Costs and Use of Health Care in Patients With Celiac Disease: A Population-Based Longitudinal Study

Karl Mårild, MD, PhD[1,2], Jonas Söderling, PhD[3], Soran R. Bozorg, MD[4], Åsa H. Everhov, MD, PhD[3,5], Benjamin Lebwohl, MD[6], Peter H.R. Green, MD[6], Martin Neovius, PhD[3] and Jonas F. Ludvigsson, MD, PhD[4,6,7]

INTRODUCTION: **Celiac disease (CD) affects 1% of the population. Its effect on healthcare cost, however, is barely understood. We estimated healthcare use and cost in CD, including their temporal relationship to diagnosis.**

METHODS: **Through biopsy reports from Sweden's 28 pathology departments, we identified 40,951 prevalent patients with CD (villous atrophy) as of January 1, 2015, and 15,086 incident patients with CD diagnosed in 2008–2015, including 2,663 who underwent a follow-up biopsy to document mucosal healing. Each patient was compared with age- and sex-matched general population comparators (n = 187,542). Using nationwide health registers, we retrieved data on all inpatient and nonprimary outpatient care, prescribed diets, and drugs.**

RESULTS: **Compared with comparators, healthcare costs in 2015 were, on average, $1,075 (95% confidence interval, $864–1,278) higher in prevalent patients with CD aged <18 years, $715 ($632–803) in ages 18–64 years, and $1,010 ($799–1,230) in ages ≥65 years. Half of all costs were attributed to 5% of the prevalent patients. Annual healthcare costs were $391 higher 5 years before diagnosis and increased until 1 year after diagnosis; costs then declined but remained 75% higher than those of comparators 5 years postdiagnosis (annual difference = $1,044). Although hospitalizations, nonprimary outpatient visits, and medication use were all more common with CD, excess costs were largely unrelated to the prescription of gluten-free staples and follow-up visits for CD. Mucosal healing in CD did not reduce the healthcare costs.**

DISCUSSION: **The use and costs of health care are increased in CD, not only before, but for years after diagnosis. Mucosal healing does not seem to lower the healthcare costs.**

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/AJG/B524

Am J Gastroenterol 2020;115:1253–1263. https://doi.org/10.14309/ajg.0000000000000652

INTRODUCTION

Celiac disease (CD) is a chronic condition in which gluten intake causes small intestinal villous atrophy (VA) (1). As in many other autoimmune diseases, there is a female preponderance in CD. Over the past decades, there has been a rise in the prevalence of CD, which today affects about 1% of the population worldwide (2). However, because of few or unspecific symptoms, most people with CD are often diagnosed with several years of delay (3). Over the life course, CD is associated with reduced life expectancy, loss of health, and lower quality of life (4). A late-diagnosed CD may cause protracted morbidity and increased social and economic costs on the individual and societal levels.

Despite its high prevalence and excess morbidity risk, data are scarce and inconsistent on the use and costs of health care in this patient group (5). Although 2 US studies found *reduced* costs of selected healthcare services after the diagnosis of CD (6,7), a UK study reported *increased* costs (8). These inconsistencies may not only be due to country-specific differences in healthcare systems but reflect methodological differences, such as selection bias and a failure to fully capture medical costs, including, for instance, ongoing dietary costs that were included in the UK study, but not in the 2 US studies. In addition, studies have had limited statistical power (8), thereby prohibiting the analysis of healthcare use in subgroups of patients with CD. Such data would be particularly relevant, given that the distribution of health care costs may be skewed across individuals of different demography (9). Finally, there are no data on whether mucosal healing in CD affects healthcare costs. A failure to heal, which has been linked to an excess risk of lymphoproliferative malignancy and hip fractures (10,11), is common in CD and especially in patients who show low adherence to a gluten-free diet (12).

[1]Department of Pediatrics, Institute of Clinical Sciences, Sahlgrenska Academy, Gothenburg, Sweden; [2]Department of Pediatric Gastroenterology, Queen Silvia Children's Hospital, Gothenburg, Sweden; [3]Clinical Epidemiology Division, Department of Medicine, Karolinska Institutet, Stockholm, Sweden; [4]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden; [5]Department of Clinical Science and Education, Södersjukhuset, Karolinska Institutet, Stockholm, Sweden; [6]Department of Medicine, Celiac Disease Center, Columbia University Medical Centre, Columbia University, New York, USA; [7]Department of Pediatrics, Örebro University Hospital, Örebro, Sweden. **Correspondence:** Karl Mårild, MD, PhD, E-mail: karlmarild@gmail.com
Received January 21, 2020; accepted March 30, 2020; published online April 28, 2020

Using population-based, prospectively recorded data from the universally accessible Swedish healthcare system (13), we aimed to determine the use and costs of health care in patients with CD both before and after diagnosis. We also aimed to test whether mucosal healing in patients with CD affects healthcare costs.

METHODS

Using the personal identity number assigned to all Swedish residents (14), we linked the histopathology data on individuals with biopsy-verified CD to individual-level national health register data to compare the use and incurred costs of health care of patients with CD with that of matched general population comparators.

Study sample

In 2006–2008 (15), with an update in 2015–2017 (16), we searched the computerized registers of all pathology departments (n = 28) in Sweden to identify individuals with CD, defined by small intestinal VA (marsh 3) (17). An earlier evaluation had shown that 95% of Swedish individuals with small intestinal VA have CD (15). In total, we identified 49,144 individuals with CD diagnosed between 1969 and 2015 (i.e. date of first biopsy showing VA). This study included 2 groups of patients with CD:

1. Fifteen thousand eighty-six incident patients diagnosed with CD between January 1, 2008 and December 31, 2015, of whom 2,663 had a follow-up biopsy performed to document mucosal healing within 0.5–5.0 years after CD diagnosis.
2. Forty thousand nine hundred fifty-one prevalent patients with CD as of January 1, 2015, including patients diagnosed between January 1, 1969, and December 31, 2014, and alive and living in Sweden as of January 1, 2015; of these, 27,274 (67%) had been diagnosed since January 1, 2000.

Through the Total Population Register (18), each individual with CD was then matched by age, calendar year at the time of diagnosis, sex, and county of residence with up to 5 comparators from the general population (16). No exclusion criteria were applied to our sample. Finally, data on CD and matched comparators were linked to the National Patient Register (19), the Prescribed Drug Register (20), and, for income and education data, the Longitudinal Integrated Database for Health Insurance and Labour Market Studies (21).

Use and costs of healthcare

The Swedish healthcare system is universal and tax funded (13). The individual patient's copayment is low.

Inpatient and nonprimary outpatient care. The National Patient Register started in 1964 gained nationwide coverage in 1987 and added nonprimary outpatient care in 2001 (19). The register contains high-quality data of virtually all inpatient and nonprimary outpatient care in Sweden (19). The register does not record primary care.

Making use of the National Patient Register, we retrieved data on hospital days and nonprimary outpatient visits from 2003 to 2016. According to the International Classification of Diseases (ICDs), 10th revision (ICD-10), the main diagnosis of each nonprimary outpatient visit was categorized into selected chronic conditions associated with CD (see Table 1, Supplementary Digital Content 1, http://links.lww.com/AJG/B524) (4). Costs trajectories of both inpatient and nonprimary outpatient care were also classified into the 10 ICD-10 chapters (based on body systems or conditions) constituting the highest overall costs in CD. Costs for nonprimary outpatient care visits and hospital admissions were calculated using the diagnosis-related group classification, a reimbursement system for grouped diagnoses and procedures based on their weighted average, hospital-specific, associated costs (22). Briefly, this system accounts for the costs from a range of services, including those from allied health professionals, imaging, etc. associated with each diagnosis-related group (22).

