inpatient admission (10.1% vs 11.3%) but had a longer length of stay when admitted (3.6 ± 4.3 days vs 3.1 ± 3.3 days) (Table 2). Patients with CeD and controls had a similar likelihood of having at least one all-cause emergency department (ED) visit (30.8% vs 29.9%) or orthopedist visit (14.7% vs 15.2%) during the baseline period. However, patients with CeD were more likely to have at least one all-cause visit with a nonspecialist (95.5% vs 90.7%), a gastroenterologist (60.6% vs 8.8%), a neurologist (8.1% vs 6.7%), or other specialist (68.0% vs 64.1%) or receive a least one laboratory service (97.6% vs 84.9%), radiology service (76.1% vs 67.9%), or other outpatient service (98.1% vs 96.2%) than the controls during the baseline period. The number of patients with at least one all-cause outpatient pharmacy claim was similar between the CeD and control cohorts (94.2% vs 94.3%); however, the mean number of unique medications per patient was higher among patients in the CeD cohort (8.3 ± 6.2 vs 7.4 ± 5.2). Overall, the trends were similar when only CeD-related claims were included (Table 2).

In the first year of the follow-up period (Y1), and the second year of the follow-up period (Y2), patients with CeD were more likely than the controls to have at least one all-cause claim in any of the examined HRU categories (Table 2). Between baseline and Y1, there was a 10.8% relative increase in the number of patients with CeD with an all-cause inpatient admission, an 11.2% relative increase in the number of patients with CeD with an all-cause neurologist visit, and a 3.3% relative increase in the number of patients with CeD with an all-cause gastroenterologist visit, but a

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**Table 1.** Baseline characteristic used in direct matching

| | CeD cohort N = 11,008 | Control cohort N = 11,008 |
|---|---|---|
| Age, mean (SD) | 40.6 (20.9) | 40.7 (21.1) |
| Sex, female, N (%) | 7,846 (71.3) | 7,846 (71.3) |
| Geographic region, N (%) | | |
| Northeast | 3,480 (31.6) | 3,480 (31.6) |
| North Central | 2,594 (23.6) | 2,594 (23.6) |
| South | 3,046 (27.7) | 3,046 (27.7) |
| West | 1,828 (16.6) | 1,828 (16.6) |
| Unknown | 60 (0.5) | 60 (0.5) |
| Primary payer type. N (%) | | |
| Commercial | 9,761 (88.7) | 9,761 (88.7) |
| Medicare | 1,247 (11.3) | 1,247 (11.3) |
| Year of index date, N (%) | | |
| 2010 | 1,793 (16.3) | 1,793 (16.3) |
| 2011 | 1,758 (16.0) | 1,758 (16.0) |
| 2012 | 2,086 (18.9) | 2,086 (18.9) |
| 2013 | 1,928 (17.5) | 1,928 (17.5) |
| 2014 | 2,020 (18.4) | 2,020 (18.4) |
| 2015 | 1,423 (12.9) | 1,423 (12.9) |
| DCI, N (%) | | |
| 0 | 7,501 (68.1) | 7,501 (68.1) |
| 1 | 2,380 (21.6) | 2,380 (21.6) |
| 2 | 619 (5.6) | 619 (5.6) |
| 3 | 269 (2.4) | 269 (2.4) |
| 4+ | 239 (2.2) | 239 (2.2) |

CeD, celiac disease; DCI, Deyo-Charlson Comorbidity Index.

6.5% relative decrease in the number of patients with CeD with an all-cause ER visit. By contrast, all-cause utilization decreased compared with the baseline in Y2 across all categories except neurologist visits, orthopedist visits, and other specialist visits. Notably, there was a 14.2% relative decrease in the number of patients with CeD with an inpatient admission, a 17.2% relative decrease in the number of patients with CeD with an ER visit, and a 45.1% relative decrease in the number of patients with CeD with a gastroenterologist visit in Y2 compared with baseline among patients with CeD.

