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ORIGINAL ARTICLE

Are we beyond the peak of celiac disease incidence in Olmsted County, Minnesota, USA?

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ABSTRACT

Background and Objectives: The incidence of celiac disease (CD) has increased over the past few decades. Recent reports suggest the incidence has peaked and plateaued in many countries. We aimed to demonstrate the CD incidence trend since 2000 in a well-defined US population. **Methods:** Using the Rochester Epidemiology Project (REP), we reviewed electronic health records for patients of Mayo Clinic and Olmsted Medical Center between 2000 and 2021. We identified patients diagnosed with CD during the study period and resided in Olmsted County, Minnesota. Incidence rates (per 100,000 person-years) were calculated by age, sex, and calendar year and adjusted to the 2020 US population. **Results:** Among 622 patients diagnosed with CD during the study period, 179 (29%) were children and 395 (64%) were female. Median age at diagnosis among pediatric and adult patients was 9.2 years and 42.2 years, respectively. Overall CD incidence rate increased and peaked at 24.9 in 2015 through 2017. Incidence plateaued in the later part but remained higher at the end of the study period. The increased incidence rate was influenced primarily by children younger than 11 years, whose incidence almost tripled during the study period. A clear decreasing trend was noted only among adults older than 64 years. **Conclusion:** Although the overall CD incidence rate is plateauing in Olmsted County, it continued to increase among children. This could indicate a shift to increase awareness and earlier diagnosis.

Key words: autoimmune, enteropathy, growth, malabsorption, small bowel

INTRODUCTION

Celiac disease (CD) is a well-described, immune-mediated enteropathy related to gluten exposure in persons with genetic susceptibility.[1] Initially described as a relatively rare disease affecting those of Northern European descent, CD has emerged as a major global disease process.[2–7]

CD diagnosis initially required multiple small bowel biopsy (SBB) taken while on and off a gluten-containing diet. More recently, use of highly sensitive screening markers such as anti–tissue transglutaminase immunoglobulin A (anti-TTG IgA) has informed current recommendations suggesting efficacy of a serologic diagnosis in pediatric patients without confirmatory SBB.[8–11] Since 2000, CD incidence has continued to increase globally, with a 1.4% global prevalence ranging from 0.4% in South America to 0.8% in Europe.[12,13] Additionally, global prevalence rates are significantly different between male and female patients (0.4% *vs.* 0.6%) and between children and adults (0.9% *vs.* 0.5%).[6]

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Increased disease burden could reflect a true increase or result from improved patient and provider awareness augmented by advancements in the ease of diagnosis. Regardless, this does not explain why women and children have been disproportionately affected.[1] A recent population study from Israel demonstrated a steadily increasing incidence of pediatric CD, despite a stable incidence in adults.[14] Pooled global data for the past 20 years estimate a female-to-male difference in incidence of nearly 10 per 100,000 person-years (17.4 *vs.* 7.8).[1]

CD prevalence estimates are complicated by a well-known disease distribution in which symptomatic patients represent a small portion of those affected.[15,16] We previously showed only a minority of pediatric patients in Olmsted County, Minnesota, have classic CD symptoms (diarrhea and poor growth) at diagnosis.[15] Therefore, current estimates more closely reflect the prevalence of symptomatic CD as opposed to the entire disease distribution. Recent efforts to identify subacute or latent disease have largely focused on proactively testing high-risk groups such as patients with a first-degree relative with CD or personal history of autoimmunity.[17–19] Aside from these specific populations, testing of lower-risk groups is reserved for symptoms suggestive of CD.

Pooled global data demonstrated a 7.5% annual increase in CD incidence over the past 2 decades, but recent reports suggest CD incidence has peaked and is plateauing in countries such as Finland, Sweden, and the UK.[1,20–22] In this retrospective cohort study, we aimed to demonstrate epidemiologic trends for both pediatric and adult CD through a population based retrospective cohort study in Olmsted County, Minnesota.

METHODS

This was a retrospective cohort study of residents of Olmsted County, Minnesota, which used epidemiologic data compiled in the Rochester Epidemiology Project (REP). All authors had access to the study data and reviewed/approved the final manuscript. Methodology was completed using the cohort study STROBE framework.