Filled prescriptions for drugs, diets, and consumables. The Swedish Prescribed Drug Register includes prospectively recorded data on all filled drug prescriptions and their costs since July 2005 (20), and for this study, captured throughout 2017. The register also contains data on prescribed medical consumables (e.g., blood glucose lancets) and prescribed diets, including gluten-free staple foods for the treatment of CD. We retrieved data on prescribed gluten-free diet for all participants when available; however, we only specified such prescriptions in participants aged greater than 18 years because such prescriptions are very limited for adults (which are because of Swedish prescription policy). Drugs were categorized according to their use for conditions relevant to CD (see Table 1, Supplementary Digital Content 1, http://links.lww.com/AJG/B524) (4).

Other data

Education level has been associated with the use of health resources (23,24) and may be associated with the ascertainment of diagnosed CD or adherence to its gluten-free dietary treatment (25,26). From Statistics Sweden, we therefore retrieved data on the highest-attained education level at baseline. For children with missing data, we used the highest-attained education category of their parents (27). For adults, we also retrieved data on disposable income (i.e., total income received minus taxes paid) at baseline (21). Data were categorized, as shown in Table 1.

Statistics

Although we expect all outcomes to be skewed, we used the mean as the measure of central tendency in that this metric best represents the overall burden on society (28). To describe the skewness of costs, we also report medians and percentages of patients with CD by category of cost/use of healthcare services and the overall cost distribution in patients with CD (see Figure 1, Supplementary Digital Content 1, http://links.lww.com/AJG/B524). All costs were reported in US dollars, adjusted for inflation to 2015. Adjusted mean differences in costs between patients with CD and matched comparators were estimated using linear regression with adjustments for education level, age at diagnosis, and sex (29). Ninety-five percent confidence intervals (95% CIs) for adjusted cost differences were estimated using nonparametric bootstrapping (28). We performed stratified analyses for incident patients according to their age ($<$18, 18–64, and $\geq$65 years), sex, and education level ($\leq$9, 10–12, and $>$12 years of education). Prevalent patients were stratified by disease duration ($<$10 vs $\geq$10 years since CD diagnosis).

Healthcare costs according to the mucosal appearance on follow-up biopsy. We also examined whether healthcare costs in CD were associated with persistent VA (marsh 3) (17) vs mucosal healing (marsh 0–2) on follow-up biopsy. Mucosal healing was defined as recovery from VA because lesser mucosal abnormalities (Marsh 1 [intraepithelial lymphocytosis] or Marsh 2 [crypt hyperplasia]) (17) may persist without clinical sequelae (30). The analysis included 2,663 incident patients diagnosed in 2008–2015 who had a follow-up biopsy performed 0.5–5.0 years after the diagnosis of CD. We restricted the timing of the follow-up biopsy to

Table 1. Baseline characteristics of prevalent and incident patients with CD and age- and sex-matched general population comparators[a]

Variable	Prevalent celiac disease[b]		Incident celiac disease[c]	
	Patients (n = 40,951)	Comparators (n = 187,542)	Patients (n = 15,086)	Comparators (n = 74,580)
Sex, n (%)				
Men, n (%)	14,734 (36.0%)	66,654 (35.5%)	5,550 (36.8%)	27,363 (36.7%)
Women, n (%)	26,217 (64.0%)	120,888 (64.5%)	9,536 (63.2%)	47,217 (63.3%)
Age				
Mean (SD)	39.9 (22.9)	38.3 (22.0)	32.5 (24.1)	32.1 (23.8)
Median (25th–75th)	33.8 (21.2–59.9)	31.9 (20.6–56.7)	26.6 (11.4–51.3)	26.1 (11.3–50.6)
Age groups, n (%)				
<18 yr	7,440 (18.2%)	36,256 (19.3%)	5,732 (38.0%)	28,643 (38.4%)
18–64 yr	25,156 (61.4%)	118,175 (63.0%)	7,155 (47.4%)	35,525 (47.6%)
≥65 yr	8,355 (20.4%)	33,111 (17.7%)	2,199 (14.6%)	10,412 (14.0%)
Level of education, n (%)[d]				
≤9 yr	7,712 (18.8%)	35,770 (19.1%)	3,147 (20.9%)	16,315 (21.9%)
10–12 yr	17,871 (43.6%)	82,647 (44.1%)	6,001 (39.8%)	30,008 (40.2%)
>12 yr	15,311 (37.4%)	68,579 (36.6%)	5,867 (38.9%)	27,345 (36.7%)
Missing	57 (0.1%)	546 (0.3%)	71 (0.5%)	912 (1.2%)
Comorbidities, ≤5 years before index date[e]				
Cancer	1,693 (4.1%)	6,141 (3.3%)	473 (3.1%)	1,742 (2.3%)
Cardiovascular disease	4,282 (10.5%)	14,012 (7.5%)	1,354 (9.0%)	4,415 (5.9%)
Diabetes, type 1 and type 2	2,308 (5.6%)	2,882 (1.5%)	763 (5.1%)	931 (1.2%)
Psychiatric disease	4,347 (10.6%)	16,755 (8.9%)	1,106 (7.3%)	4,648 (6.2%)
Accumulated resource use, mean (SD)[f]				
Drug cost (USD), ≤2 years before index date	1,265 (5,860)	623 (9,840)	922 (4,312)	490 (4,029)
Nonprimary outpatient visits, ≤5 yr before index date	9.6 (14.5)	5.5 (9.8)	8.0 (12.7)	4.3 (8.1)
Related to CD[g]	0.9 (1.8)	—	0.5 (0.9)	—
N (%) with visit related to CD[g]	13,891 (33.9%)	—	5,695 (37.8%)	—
Inpatient days, ≤5 years before index date	4.2 (21.8)	2.6 (16.4)	4.2 (17.0)	2.2 (16.6)
Disposable income (USD) age 18–64 years[h]				
Mean (SD)	25,628 (25,503)	25,522 (65,061)	23,808 (24,846)	23,273 (32,010)
Median (25th–75th)	23,469 (14,484–32,000)	23,527 (13,966–32,178)	21,973 (13,483–30,107)	21,237 (11,930–29,866)
Disposable income (USD) age ≥65 yr				
Mean (SD)	23,894 (28,465)	24,166 (32,997)	22,477 (22,551)	22,549 (31,460)
Median (25th–75th)	18,027 (15,002–24,666)	18,073 (15,013–24,999)	17,211 (13,886–23,849)	16,980 (13,656–23,820)
Less than 1 year of follow-up, n (%)	433 (1.1%)	1,658 (0.9%)	210 (1.4%)	790 (1.1%)
Death	344 (0.8%)	1,151 (0.6%)	174 (1.2%)	364 (0.5%)

Table 1. (*continued*)

Variable	Prevalent celiac disease[b] Patients (n = 40,951)	Prevalent celiac disease[b] Comparators (n = 187,542)	Incident celiac disease[c] Patients (n = 15,086)	Incident celiac disease[c] Comparators (n = 74,580)
Emigrated	89 (0.2%)	507 (0.3%)	36 (0.2%)	426 (0.6%)
Less than 5 years of follow-up, n (%)	—	—	7,395 (49.0%)	36,474 (48.9%)
Death	—	—	474 (3.1%)	1,667 (2.2%)
Emigrated	—	—	148 (1.0%)	1,355 (1.8%)
End of data capture	—	—	6,773 (44.9%)	33,452 (44.9%)

CD, celiac disease.
[a]Baseline is defined as January 1, 2015, for the analysis of prevalent patients and matched comparators, and for incident patients, the date of CD diagnosis and corresponding date of matched comparators.
[b]Prevalent patients with CD as of January 1, 2015, including patients diagnosed between January 1, 1969, and December 31, 2014, and alive and living in Sweden as of January 1, 2015.
[c]Incident patients diagnosed with CD between January 1, 2008, and December 31, 2015. Incident patients were diagnosed between 2008 and 2015 (2008–2009: n = 3,950 [26.2% of incident patients]; 2010–2011: n = 4,150 [27.5%]; 2012–2013: n = 3,739 [24.8%]; 2014–2015: n = 3,243 [21.5%]), with age- and sex-matched comparators enrolled in corresponding years.
[d]In children with missing educational data we used the highest level of education of their parents.
[e]Index date refers to the time of CD diagnosis as defined by the date of diagnostic small intestinal biopsy with the corresponding date in matched comparators; *P* value <0.05 for all comparisons.
[f]Cumulative cost of prescribed drugs, numbers of nonprimary outpatient visits, and hospital days in the past 2, respectively, 5 years before index date; *P* value <0.05 for all comparisons.
[g]International Classification of Disease (ICD)-10 code K90.0 for CD recorded as the main (primary) diagnosis.
[h]Disposable income equals the total income received (including allowances) minus taxes paid.

maximize the probability that it was performed as routine practice to document mucosal healing, rather than being prompted by a clinical event.