In all periods, patients with CeD were more likely than controls to have had a dietician visit, a GI imaging procedure, or a CeD-related blood test (Table 3). In Y2, 11.7% of patients with CeD had an endoscopic biopsy compared with only 3.9% of the controls. In addition, patients with CeD were more likely to be prescribed antidepressants, anxiolytics, oral budesonide, gastroprotective agents, immunosuppressants, or prescription vitamin supplements than the controls in all periods. In the baseline period, patients with CeD were less likely than the controls to be prescribed either opioids or nonopioid pain relief; however, in Y1 and Y2, the use of opioids was more common among patients with CeD and the use of nonopioid prescription pain medication

was equivalent between patients in the CeD and control cohorts. Use of corticosteroids (excluding oral budesonide) was similar between CeD and control cohorts at baseline but became more prevalent among the CeD cohort in Y1 and Y2 (both, $P < 0.001$).

### Healthcare costs

Mean PPPY total all-cause healthcare costs were higher for patients with CeD compared with controls at baseline ($15,687 ± $32,261 vs $12,220 ± $17,160), Y1 ($19,181 ± $47,408 vs $11,260 ± $25,165), and Y2 ($15,355 ± $36,952 vs $11,579 ± $29,374) (Figure 2a). At the baseline, patients with CeD had higher all-cause inpatient admissions costs and outpatient services costs but had similar outpatient pharmacy costs compared with the controls. As a percentage of total healthcare costs, patients with CeD spent more on outpatient services (64.5% vs 59.4%) but less on outpatient pharmacy (16.6% vs 22.3%) at the baseline than the controls.

In Y1, mean total all-cause healthcare costs for patients with CeD increased by $3,484 PPPY compared with the baseline (Figure 2a and Table, Supplementary Digital Content 3, http://links.lww.com/AJG/B602). This was predominantly because of increases in inpatient admission costs and outpatient services costs. In Y2, mean total all-cause healthcare costs for patients with CeD returned to baseline levels as a $1,215 PPPY decrease in outpatient services costs were offset by increases in inpatient admissions costs and outpatient pharmacy costs.

For patients in the CeD cohort, roughly 7.9% of costs at baseline, 16.2% of costs at Y1, and 7.7% of costs at Y2 were directly CeD related. Over half of the Y1 increase in healthcare costs came from CeD-related expenditures. By definition, patients in the control cohort did not have any claims with a CeD diagnosis; however, they may have had claims for immunosuppressant medications, procedures, or healthcare encounters flagged as CeD related. Overall, these claims comprised only 1.7%–2.1% of healthcare costs at any time point for patients in the control cohort. A full breakdown of inpatient, outpatient, and outpatient pharmacy costs by cohort and period can be found in Table (see Supplementary Digital Content 3, http://links.lww.com/AJG/B602).

### DISCUSSION

Management of CeD requires long-term commitment to a highly restrictive diet. To examine the real-world healthcare burden of CeD, this large retrospective-matched cohort study examined HRU and costs during a 24-month observation period. Compared with the controls, patients with CeD had higher GI-related HRU and higher all-cause and CeD-related costs at baseline, Y1, and Y2. In Y1, the CeD cohort had more inpatient admissions and greater utilization of CeD-related outpatient services, contributing to an overall increase of $3,484 in all-cause costs and $1,866 in CeD-related costs compared with the baseline. By contrast, several indicators of disease severity, such as the likelihood of an inpatient admission, an ER visit, or a gastroenterologist visit, were lower among patients with CeD in Y2 compared with Y1 or baseline, and costs returned to baseline levels. In Y2, patients with CeD spent an average of $3,779 more PPPY on all-cause health care and $935 more PPPY on CeD-related health care compared with the controls. By comparison, the mean annual all-cause healthcare costs of patients with ulcerative colitis have been reported as $3,821 PPPY higher than controls propensity matched on demographic and clinical characteristics (17).