The REP is a continuously updated data linkage system containing the health record of patients evaluated by all health care providers at Mayo Clinic and Olmtead Medical Center, the 2 main centers in Olmstead County. Since its initiation in 1966, more than 1,000,000 medical records from both outpatient and inpatient settings have been collected from over 500,000 persons.[23–25] Recognizing the importance of this unique database, the National Institutes of Health has supported its growth, prompting numerous epidemiologic studies.[23,25] Importantly, the demographics of Olmsted County have been comparable to the census of both Minnesota and the Upper Midwest of the US.[24] To complete an exhaustive query of the REP, we searched for potential cases of CD using *International Classification of Diseases, Ninth Revision* code 579.0 and *International Classification of Diseases, Tenth Revision* code K90.0.

Case ascertainment and characterization

After identifying a potential cohort from the REP, we retrospectively reviewed pertinent medical records after obtaining approval from the institutional review boards of both Mayo Clinic and Olmstead Medical Center. Patients without research authorization were excluded. We identified all patients who met CD diagnostic guidelines with a documented clinical diagnosis date between January 1, 2000, and December 31, 2021. Olmsted County residency was confirmed electronically using the REP linkage system. Cases were considered incident if the patient was living in Olmsted County at the time of diagnosis to exclude referral cases seeking tertiary care.

The following data were collected from the health records: birth date, race, sex, date of diagnosis, CD-specific antibody tests, and anti-TTG IgA levels at time of diagnosis.[15,26,27] CD diagnosis was confirmed if patients had documented positive CD serologic markers, such anti-TTG IgA, anti-endomysial antibodies, or deamidated gliadin peptide antibodies followed by confirmatory SBB with characteristic histology (*i.e.*, increase in intraepithelial lymphocytes, crypt hyperplasia, and villous atrophy). Diagnosis was also confirmed for pediatric patients meeting ESPGHAN (European Society for Pediatric Gastroenterology Hepatology and Nutrition) criteria for avoiding SBB.[9] Relevant antibody titers were recorded at the time of diagnosis but not trended over time.

Statistical analysis

Number of patients (percentage) is reported for categorical variables and median (IQR) is reported for continuous variables. Incidence was calculated between 2000 and 2021. Incidence rates for diagnosis of CD by age, sex, and calendar year were calculated as the number of new patients with CD living in Olmsted County at diagnosis divided by the number of residents based on REP census data, assuming all persons were at risk. Rates were adjusted to the White population of the US in 2020 based on age and sex. Incidence rates were determined for 5 age categories (0–5, 6–10, 11–17, 18–64, 65 years or older) for each sex. Multivariable Poisson regression was used to assess associations of age, sex, and calendar year using count as the outcome with an offset of natural log of the population. The

functional forms of calendar year and age were assessed visually with Loess curves and polynomials in addition to considering age in the 5 categories. Data were analyzed with SAS statistical software version 9.4M7 (SAS Institute Inc), and the level of statistical significance was set to 0.05.

RESULTS

Study patients

We identified 622 patients (179 children [0–17 years] and 443 adults [18 years]) residing in Olmsted County diagnosed with CD during the study period. Median age was 31.8 years, 395 (63.5%) were female, and 581 (94.8%) were White. Among non-White patients, 13 (2.1%) were Black/African American, 7 (1.1%) were Asian, and 12 (2%) were other. Among pediatric patients diagnosed with CD, median (IQR) age was 9.2 (6.3–12.8) years; adult patients with CD had a median (IQR) age of 42.2 (30.2–56.9) years. Only 15 pediatric patients were diagnosed using ESPGHAN serologic guidelines, first in 2012 and peaking with 4 new diagnoses per year in both 2018 and 2019. At diagnosis, 42 patients were aged 5 years or younger, 78 were between 6 and 10 years, 59 were between 11 and 17 years, 374 were between 18 and 64 years, and 69 were 65 years or older (the oldest patient was 84 years old). All included study subjects had documentation of gluten-free diet (GFD) as a treatment.

Overall temporal trend of incidence

From 2000 through 2002, 36 patients were identified, for an incidence rate of 9.2 (95% CI, 6.1–12.4) per 100,000 person-years, compared with 103 patients identified from 2018 through 2021 with an incidence rate of 15.3 (95% CI, 12.3–18.3) per 100,000 person-years (Table 1). Although higher at the end of the study period than the beginning, the overall incidence peaked between 2015 and 2017 at 24.9 (95% CI, 20.5–29.4) per 100,000 person-years (Table 1). For modeling of incidence, a quadratic temporal trend was significant ($P < 0.001$), further suggesting a peak occurring in the late 2000s followed by a decline in incidence in the 2010s (Figure 1). However, age and time interactions were significant ($P < 0.001$), which suggested different temporal changes by age.