Follow-up period. For the analyses of incident patients diagnosed in 2008–2015, follow-up started up to 5 years before the diagnosis of CD, except for prescribed drug data (available since July 1, 2005) for patients diagnosed in 2008–June 2010. We followed up incident patients until 5 years after their CD diagnosis, death, emigration, or end of follow-up (December 31, 2016, for inpatient and nonprimary outpatient care; December 31, 2017, for prescribed drug use), whichever occurred first. In comparators, follow-up also ended if the individual was diagnosed with CD. In the analyses of healthcare costs according to the mucosal appearance on follow-up biopsy costs were assessed from the day after the diagnostic biopsy and until 5 years after follow-up biopsy or censoring by death, emigration, or the end of follow-up, as defined above.

Ethics

All data were pseudonymized before delivery to the researchers, and the study was approved by the Stockholm Ethics Review Board (No. 2014/1287-31/4 and 2017/1497-32).

RESULTS

Of 40,951 prevalent patients with CD as of January 1, 2015, most were women (64.0%), with a mean current age of 39.9 years (Table 1). In 2015, prevalent patients had, on average, been diagnosed with CD for 12.1 (SD, 8.0) years. Of 15,086 incident patients with CD, the mean age at diagnosis was 32.5 years (Table 1).

Prevalent patients

The absolute healthcare costs in 2015 increased with patient age, from an average of $1,762 (SD, $7,952) for patients aged greater than 18 years to $4,486 (SD, $9,062) for patients aged greater than or equal to 65 years, which was related to a higher need for inpatient care (Table 2 and see Table 2, Supplementary Digital Content 1, http://links.lww.com/AJG/B524). Across age bands, the use and costs of health care were highest in more newly diagnosed prevalent patients (<10 vs ≥10 years since CD diagnosis) (see Tables 3 and 4, Supplementary Digital Content 1, http://links.lww.com/AJG/B524). This cost increase reflected a higher use of all recorded healthcare categories.

Compared with matched comparators, healthcare costs in 2015 were, on average, $1,075 (95% CI, $864–1,278) higher in prevalent CD patients aged greater than 18 years, $715 ($632–803) in ages 18–64 years, and $1,010 ($799–1,230) in ages greater than or equal to 65 years (Figure 1 and Table 2). Half of all costs were attributed to 5% of the prevalent patients (see Figure 1, Supplementary Digital Content 1, http://links.lww.com/AJG/B524).

Incident patients

Cost and use of health care in the year after diagnosis of CDs. As for prevalent patients, incident patients aged greater than or equal to 65 years incurred a noticeably higher total healthcare cost (mean, $6,501 [SD, $11,703]) than younger patients (age <18 years, $2,722 [SD, $8,489]; age 18–64 years, $2,763 [SD, $7,663]), which was primarily because of higher hospitalization rates in the oldest age group (Table 3 [CD] and see Table 5, Supplementary Digital Content 1, http://links.lww.com/AJG/B524 [comparators]). In children, only one-third of the total healthcare costs incurred during the first year after CD diagnosis could be directly attributed to the disease in costs for prescribed gluten-free diet (mean $278 [SD, $509]) and follow-up visits for CD ($634 [SD, $540]). In adult patients, costs from follow-up visits for CD had an even lesser impact on the total healthcare costs (Table 3).

Compared with matched general population comparators, the adjusted mean excess healthcare costs in the year after CD diagnosis were $2,147 (95% CI, $1,936–2,393) in patients aged

Table 2. Average use and costs (USD) of health care in 2015 by prevalent patients with CD as of January 1, 2015[a]

	<18 years (n = 7,440)		18–64 years (n = 25,156)		≥65 years (n = 8,355)	
	Resource use[b]	Mean cost (SD)[c]	Resource use[b]	Mean cost (SD)[c]	Resource use[b]	Mean cost (SD)[c]
Celiac disease						
Prescribed drugs, diets, and consumables						
Any prescription, % of patients	71.9%	703 (5,939)	77.8%	544 (2,539)	96.4%	899 (2,698)
Classes by indication and usage[d]						
Analgesics	2.7%	1 (7)	17.7%	17 (184)	38.8%	41 (132)
Anemia	3.9%	1 (34)	12.9%	9 (102)	44.0%	42 (326)
Cardiovascular disease	1.7%	5 (177)	12.2%	13 (438)	63.4%	71 (510)
Consumables[e]	5.9%	116 (843)	5.2%	49 (391)	7.9%	53 (393)
Diabetes, type 1 and type 2	6.3%	51 (222)	6.4%	47 (218)	10.8%	46 (200)
Gastrointestinal disease	10.3%	16 (158)	19.3%	26 (153)	48.8%	59 (209)
Gluten-free diet[f]	31.9%	151 (466)	—	—	—	—
Immunosuppressive drugs	1.1%	36 (665)	2.6%	107 (1,205)	2.7%	64 (948)
Obstructive airway disease	10.0%	12 (135)	9.1%	19 (174)	14.7%	55 (208)
Other	46.5%	267 (5,312)	68.1%	205 (1,899)	90.3%	421 (2,111)
Psychiatric disease	7.3%	43 (262)	21.6%	48 (270)	40.0%	44 (169)
Hospital-based care						
Nonprimary outpatient care, no. of visits[g]	1.9 (2.7)	711 (1,131)	1.8 (3.9)	712 (1,670)	2.9 (4.9)	1,170 (2,220)
Cancer	0.0 (0.1)	1 (73)	0.0 (0.4)	14 (246)	0.2 (1.0)	99 (583)
Cardiovascular disease	0.0 (0.1)	2 (47)	0.0 (0.3)	14 (157)	0.2 (0.7)	89 (390)
CD-related	0.5 (0.7)	159 (237)	0.0 (0.3)	21 (123)	0.1 (0.3)	22 (141)
Diabetes, type 1 and type 2	0.2 (1.0)	85 (390)	0.1 (0.5)	28 (187)	0.1 (0.5)	23 (181)
Other	1.0 (2.2)	392 (939)	1.4 (3.5)	564 (1,496)	2.3 (4.4)	910 (1,948)
Psychiatric disease	0.2 (0.9)	69 (373)	0.2 (1.0)	69 (412)	0.1 (0.7)	24 (256)
Inpatient care, no. of days	0.3 (4.7)	347 (2,796)	0.7 (5.8)	769 (4,721)	2.6 (9.0)	2,416 (7,185)
Total hospital-based care		1,058 (3,360)		1,481 (5,518)		3,586 (8,201)
Healthcare costs (overall)		1,762 (7,952)		2,027 (6,481)		4,486 (9,062)