**Table 2.** All-cause and CeD-related healthcare resource utilization by patients with CeD and matched controls

| | 12-mo baseline period | | First year of follow-up period | | Second year of follow-up period | |
|---|---|---|---|---|---|---|
| | CeD cohort N = 11,008 | Control cohort N = 11,008 | CeD cohort N = 11,008 | Control cohort N = 11,008 | CeD cohort N = 11,008 | Control cohort N = 11,008 |
| All-cause | | | | | | |
| Inpatient admissions | | | | | | |
| Patients with an admission, N (%) | 1,113 (10.1) | 1,247 (11.3)* | 1,233 (11.2) | 832 (7.6)** | 955 (8.7) | 831 (7.5)* |
| Admissions per patient, mean (SD) | 1.3 (1.0) | 1.1 (0.5)** | 1.5 (1.3) | 1.3 (0.7)** | 1.4 (1.0) | 1.3 (0.9)* |
| Length of stay,[a] N (%) | 3.6 (4.3) | 3.1 (3.3)* | 4.2 (5.5) | 3.7 (3.7)* | 3.9 (4.1) | 3.9 (4.5) |
| Outpatient services | | | | | | |
| Patients with an ER visit, N (%) | 3,389 (30.8) | 3,288 (29.9) | 3,169 (28.8) | 2,487 (22.6)** | 2,805 (25.5) | 2,425 (22.0)** |
| ER visits per patient,[b] mean (SD) | 1.8 (1.9) | 1.6 (1.4)** | 1.9 (2.1) | 1.6 (1.3)** | 1.8 (2.1) | 1.8 (2.0) |
| Patients with a nonspecialist office visit, N (%) | 10,518 (95.5) | 9,989 (90.7)** | 10,388 (94.4) | 9,807 (89.1)** | 10,118 (91.9) | 9,575 (87.0)** |
| Nonspecialist office visits per patient,[b] mean (SD) | 5.8 (5.0) | 4.8 (4.0)** | 6.0 (5.4) | 4.4 (4.0)** | 5.4 (4.9) | 4.4 (4.2)** |
| Patients with a gastroenterologist visit, N (%) | 6,671 (60.6) | 969 (8.8)** | 6,894 (62.6) | 799 (7.3)** | 3,661 (33.3) | 842 (7.6)** |
| Gastroenterologist visits per patient,[b] mean (SD) | 1.6 (1.2) | 1.7 (1.2)* | 2.2 (1.6) | 1.7 (1.2)** | 1.8 (1.3) | 1.7 (1.2)* |
| Patients with a neurologist visit, N (%) | 891 (8.1) | 733 (6.7)** | 991 (9.0) | 707 (6.4)** | 973 (8.8) | 696 (6.3)** |
| Neurologist visits per patient,[b] mean (SD) | 2.3 (1.9) | 2.2 (1.7) | 2.3 (1.9) | 2.1 (1.9) | 2.3 (1.8) | 2.2 (1.8) |
| Patients with an orthopedist visit, N (%) | 1,613 (14.7) | 1,672 (15.2) | 1,716 (15.6) | 1,475 (13.4)** | 1,756 (16.0) | 1,506 (13.7)** |
| Orthopedist visits per patient,[b] mean (SD) | 2.2 (1.7) | 2.1 (1.6) | 2.3 (1.9) | 2.1 (1.5)* | 2.2 (1.7) | 2.1 (1.6)* |
| Patients with other specialist office visit, N (%) | 7,490 (68.0) | 7,052 (64.1)** | 7,709 (70.0) | 6,620 (60.1)** | 7,540 (68.5) | 6,550 (59.5)** |
| Other specialist visits per patient,[b] mean (SD) | 4.3 (4.4) | 3.8 (3.6)** | 4.5 (4.8) | 3.7 (3.7)** | 4.5 (4.6) | 3.8 (3.9)** |
| Patients with a laboratory service, N (%) | 10,745 (97.6) | 9,349 (84.9)** | 10,701 (97.2) | 8,780 (79.8)** | 9,903 (90.0) | 8,671 (78.8)** |
| Laboratory services per patient,[b] mean (SD) | 22.9 (21.4) | 13.2 (15.4)** | 22.6 (25.7) | 12.6 (16.0)** | 19.4 (25.5) | 13.1 (20.4)** |
| Patients with a radiology service, N (%) | 8,377 (76.1) | 7,475 (67.9)** | 8,063 (73.2) | 6,562 (59.6)** | 7,470 (67.9) | 6,484 (58.9)** |
| Radiology services per patient,[b] mean (SD) | 5.8 (6.1) | 5.3 (6.4)** | 6.0 (6.5) | 5.3 (6.8)** | 5.9 (6.6) | 5.3 (6.9)** |
| Patients with an other outpatient service, N (%) | 10,804 (98.1) | 10,587 (96.2)** | 10,857 (98.6) | 9,965 (90.5)** | 10,353 (94.0) | 9,815 (89.2)** |
| Outpatient pharmacy | | | | | | |
| Patients with a pharmacy claim, N (%) | 10,374 (94.2) | 10,382 (94.3) | 10,335 (93.9) | 10,061 (91.4)** | 10,177 (92.5) | 9,998 (90.8)** |
| Medications per patient,[b,c] mean (SD) | 8.3 (6.2) | 7.4 (5.2)** | 8.4 (6.4) | 7.2 (5.5)** | 8.2 (6.4) | 7.3 (5.6)** |
| CeD-related[d] | | | | | | |
| Inpatient admissions | | | | | | |
| Patients with an admission, N (%) | 420 (3.8) | 178 (1.6)** | 469 (4.3) | 143 (1.3)** | 240 (2.2) | 150 (1.4)** |
| Admissions per patient, mean (SD) | 1.2 (0.9) | 1.1 (0.2)* | 1.3 (0.9) | 1.1 (0.5)* | 1.3 (0.7) | 1.1 (0.5)* |
| Length of stay,[a] N (%) | 4.4 (4.0) | 4.5 (7.6) | 6.4 (9.9) | 5.0 (4.3) | 5.7 (6.8) | 5.5 (6.0) |
| Outpatient services | | | | | | |
| Patients with an ER visit, N (%) | 277 (2.5) | 94 (0.9)** | 630 (5.7) | 70 (0.6)** | 374 (3.4) | 88 (0.8)** |
| ER visits per patient,[b] mean (SD) | 1.2 (0.8) | 1.2 (0.5) | 1.3 (0.8) | 1.2 (0.4) | 1.2 (0.6) | 1.1 (0.4) |