	<18 years (n = 36,256)		18–64 years (n = 118,175)		≥65 years (n = 33,111)	
	Resource use[b]	Mean cost (SD)[c]	Resource use[b]	Mean cost (SD)[c]	Resource use[b]	Mean cost (SD)[c]
General population comparators						
Healthcare costs (overall)[h]		690 (9,369)		1,318 (5,803)		3,350 (7,613)
Adjusted mean difference (95% CI)[i]		1,075 (864–1,278)		715 (632–803)		1,010 (799–1,230)

For comparison, bottom rows represent adjusted mean differences in overall healthcare costs in age- and sex-matched general population comparators.
CD, celiac disease.
[a]CD diagnosis is defined by the date of diagnostic small intestinal biopsy.
[b]Resource use according to the healthcare services is defined in the left column. Mean (SD) if not otherwise stated.
[c]All costs were reported in USD adjusted for inflation to 2015.
[d]Classes based on the Anatomical Therapeutic Chemical (ATC) classification system as described in Table 1 (see Supplementary Digital Content 1, http://links.lww.com/AJG/B524).
[e]Medical consumables include syringes, blood glucose lancets, etc.
[f]We retrieved data on the prescribed gluten-free diet for all participants when available; however, we only specified such prescriptions in participants aged greater than18 years because such prescriptions are very limited for adults (which are due to Swedish prescription policy); any costs from prescribed gluten-free diets in adults were instead included under "Other" costs.
[g]Mean (SD) number of nonprimary outpatient visits grouped by main (primary) diagnoses as detailed in Table 1 (see Supplementary Digital Content 1, http://links.lww.com/AJG/B524).
[h]See Table 2 (see Supplementary Digital Content 1, http://links.lww.com/AJG/B524) for costs by category of health care services in comparators.
[i]Adjusted mean differences in overall healthcare costs by prevalent patients with CD and general population comparators adjusted for age, sex, and level of education; 95% confidence interval (CI) estimated using the bootstrap method.

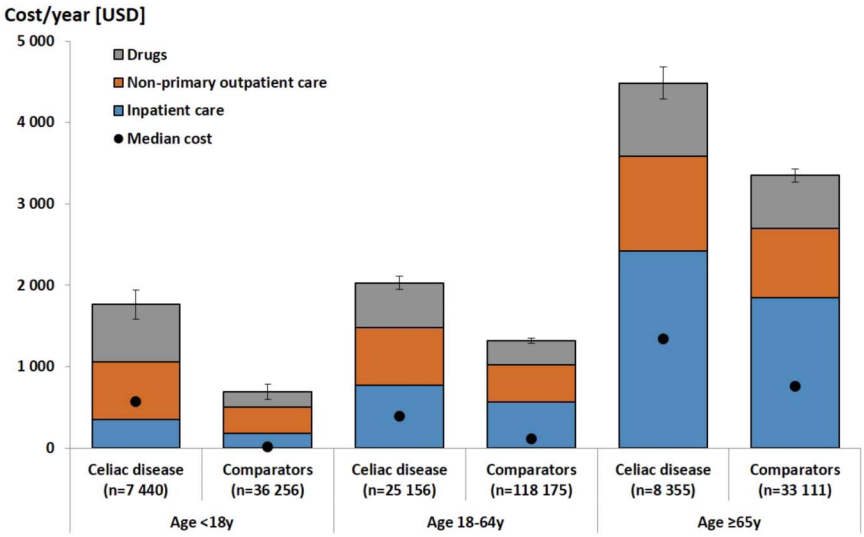

Figure 1. Mean and median annual costs in 2015 by age group of prevalent patients with celiac disease and age- and sex-matched general population comparators. Brackets indicate 95% confidence intervals for means.

greater than 18 years, $1,540 (95% CI, $1,369–1,748) in ages 18–64 years, and $3,444 (95% CI, $3,014–3,985) in ages greater than or equal to 65 years (Table 3). When stratifying for age, sex, and education level, excess healthcare costs were higher in men than in women and in those with a maximum of 9-year compulsory schooling vs a higher education level (see Table 6, Supplementary Digital Content 1, http://links.lww.com/AJG/B524). Between 2008 and 2015, there was no significant temporal trend in excess healthcare costs by the year of CD diagnosis (*P* value for trend 0.26; see Table 6, Supplementary Digital Content 1, http://links.lww.com/AJG/B524). Half of all costs were attributed to 6% of the incident patients (see Figure 1, Supplementary Digital Content 1, http://links.lww.com/AJG/B524).

The temporal relationship of healthcare use and costs to diagnosis of CD. Compared with matched general population comparators, the overall mean costs of health care per patient and year were higher even 5 years before diagnosis (the mean difference was $391 [95% CI, $296–515]) and increased until 1 year postdiagnosis ($2,039 [95% CI, $1,909–2,198]). Overall, excess costs then declined but were, on average, some 75% higher compared with general population comparators (mean difference $1,044 [95% CI, $907–1,241]) 5 years after diagnosis (Figure 2 and see Table 7, Supplementary Digital Content 1, http://links.lww.com/AJG/B524). Similar cost trajectories were observed across patient subgroups defined by sex (Figure 2), age, and education level (see Figure 2, Supplementary Digital Content 1, http://links.lww.com/AJG/B524) or index year of diagnosis (see Figure 3, Supplementary Digital Content 1, http://links.lww.com/AJG/B524).

Nonprimary outpatient visits, hospitalization days, and drug costs were, on average, all higher in the years before CD diagnosis (Figures 2–3). Still, as indicated by the median estimates of Figures 2–3, most children had virtually no use of healthcare services until the year leading up to CD diagnosis. One year postdiagnosis, the average number of annual nonprimary outpatient visits and hospitalization days declined but remained strikingly higher during the first 5 years compared with matched general population comparators. By contrast, overall, and for adult patients in particular, drug costs did not appreciably decrease during the 5 years after diagnosis. According to the recorded categories of ICD-10 diagnoses, cost trajectories for CD diagnosis were, in all age groups, mostly driven by extraintestinal complaints (see Figures 4–9, Supplementary Digital Content 1, http://links.lww.com/AJG/B524). Figure 10 (see Supplementary Digital Content 1, http://links.lww.com/AJG/B524) presents the annual costs by categories of filled prescriptions for drugs and gluten-free staples (for children) in relation to the date of CD diagnosis.

Healthcare costs according to the mucosal appearance on follow-up biopsy. Of 2,663 incident patients who underwent a follow-up biopsy, 717 had persistent VA and 1,946 had mucosal healing (see Table 8, Supplementary Digital Content 1, http://links.lww.com/AJG/B524). Adjusting for sex, age, and education level, overall excess healthcare costs were largely similar between patients with mucosal healing and patients with persistent VA on follow-up biopsy (Figure 4). Cost trajectories were also similar across the categories of healthcare services (see Figure 11, Supplementary Digital Content 1, http://links.lww.com/AJG/B524).

DISCUSSION

In this large population-based longitudinal study, the use and cost of health care were increased in patients with CD, not only before, but for years after diagnosis. Mucosal healing in CD did not predict the lower healthcare costs.

Strengths and limitations

The strengths of this study include its population-based design and use of prospectively recorded data, which reduces the risk of bias introduced by the selection of participants or from erroneous recall, which has hampered many previous studies (7,31,32). In addition, our study sample (>40,000 patients with CD) greatly exceeds that of all earlier studies in this field combined. The statistical power allowed us to provide robust estimates of costs and healthcare use within subgroups of individuals with CD. Although most studies have included working-age adults with CD (6,7), there is a paucity of data available from pediatric patients and patients aged greater than 65 years. Data on the healthcare resource use across subgroups of patients with CD before and after diagnosis are needed to

Table 3. Average use and costs (USD) of health care in the year after CD diagnosis in incident patients between 2008 and 2015[a]

	<18 years (n = 5,732)		18–64 years (n = 6,998)		≥65 years (n = 2,356)	
	Resource use[b]	Mean cost (SD)[c]	Resource use[b]	Mean cost (SD)[c]	Resource use[b]	Mean cost (SD)[c]
Celiac disease						
Prescribed drugs, diets, and consumables						
Any prescription, % of patients	89.8%	823 (4,633)	89.3%	577 (2,605)	98.2%	952 (2,038)
Classes by indication and usage[d]						
Analgesics	2.1%	1 (8)	19.7%	20 (140)	35.0%	37 (139)
Anemia	6.9%	5 (135)	32.6%	27 (232)	58.4%	71 (338)
Cardiovascular disease	2.0%	1 (17)	14.3%	13 (61)	63.5%	80 (134)
Consumables[e]	7.9%	193 (1,210)	4.8%	50 (428)	9.7%	63 (396)
Diabetes, type 1 and type 2	6.4%	44 (197)	4.7%	31 (185)	11.4%	42 (180)
Gastrointestinal disease	15.7%	27 (320)	34.3%	42 (174)	63.1%	85 (210)
Gluten-free diet[f]	64.2%	278 (509)	—	—	—	—
Immunosuppressive drugs	1.2%	25 (460)	2.0%	76 (1,143)	1.8%	50 (778)
Obstructive airway disease	11.9%	14 (86)	8.8%	26 (287)	11.8%	50 (215)
Other	54.6%	212 (3,448)	77.0%	247 (1,963)	91.4%	431 (1,556)
Psychiatric disease	4.2%	18 (165)	22.9%	40 (281)	37.6%	38 (160)
Hospital-based care						
Nonprimary outpatient care, no. of visits[g]	3.3 (3.2)	1,280 (1,320)	2.7 (4.8)	1,068 (1,771)	3.9 (6.6)	1,633 (3,247)
Cancer	0.0 (0.4)	2 (188)	0.1 (0.6)	24 (291)	0.3 (1.8)	150 (1,027)
Cardiovascular disease	0.0 (0.4)	5 (191)	0.0 (0.3)	20 (163)	0.2 (0.9)	114 (532)
CD-related	1.6 (1.2)	634 (540)	0.5 (0.8)	196 (349)	0.4 (0.8)	169 (340)
Diabetes, type 1 and type 2	0.2 (1.0)	86 (387)	0.1 (0.4)	20 (153)	0.1 (0.6)	30 (265)
Other	1.4 (2.8)	507 (1,084)	1.9 (4.4)	740 (1,577)	2.8 (5.9)	1,152 (2,771)
Psychiatric disease	0.1 (0.7)	42 (304)	0.2 (1.0)	65 (386)	0.0 (0.3)	15 (136)
Inpatient care, no. of days	0.6 (5.9)	617 (5,003)	1.3 (9.5)	1,117 (6,109)	4.8 (14.2)	3,915 (9,732)
Total hospital-based care		1,898 (5,637)		2,186 (6,795)		5,548 (11,056)
Healthcare cost (overall)		2,722 (8,489)		2,763 (7,663)		6,501 (11,703)

	<18 years (n = 28,643)		18–64 years (n = 34,788)		≥65 years (n = 11,149)	
	Resource use[b]	Mean cost (SD)[c]	Resource use[b]	Mean cost (SD)[c]	Resource use[b]	Mean cost (SD)[c]
General population comparators						
Healthcare cost (overall)[h]		581 (3,623)		1,236 (5,015)		3,031 (7,011)
Adjusted mean difference (95% CI)[i]		2,147 (1,936–2,393)		1,540 (1,369–1,748)		3,444 (3,014–3,985)

For comparison, bottom rows represent adjusted mean differences in overall healthcare costs in age- and sex-matched general population comparators.
CD, celiac disease.
[a]CD diagnosis is defined by the date of diagnostic small intestinal biopsy.
[b]Resource use according to the healthcare services is defined in the left column. Mean (SD) if not otherwise stated.
[c]All costs were reported in USD adjusted for inflation to 2015.
[d]Classes based on the Anatomical Therapeutic Chemical (ATC) classification system as described in Table 1 (see Supplementary Digital Content 1, http://links.lww.com/AJG/B524).
[e]Medical consumables include syringes, blood glucose lancets, etc.
[f]We retrieved data on the prescribed gluten-free diet for all participants when available; however, we only specified such prescriptions in participants aged <18 years because such prescriptions are very limited for adults (which are because of Swedish prescription policy); any costs from the prescribed gluten-free diet in adults were instead included under "Other" costs.
[g]Mean (SD) number of nonprimary outpatient visits grouped by main (primary) diagnoses, as detailed in Table 1 (see Supplementary Digital Content 1, http://links.lww.com/AJG/B524).
[h]Table 5 (see Supplementary Digital Content 1, http://links.lww.com/AJG/B524) for costs by category of healthcare services in comparators.
[i]Adjusted mean differences in overall healthcare costs by incident patients with CD and general population comparators adjusted for age, sex, and level of education; 95% confidence interval (CI) estimated using the bootstrap method.

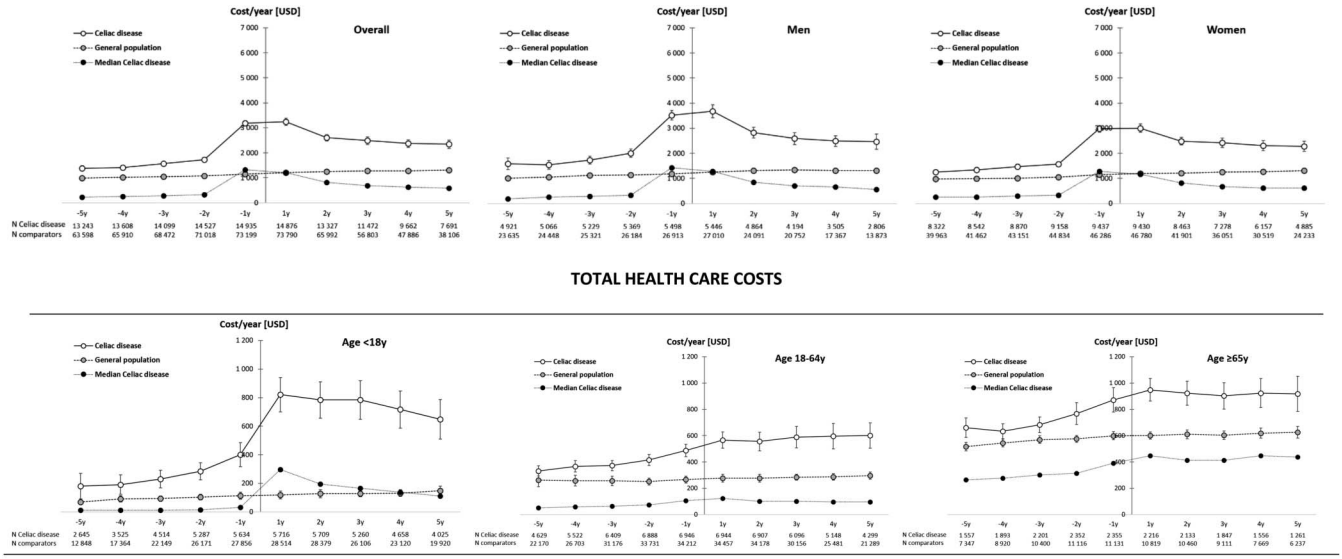

Figure 2. Mean and median annual the total healthcare costs (upper panel) in relation to the date of incident celiac disease diagnosis, overall and by sex. Mean and median annual costs of filled prescriptions for drugs, diets, and consumables (lower panel) in relation to the date of incident celiac disease diagnosis stratified by age group. Dashed lines indicate the mean annual total healthcare costs (upper panel) and drug costs (lower panel) in age- and sex-matched general population comparators. Brackets indicate 95% confidence intervals for means.

characterize the societal burden of illness and to provide input into economic evaluations.