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**Table 2.** (*continued*)

| | 12-mo baseline period | | First year of follow-up period | | Second year of follow-up period | |
|---|---|---|---|---|---|---|
| | CeD cohort N = 11,008 | Control cohort N = 11,008 | CeD cohort N = 11,008 | Control cohort N = 11,008 | CeD cohort N = 11,008 | Control cohort N = 11,008 |
| Patients with a nonspecialist office visit, N (%) | 1,537 (14.0) | 52 (0.5)** | 6,093 (55.4) | 85 (0.8)** | 3,260 (29.6) | 106 (1.0)** |
| Nonspecialist office visits per patient,[b] mean (SD) | 1.6 (1.2) | 1.8 (2.9) | 2.0 (1.5) | 1.7 (2.8) | 1.7 (1.3) | 1.5 (1.3) |
| Patients with a gastroenterologist visit, N (%) | 1,857 (16.9) | 0 (0.0)** | 6,142 (55.8) | 0 (0.0)** | 2,651 (24.1) | 1 (0.0)** |
| Gastroenterologist visits per patient,[b] mean (SD) | 1.2 (0.6) | 0.0 (0.0) | 1.8 (1.0) | 0.0 (0.0) | 1.5 (0.9) | 1.0 (0.0) |
| Patients with a neurologist visit, N (%) | 10 (0.1) | 1 (0.0)* | 77 (0.7) | 1 (0.0)** | 41 (0.4) | 0 (0.0)** |
| Neurologist visits per patient,[b] mean (SD) | 1.3 (0.7) | 2.0 (0.0) | 1.5 (1.0) | 1.0 (0.0) | 1.5 (0.9) | 0.0 (0.0) |
| Patients with an orthopedist visit, N (%) | 3 (0.0) | 0 (0.0) | 23 (0.2) | 1 (0.0)** | 10 (0.1) | 1 (0.0)** |
| Orthopedist visits per patient,[b] mean (SD) | 1.0 (0.0) | 0.0 (0.0) | 1.2 (0.5) | 1.0 (0.0) | 1.8 (2.2) | 1.0 (0.0) |
| Patients with other specialist office visit, N (%) | 228 (2.1) | 6 (0.1)** | 1,267 (11.5) | 8 (0.1)** | 773 (7.0) | 10 (0.1)** |
| Other specialist visits per patient,[b] mean (SD) | 1.3 (0.7) | 1.2 (0.4) | 1.7 (1.2) | 1.0 (0.0) | 1.6 (1.2) | 1.6 (1.0) |
| Patients with a laboratory service, N (%) | 6,114 (55.5) | 287 (2.6)** | 7,855 (71.4) | 259 (2.4)** | 4,364 (39.6) | 257 (2.3)** |
| Laboratory services per patient,[b] mean (SD) | 3.3 (5.0) | 1.3 (1.5)** | 7.6 (9.8) | 1.3 (1.1)** | 6.9 (7.8) | 1.7 (3.4)** |
| Patients with a radiology service, N (%) | 3,064 (27.8) | 1,069 (9.7)** | 3,012 (27.4) | 894 (8.1)** | 1,784 (16.2) | 917 (8.3)** |
| Radiology services per patient,[b] mean (SD) | 2.1 (1.8) | 1.9 (1.4)* | 2.2 (1.9) | 2.1 (1.7) | 2.2 (2.2) | 2.0 (1.5)* |
| Patients with an other outpatient service, N (%) | 2,450 (22.3) | 208 (1.9)** | 7,749 (70.4) | 184 (1.7)** | 3,195 (29.0) | 198 (1.8)** |
| Outpatient pharmacy | | | | | | |
| Patients with a pharmacy claim, N (%) | 334 (3.0) | 216 (2.0)** | 425 (3.9) | 198 (1.8)** | 356 (3.2) | 197 (1.8)** |
| Medications per patient,[b,c] mean (SD) | 1.1 (0.2) | 1.1 (0.3) | 1.1 (0.3) | 1.1 (0.3) | 1.1 (0.3) | 1.1 (0.2) |

CeD, celiac disease; ED, emergency department.
[a]Among patients with at least 1 inpatient admission.
[b]Among patients with at least 1 claim in that service category.
[c]Number of unique medications per patient at the generic name level.
[d]In addition to claims with a diagnosis of CeD, CeD-related claims included pharmacy or office claims for immunosuppressants and claims for the CeD-related treatments or healthcare encounters listed in Table (see Supplementary Digital Content 1, http://links.lww.com/AJG/B600).
*P < 0.05; **P < 0.001.

In this study, the mean annual all-cause healthcare costs of CeD ranged from $15,355 to $19,181. This is comparable with a recent analysis of patients with Crohn's disease, which reported mean annual direct healthcare costs of $18,637 (18). Two previous studies have examined the cost of patients with CeD in the United States compared with matched controls (12,13), and a third compared the costs between patients with CeD and those with prodromal symptoms of CeD but no diagnosis (11). In a study of 306 residents of Olmsted County, Minnesota, patients with CeD had higher inpatient and outpatient medical costs than controls; however, the study was reporting on costs in the 4 years before diagnosis and lacked data on pharmacy costs (13). A 2016 analysis of patients in the Optum Health dataset found that patients with CeD cost $12,217, whereas controls matched on demographic characteristics cost only $4,935 (12). By not matching patients on comorbidity burden, this study inflated the cost differential between cases and controls compared with our own study. In addition, this analysis may have underestimated the burden of CeD by including patients with only a single claim indicating a diagnosis of CeD and no other confirmatory claims,

**Table 3.** Utilization of CeD-related procedures, healthcare encounters, and pharmaceutical therapy by patients with CeD and matched controls

| | 12-mo baseline period | | First year of follow-up period | | Second year of follow-up period | |
|---|---|---|---|---|---|---|
| | CeD cohort N = 11,008 | Control cohort N = 11,008 | CeD cohort N = 11,008 | Control cohort N = 11,008 | CeD cohort N = 11,008 | Control cohort N = 11,008 |
| Procedures and healthcare encounters, N (%) | | | | | | |
|   Dietician visit | 414 (3.8%) | 162 (1.5%)** | 1,959 (17.8) | 199 (1.8)** | 460 (4.2%) | 220 (2.0%)** |
|   GI imaging | 3,143 (28.6%) | 1,221 (11.1%)** | 2,411 (21.9) | 992 (9.0)** | 1,600 (14.5%) | 1,027 (9.3%)** |
|   Partial bowel resection | 5 (0.0%) | 2 (0.0%) | 13 (0.1) | 2 (0.0)* | 5 (0.0%) | 7 (0.1%) |
|   CeD-related blood testing[a] | 4,872 (44.3%) | 256 (2.3%)** | 2,914 (26.5) | 223 (2.0)** | 1,747 (15.9%) | 215 (2.0%)** |
| Pharmaceutical therapy, N (%) | | | | | | |
|   Antidepressants | 2,743 (24.9%) | 2,520 (22.9%)** | 2,990 (27.2) | 2,608 (23.7)** | 3,017 (27.4%) | 2,653 (24.1%)** |
|   Anxiolytics | 2,315 (21.0%) | 1,885 (17.1%)** | 2,601 (23.6) | 1,682 (15.3)** | 2,064 (18.8%) | 1,729 (15.7%)** |
|   Budesonide (oral) | 171 (1.6%) | 22 (0.2%)** | 338 (3.1) | 14 (0.1)** | 219 (2.0%) | 19 (0.2%)** |
|   Corticosteroids (IV and oral)[b] | 3,069 (27.9%) | 3,107 (28.2%) | 3,419 (31.1) | 2,850 (25.9)** | 3,358 (30.5%) | 2,907 (26.4%)** |
|   Gastroprotective agents | 4,092 (37.2%) | 1,991 (18.1%)** | 4,193 (38.1) | 1,936 (17.6)** | 3,317 (30.1%) | 1,981 (18.0%)** |
|   Immunosuppressants | 352 (3.2%) | 227 (2.1%)** | 444 (4.0) | 215 (2.0)** | 380 (3.5%) | 216 (2.0%)** |
|   Muscle relaxants | 1,104 (10.0%) | 1,103 (10.0%) | 1,196 (10.9) | 1,058 (9.6)* | 1,182 (10.7%) | 1,031 (9.4%)** |
|   NSAIDs/COX-2 inhibitors | 2,378 (21.6%) | 2,697 (24.5%)** | 2,369 (21.5) | 2,354 (21.4) | 2,374 (21.6%) | 2,336 (21.2%) |
|   Opioids | 3,676 (33.4%) | 4,039 (36.7%)** | 4,055 (36.8) | 3,216 (29.2)** | 3,343 (30.4%) | 3,083 (28.0%)** |
|   Prescription vitamin supplements | 1,065 (9.7%) | 754 (6.8%)** | 1,241 (11.3) | 664 (6.0)** | 999 (9.1%) | 647 (5.9%)** |

CeD, celiac disease; COX-2, cyclooxygenase-2; GI, gastroenterology; IgA, immunoglobulin A; IV, intravenous; NSAID, nonsteroidal anti-inflammatory drug.
[a]Includes immunoglobulin testing or HLA typing.
[b]Does not include budesonide.
*$P < 0.05$; **$P < 0.001$.

such as a claim for endoscopic biopsy, which was required in this study. The high frequency of misdiagnosis (19,20), both over diagnosis and underdiagnosis, among patients with CeD necessitates higher stringency in patient selection. In contrast to the previous 2 studies, an analysis of patients in a managed care setting before the widespread adoption of serological screening for CeD found that patients with a CeD diagnosis had lower medical costs in the 3 years after diagnosis than those with CeD symptoms but without a diagnosis of CeD (11). The authors of that study hypothesized that diagnosis enabled patients to receive appropriate treatment, such as nutritional guidance, and reduced the incidence of downstream complications. In all studies, outpatient services were the primary driver of high costs among patients with CeD.