We defined CD by the presence of small intestinal VA which, until recently, has been the gold standard to diagnose CD in children (33) and remains so in adults (34). The use of histopathology data also allowed us to identify a more representative population with CD than what could be identified by inpatient registers or at referral centers, where patients often suffer from a more severe disease. Earlier data also suggest that the Swedish National Patient Register will have low sensitivity for CD because it does not cover general practice (where many adult patients are followed up) and covers only hospital-based outpatient care since 2001 (19). In a previous patient chart review, we showed that 95% of individuals with VA had a clinical diagnosis of CD (15). Hence, although there

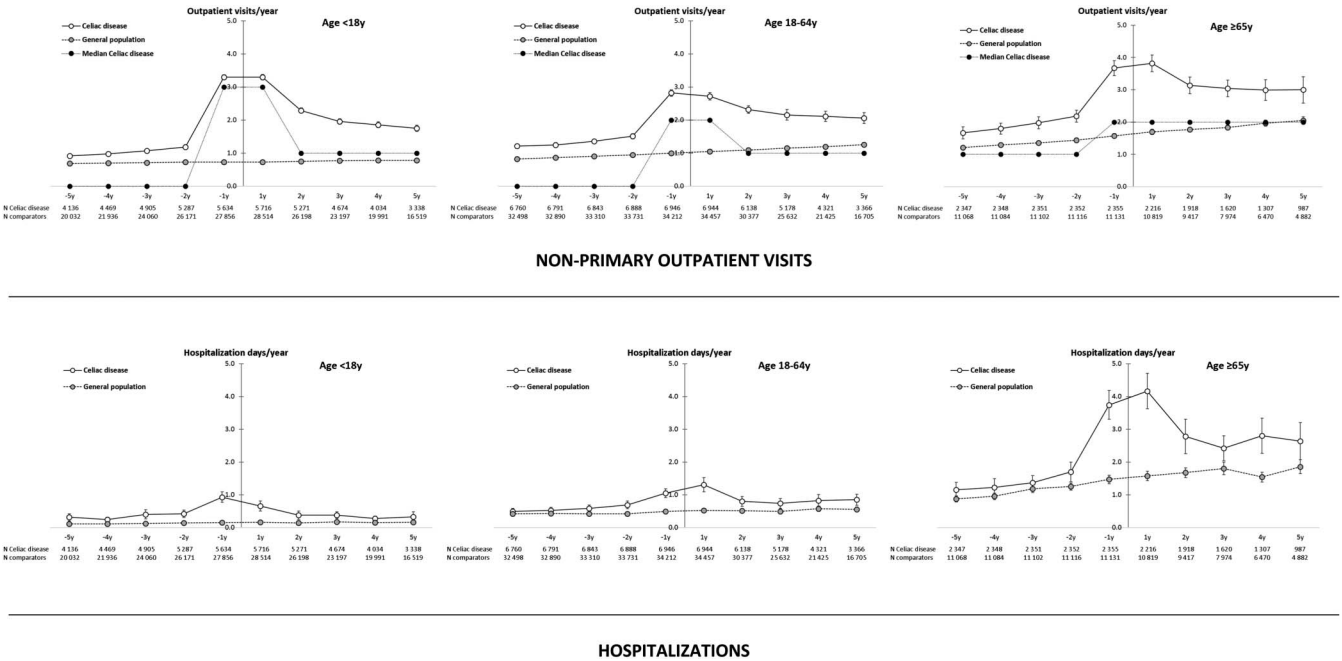

Figure 3. Mean and median annual number of nonprimary outpatient visits (upper panel) and the mean annual number of hospital days (lower panel) in relation to the date of celiac disease diagnosis (median hospital days were 0 across all age groups and years). Dashed lines indicate the mean annual number of nonprimary outpatient visits (upper panel) and hospital days (lower panel) in age- and sex-matched general population comparators. Brackets indicate 95% confidence intervals for means.

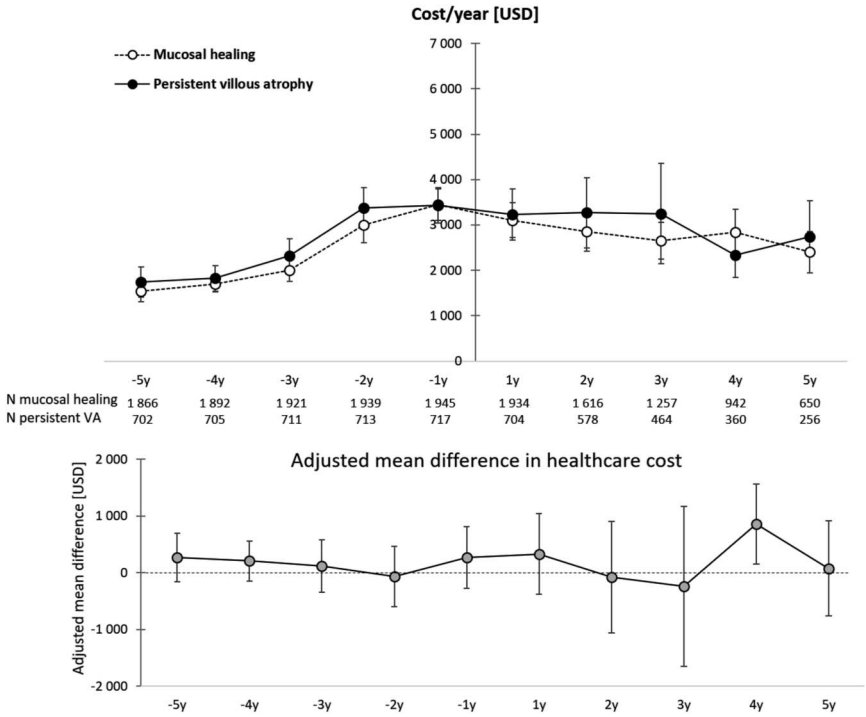

Figure 4. Mean annual total healthcare costs (upper panel) by incident patients with celiac disease in relation to the date of follow-up biopsy showing persistent villous atrophy (VA, marsh 3) or mucosal healing (marsh 0–2). Lower panel shows the adjusted mean differences in the annual total healthcare costs by incident patients with celiac disease with mucosal healing vs persistent VA (reference group) adjusted for age, sex, and level of education. Brackets indicate 95% confidence intervals for means.

are other causes of VA besides CD (35), the risk of misclassification in CD seems to be low. New European guidelines allowing for a nonbiopsy celiac diagnosis in certain children (33), but not in adults, mean that not all children with incident CD after 2012 may have been identified. However, from 2008 to 2015, we found no appreciable trend in healthcare costs by the year of CD diagnosis (*P* value for trend 0.26), arguing against a change in healthcare costs in CD during that period.

Taking advantage of histopathology data allowed us to determine the economic consequences of persistent VA vs mucosal healing in CD. We have previously shown that 90% of biopsies with VA, according to the gold standard, are correctly classified by Swedish pathologists (15). Although only a minority of patients diagnosed with CD in 2008–2015 underwent a follow-up biopsy, our study is still likely to detect any health economic impact of mucosal healing. We found no difference in healthcare use and cost between patients with and without mucosal healing.

Obviously, this study has some limitations. Most importantly, the National Patient Register (19) does not include primary care data. Swedish children with CD and CD-related comorbidities (such as diabetes) are typically managed at inpatient and outpatient settings reporting to the National Patient Register. In adults, however, such care is sometimes provided by primary care, potentially leading to underestimation of the actual healthcare costs. Although we accounted for costs of prescribed gluten-free food staples in children, we were largely unable to account for the excess costs from gluten-free diet borne by adult patients for whom such prescriptions are very limited because of Swedish prescription policies.