Among patients with CeD, utilization of healthcare services associated with diagnosis, such as CeD-related blood testing and GI-related imaging, was highest in the baseline period and decreased in Y1 and Y2, whereas utilization of services associated with the treatment of comorbidities and complications of CeD, such as CeD-related inpatient admissions, ER visits, specialist office visits, and pharmacy claims, peaked in Y1. The fact that utilization of most CeD-related services by patients with CeD remains elevated compared with utilization by controls and above baseline utilization suggests that these services are also associated with long-term CeD management and may be amenable to reduction through improved disease management. By contrast, the use of nonsteroidal anti-inflammatory drugs/cyclooxygenase-2 inhibitors and muscle

relaxants by patients with CeD was relatively constant, which, as expected, suggests these treatments may not be associated with diagnosis, treatment, or management of CeD.

Previous studies of patients with CeD reported a spike in HRU and costs in the year following the record of diagnosis. A single-payer, US administrative claims study of 525 patients with CeD reported that after the diagnosis, medical costs increased 41% above the baseline in Y1 but then fell to 16% below baseline in Y2 (11). This was driven predominantly by changes in utilization of inpatient and ER services. The overall trend is similar to our findings, but direct comparisons are limited by the use of procedure-based cost estimate from the Medicare Prospective Payment Commission in the study by Green et al. A study of outpatient and prescription costs of 3,546 patients with CeD living in the United Kingdom, who were followed for an average of 5 years prediagnosis and postdiagnosis, found that costs began increasing 2 years before diagnosis but peaked in the year after diagnosis before beginning to decline in the subsequent years (15). In that study, most of the increase, roughly 62%, came from prescriptions for gluten-free food, a subsidy not available in the United States, which may explain the continued elevation of costs above the baseline in Y2 and beyond.

This study only captures a portion of the burden of CeD. Specifically, we do not capture the costs of gluten-free food, nonprescription dietary supplements, or nutritional or other consultations paid for out of pocket. In particular, the cost of gluten-free foods may be a substantial burden to patients with
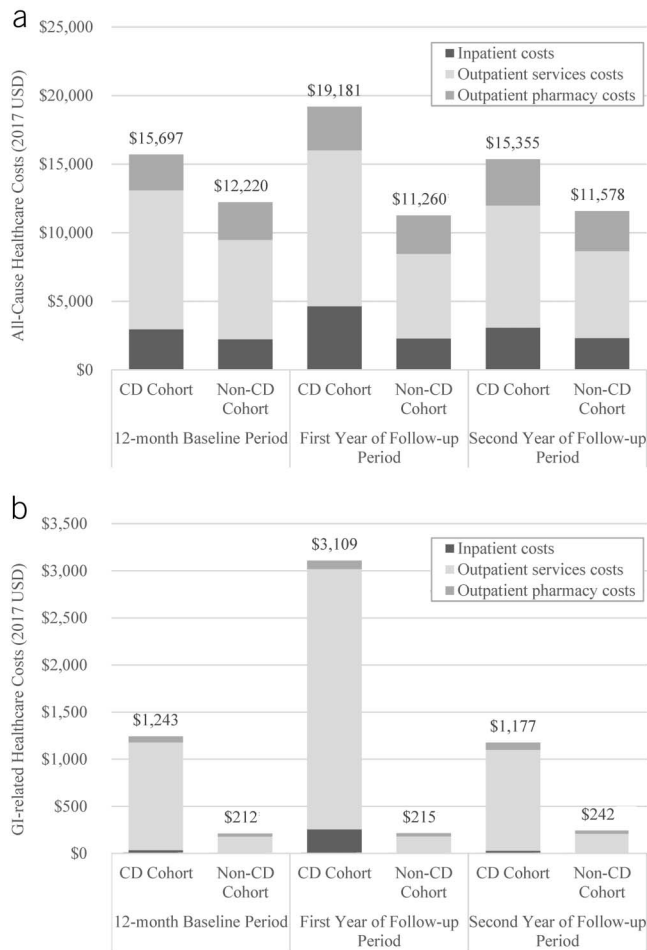
**Figure 2.** (**a**) All-cause and (**b**) CeD-related costs by patients with CeD by severity cohort and by matched control patients. CeD-related claims included claims with a diagnosis of CeD along with pharmacy or office claims for immunosuppressants and claims for the CeD-related treatments or healthcare encounters (dietician visits, endoscopic biopsies, gastroenterology imaging, partial bowel resection, and CeD-related blood testing). CeD, celiac disease; USD, US dollars.

CeD. In the United Kingdom, where patients can receive prescriptions for gluten-free foods, one study found that 51% of annual prescription costs were because of prescription food supplements (15). In the United States, gluten-free foods are not subsidized, and they cost more than their gluten-containing counterparts (21,22). This relative cost inflation decreased between 2006 and 2016; however, gluten-free foods cost on average 183% more than their gluten-containing counterparts (22). Of additional concern is the evidence that gluten-free foods are less nutritionally dense than their gluten-containing counterparts (23,24), which may then contribute to greater spending on dietary supplements and nutritional consultations.

### Limitations

This study is subject to many of the same limitations of other administrative claims-based studies. In particular, test results, including pathology results, are not available; therefore, diagnosis must be based on claims coding, and these data are subject to miscoding and undercoding. To improve the chances of including only true cases in our CeD cohort, patients were required to have a record of ≥1 endoscopic biopsy and ≥2 subsequent claims with a diagnosis code for CeD. This stringent approach is less likely to include patients without CeD but may exclude patients who are diagnosed without a biopsy or in whom the biopsy was performed outside of the current claims database. In addition, this methodology is unable to definitively exclude patients who had a previous diagnosis of CeD but who are seen and undergo repeat endoscopy in the claims database because of recurrent active or otherwise complicated CeD. In addition, because CeD is underdiagnosed, patients in the control group may have had CeD, which may reduce differences between the control and celiac cohorts. However, the rates of comorbid autoimmune diseases, particularly type 1 diabetes and autoimmune thyroid disease, in the celiac population are similar to rates in the previous literature and higher than seen in controls, suggesting patient designation is largely accurate.

Another complicating factor is that the comorbidity burden, as measured by DCI, was included as a matching factor to facilitate parsing the specific burden of CeD from the general burden of multiple comorbidities. Therefore, our control population has a higher comorbidity burden and likely higher annual HRU and costs than a random selection of healthy adults. In addition, utilization and costs for products and services not billed to insurance such as gluten-free foods, over-the-counter medications and supplements, visits to cash pay providers, and other self-management approaches are not available in claims data. As a result, we may be underestimating the economic burden of CeD. In addition, this analysis was limited to patients with 36 months of continuous enrollment in commercial or Medicare supplemental insurance; therefore, the results may not be applicable to patients who are uninsured, have other health insurance, or have less stable insurance coverage. Patients with less stable health insurance or no health insurance may face greater barriers to CeD diagnosis and management because they lack access to healthcare providers and services.

Compared with patients matched on demographic characteristics and comorbidity burden, patients with CeD had higher all-cause and CeD-related HRU and costs. Patients with CeD had higher inpatient admission, outpatient services, and outpatient pharmacy costs than controls, although outpatient services costs comprised most of the direct healthcare costs of CeD. These data suggest that further studies assessing drivers of increased utilization and strategies to improve care and potentially reduce costs and burden of disease are needed.

### CONFLICTS OF INTEREST

## Study Highlights

**WHAT IS KNOWN**

✓ CeD is chronic and linked to a higher comorbidity burden.
✓ Data on direct healthcare costs of CeD are limited and lack procedure-level detail.

**WHAT IS NEW HERE**

✓ Patients with CeD had higher 2-year healthcare costs than the controls matched on comorbidity burden and demographics.
✓ Costs peaked in the first year after diagnosis and remained higher than the controls in the second year.
✓ Outpatient services, including visits to specialists and use of diagnostic services, were the primary driver of high costs.

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