We were unable to distinguish between screening-detected and clinically detected CD (and across CD phenotypes) and whether healthcare costs differ between these 2 groups. Finally, we were not able to adjust for smoking or obesity status, both of which have been associated with increased healthcare use (36). Adjusting for such data would probably have increased the difference even more in healthcare use between patients with CD and comparators because smoking and obesity are negatively associated (or not associated at all) with CD (37,38).

Interpretation of results in relation to the previous literature

Consistent with the literature in this area (5), we found the use and costs of health care to be highest in the years around CD diagnosis, but only partly to represent the costs from a gluten-free diet and follow-up visits directly related to CD. Instead, excess costs were attributable to a wide range of conditions and prescribed drug classes. Although hospitalizations were relatively rare in CD, such care was costly and often represented a serious health issue for the individual patient. We, as well as European and US studies (6,39,40), have shown significantly higher costs and use of health care in individuals with CD vs those without CD, even 5–10 years after diagnosis.

Swedish health care is tax funded (as opposed to, for instance, the United States in which private insurance plans play a major role (7,41)). Thus, our cost measurements may provide a lower limit of estimated healthcare costs compared with countries with larger health care expenditures (13). Some studies have presented higher absolute cost differences between CD and comparators in the United States than elsewhere (6,7,41).

We found excess use and costs of health care to be higher several years before diagnosis of CD. Although similar findings have been reported by others (5), our study adds to the literature

by its long follow-up and detailed, annualized trajectories of the use and cost of health care before diagnosis for both patients and age- and sex-matched comparators. There may be several explanations for this increase in prediagnostic cost in CD, including that it could be due to the burden of yet undiagnosed/untreated CD or related to conditions known to co-occur with CD (e.g., type 1 diabetes) (42). From our data it is, however, not clear to what extent these excess costs may reflect the usual latency period before being diagnosed with CD.

As recently reviewed by Mearns et al. (5), there is controversy as to whether diagnosing and treating CD will reduce healthcare costs as compared to those incurred before the diagnosis. Three prospectively recorded claims analyses in the United States have suggested significant economic benefits from diagnosing CD (6,7,41). Although studies from Sweden (43) and other Scandinavian countries (31,32) have also reported falling costs and use of health care after diagnosis, those studies were limited to retrospective data, which are prone to recall bias. Instead, in line with UK primary care data (8), we show that annual excess costs dropped after the year of CD diagnosis but, perhaps most importantly, that they remained strikingly higher even 5 years after diagnosis. Notably, postdiagnostic excess healthcare costs continued to be high, particularly in incident patients aged greater than 65 years, an age group of patients poorly represented in previous works (5). This novel finding is important, given that CD is increasingly recognized as a disease in the elderly (44,45). Conversely, despite the added societal costs of providing subsidized gluten-free food staples in children with CD, pediatric patients had the largest decrease in healthcare costs after diagnosis of CD. In the UK study, the gluten-free diet was a major factor responsible for ongoing healthcare costs (8). Our study also adds to the research by showing that mucosal healing in CD does not result in reduced healthcare costs. This novel finding is consistent with data, indicating that the mucosal appearance on follow-up histology is a poor predictor for many health outcomes, including death (46).

There is a rapidly rising prevalence of CD in general, and of adult diagnosed disease in particular, which is estimated to have increased 5- to 10-fold over the past 30 years (47,48). With now 1% of the population worldwide being affected by this lifelong condition (2,49), our results have important implications for health care practice. Although our results do not emphasize the importance of early CD diagnosis through medical cost savings, many people benefit from early diagnosis of CD (50).

In conclusion, we found the use and cost of health care to be distinctly increased in patients with CD, not only before, but for years after diagnosis. Although mucosal healing has clinical benefits, it does not seem to lower the healthcare costs.

CONFLICTS OF INTEREST

Guarantor of the article: Jonas F. Ludvigsson, MD, PhD.

Specific author contributions: K.M., J.S., S.R.B., Å.H.E., B.L., P.H.R.G., M.N., J.F.L. ICMJE criteria for authorship read and met; K.M., J.S., S.R.B., Å.H.E., B.L., P.H.R.G., M.N., J.F.L. agree with the manuscript's results and conclusions: K.M., J.S., M.N., J.F.L. designed the study: J.F.L. collected data; J.S. analyzed the data; K.M., J.F.L. wrote the first draft of the manuscript; J.S., S.R.B., Å.H.E., B.L., P.H.R.G., M.N. contributed to the writing of the manuscript; K.M., J.S., S.R.B., Å.H.E., B.L., P.H.R.G., M.N., J.F.L. interpretation of data, approved the final version of the manuscript; J.F.L. responsible for data integrity; J.F.L. supervised the project; K.M., J.F.L obtained funding.

Financial support: K.M.: Swedish state under the agreement between the Swedish government and the county councils, the A.L.F. agreement; Å.H.E.: Bengt Ihre Research Foundation and the Bengt Ihre Research Fellowship; B.L.: The Louis and Gloria Flanzer Philanthropic Trust. The funding sources did not influence any aspect of the study (its design, the collection, analysis and interpretation of data), or approval of the manuscript and the decision to submit it for publication.

Potential competing interests: J.F.L. coordinates a study on behalf of the Swedish IBD quality register (SWIBREG), which has received funding from Janssen corporation. Å.H.E. has worked on projects at Karolinska Institutet and SWIBREG, partly financed by grants from Ferring and Janssen. The other authors report no conflicts of interest.

Study Highlights

WHAT IS KNOWN

- ✓ Although CD affects 1% of the population, its effect on healthcare cost is barely understood.
- ✓ In particular, there are few population-based estimates and uncertainty about the cost distribution across patient subgroups.
- ✓ There are no data on whether mucosal healing in CD affects healthcare costs.

WHAT IS NEW HERE

- ✓ We report detailed, annualized trajectories of the use/cost of healthcare services in >40,000 patients with CD and age- and sex-matched general population comparators.
- ✓ The use and cost of health care were distinctly increased in patients with CD, not only before, but for years after diagnosis.
- ✓ Excess healthcare costs were observed across patient subgroups defined by sex, age, and education level.
- ✓ Mucosal healing in CD did not result in reduced healthcare costs.

REFERENCES

1. Lebwohl B, Sanders DS, Green PHR. Coeliac disease. Lancet 2018;391:70–81.
2. Singh P, Arora A, Strand TA, et al. Global prevalence of celiac disease: Systematic review and meta-analysis. Clin Gastroenterol Hepatol 2018;16:823–36.e2.
3. Ludvigsson JF, Sjolander A, Murray JA, et al. Haemoglobin decline before coeliac disease diagnosis: A nationwide transfusion cohort study of 1.1 million blood donors. Gut 2017;66:2036–7.
4. Ludvigsson JF. Mortality and malignancy in celiac disease. Gastrointest Endosc Clin N Am 2012;22:705–22.
5. Mearns ES, Taylor A, Boulanger T, et al. Systematic literature review of the economic burden of celiac disease. Pharmacoeconomics 2019;37:45–61.
6. Long KH, Rubio-Tapia A, Wagie AE, et al. The economics of coeliac disease: A population-based study. Aliment Pharmacol Ther 2010;32:261–9.
7. Green PH, Neugut AI, Naiyer AJ, et al. Economic benefits of increased diagnosis of celiac disease in a national managed care population in the United States. J Insur Med 2008;40:218–28.
8. Violato M, Gray A, Papanicolas I, et al. Resource use and costs associated with coeliac disease before and after diagnosis in 3,646 cases: Results of a UK primary care database analysis. PLoS One 2012;7:e41308.
9. Mitchell EM. Concentration of Health Expenditures in the U.S. Civilian Noninstitutionalized Population, 2014. In: US Statistical Brief Medical Expenditure Panel Survey (Internet). Rockville, MD: US Agency for Healthcare Research and Quality; 2001–. STATISTICAL BRIEF #497. Available from: https://www.ncbi.nlm.nih.gov/books/NBK425792/.

10. Lebwohl B, Michaelsson K, Green PH, et al. Persistent mucosal damage and risk of fracture in celiac disease. J Clin Endocrinol Metab 2014;99: 609–16.
11. Lebwohl B, Granath F, Ekbom A, et al. Mucosal healing and risk for lymphoproliferative malignancy in celiac disease: A population-based cohort study. Ann Intern Med 2013;159:169–75.
12. Rubio-Tapia A, Rahim MW, See JA, et al. Mucosal recovery and mortality in adults with celiac disease after treatment with a gluten-free diet. Am J Gastroenterol 2010;105:1412–20.
13. Anell A, Glenngård AH, Merkur S. Sweden health system review. Health Syst Transit 2012;14:1–159.
14. Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, et al. The Swedish personal identity number: Possibilities and pitfalls in healthcare and medical research. Eur J Epidemiol 2009;24:659–67.
15. Ludvigsson JF, Brandt L, Montgomery SM, et al. Validation study of villous atrophy and small intestinal inflammation in Swedish biopsy registers. BMC Gastroenterol 2009;9:19.
16. Ludvigsson JF, Lashkariani M. Cohort profile: ESPRESSO (Epidemiology Strengthened by HistoPathology Reports in Sweden). Clin Epidemiol 2019;11:101–14.
17. Marsh MN. Grains of truth: Evolutionary changes in small intestinal mucosa in response to environmental antigen challenge. Gut 1990;31:111–4.
18. Ludvigsson JF, Almqvist C, Bonamy AK, et al. Registers of the Swedish total population and their use in medical research. Eur J Epidemiol 2016; 31:125–36.
19. Ludvigsson JF, Andersson E, Ekbom A, et al. External review and validation of the Swedish national inpatient register. BMC Public Health 2011;11:450.
20. Wettermark B, Hammar N, Fored CM, et al. The new Swedish Prescribed Drug Register—Opportunities for pharmacoepidemiological research and experience from the first six months. Pharmacoepidemiol Drug Saf 2007;16:726–35.
21. Ludvigsson JF, Svedberg P, Olen O, et al. The longitudinal integrated database for health insurance and labour market studies (LISA) and its use in medical research. Eur J Epidemiol 2019;34:423–37.
22. Busse R. Diagnosis-related Groups in Europe Moving Towards Transparency, Efficiency and Quality in Hospitals. Maidenhead: Open University Press; 2011.
23. Weitoft GR, Rosen M, Ericsson O, et al. Education and drug use in Sweden—A nationwide register-based study. Pharmacoepidemiol Drug Saf 2008;17:1020–8.
24. Westin M, Ahs A, Brand Persson K, et al. A large proportion of Swedish citizens refrain from seeking medical care—Lack of confidence in the medical services a plausible explanation? Health Policy 2004;68:333–44.
25. Riddle MS, Murray JA, Porter CK. The incidence and risk of celiac disease in a healthy US adult population. Am J Gastroenterol 2012;107:1248–55.
26. Villafuerte-Galvez J, Vanga RR, Dennis M, et al. Factors governing long-term adherence to a gluten-free diet in adult patients with coeliac disease. Aliment Pharmacol Ther 2015;42:753–60.
27. Olen O, Bihagen E, Rasmussen F, et al. Socioeconomic position and education in patients with coeliac disease. Dig Liver Dis 2012;44:471–6.
28. Thompson SG, Barber JA. How should cost data in pragmatic randomised trials be analysed? BMJ 2000;320:1197–200.
29. Pearce N. Analysis of matched case-control studies. BMJ 2016;352:i969.
30. Tuire I, Marja-Leena L, Teea S, et al. Persistent duodenal intraepithelial lymphocytosis despite a long-term strict gluten-free diet in celiac disease. Am J Gastroenterol 2012;107:1563–9.
31. Ukkola A, Kurppa K, Collin P, et al. Use of health care services and pharmaceutical agents in coeliac disease: A prospective nationwide study. BMC Gastroenterol 2012;12:136.
32. Mattila E, Kurppa K, Ukkola A, et al. Burden of illness and use of health care services before and after celiac disease diagnosis in children. J Pediatr Gastroenterol Nutr 2013;57:53–6.
33. Husby S, Koletzko S, Korponay-Szabo IR, et al. European Society for pediatric gastroenterology, Hepatology, and nutrition Guidelines for the diagnosis of coeliac disease. J Pediatr Gastroenterol Nutr 2012;54: 136–60.
34. Ludvigsson JF, Bai JC, Biagi F, et al. Diagnosis and management of adult coeliac disease: Guidelines from the British Society of gastroenterology. Gut 2014;63:1210–28.
35. Jansson-Knodell CL, Hujoel IA, Rubio-Tapia A, et al. Not all that flattens villi is celiac disease: A review of enteropathies. Mayo Clin Proc 2018;93: 509–17.
36. Neovius M, Narbro K, Keating C, et al. Health care use during 20 years following bariatric surgery. JAMA 2012;308:1132–41.
37. Olen O, Montgomery SM, Marcus C, et al. Coeliac disease and body mass index: A study of two Swedish general population-based registers. Scand J Gastroenterol 2009;44:1198–206.
38. Ludvigsson JF, Montgomery SM, Ekbom A. Smoking and celiac disease: A population-based cohort study. Clin Gastroenterol Hepatol 2005;3: 869–74.
39. Canova C, Pitter G, Ludvigsson JF, et al. Risks of hospitalization and drug consumption in children and young adults with diagnosed celiac disease and the role of maternal education: A population-based matched birth cohort study. BMC Gastroenterol 2016;16:1.
40. Roos S, Wilhelmsson S, Hallert C. Swedish women with coeliac disease in remission use more health care services than other women: A controlled study. Scand J Gastroenterol 2011;46:13–9.
41. Guandalini S, Tundia N, Thakkar R, et al. Direct costs in patients with celiac disease in the USA: A retrospective claims analysis. Dig Dis Sci 2016;61:2823–30.
42. Elfström P, Sundström J, Ludvigsson JF. Systematic review with meta-analysis: Associations between coeliac disease and type 1 diabetes. Aliment Pharmacol Ther 2014;40:1123–32.
43. Norström F, Sandström O, Lindholm L, et al. A gluten-free diet effectively reduces symptoms and health care consumption in a Swedish celiac disease population. BMC Gastroenterol 2012;12:125.
44. Rashtak S, Murray JA. Celiac disease in the elderly. Gastroenterol Clin North Am 2009;38:433–46.
45. Vilppula A, Kaukinen K, Luostarinen L, et al. Increasing prevalence and high incidence of celiac disease in elderly people: A population-based study. BMC Gastroenterol 2009;9:49.
46. Lebwohl B, Granath F, Ekbom A, et al. Mucosal healing and mortality in coeliac disease. Aliment Pharmacol Ther 2013;37:332–9.
47. Catassi C, Kryszak D, Bhatti B, et al. Natural history of celiac disease autoimmunity in a USA cohort followed since 1974. Ann Med 2010;42: 530–8.
48. Lohi S, Mustalahti K, Kaukinen K, et al. Increasing prevalence of coeliac disease over time. Aliment Pharmacol Ther 2007;26:1217–25.
49. Walker MM, Murray JA, Ronkainen J, et al. Detection of celiac disease and lymphocytic enteropathy by parallel serology and histopathology in a population-based study. Gastroenterology 2010;139:112–9.
50. Kivelä L, Kurppa K. Screening for coeliac disease in children. Acta Paediatr 2018;107:1879–87.