Pediatric temporal trend of incidence

The incidence rate of children aged 6 to 10 years was 23.4 per 100,000 person-years, which remained consistently greater than adolescents between 11 and 17 years (19.3 per 100,000 person-years). Nevertheless, both groups showed a similar overall trend, with total pediatric incidence peaking between 2015 and 2017. This was after a near-linear increase during the first decade of the 21st century before transitioning to a slightly slower rate of increase in the subsequent decade (Figure 2). Each pediatric age group demonstrated an upward trend in CD incidence since 2000, most notably among children aged 6 to 10 years from 18.0 (2000–2002) to 42.9 (2018–2021) per 100,000 person-years (Table 1). CD incidence in children younger than 6 years nearly tripled from 5.7 (2000–2002) to 15.2 (2018–2021) per 100,000 person-years. Adolescents between 11 and 17 years had an absolute increase in incidence of 21.0 per 100,000 person-years during the study period.

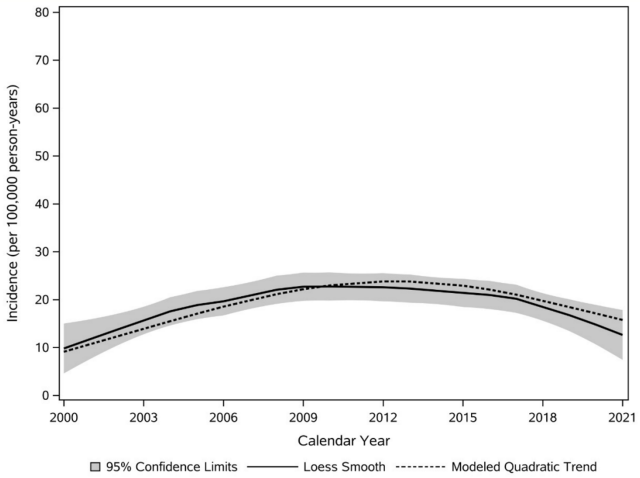

Figure 1. Loess smooth of calendar-year trends. Overall incidence is shown with 95% confidence limits and modeled quadratic trend.

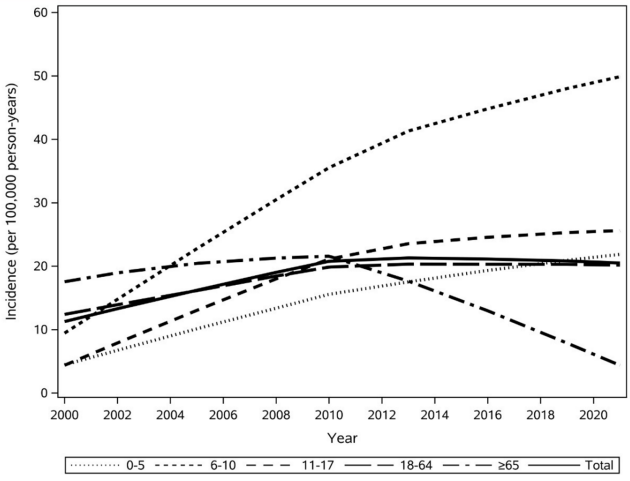

Figure 2. Loess smooth of calendar-year trends of incidence by age group.

Adult temporal trend of incidence

As in the pediatric population, adult CD incidence increased in the first half of the study period, between 2000 and 2011. The incidence for younger adults between 18 and 64 years more than doubled between the 2000 through 2002 and 2009 through 2011 study periods (9.1 to 18.5 per 100,000 person-years) (Table 1). Unlike

Table 1: Incidence of celiac disease in olmsted county, minnesota, 2000–2021, by age group, sex, and time period, *n* (%)

Group[a]	2000–2002 (*n* = 36)	2003–2005 (*n* = 79)	2006–2008 (*n* = 78)	2009–2011 (*n* = 103)	2012–2014 (*n* = 99)	2015–2017 (*n* = 124)	2018–2021 (*n* = 103)
Female							
0–5 yr	1 (5.8)	2 (10.7)	2 (10.0)	6 (29.6)	6 (30.0)	6 (29.8)	3 (11.5)
6–10 yr	3 (22.7)	2 (14.8)	5 (35.7)	7 (46.6)	6 (38.1)	11 (69.6)	10 (49.7)
11–17 yr	0 (0.0)	3 (14.8)	4 (20.3)	7 (35.9)	6 (30.1)	7 (33.4)	10 (34.2)
18–64 yr	16 (12.2)	36 (26.1)	31 (21.3)	33 (22.3)	47 (31.2)	50 (32.4)	36 (17.3)
⩾ 65 yr	3 (12.3)	7 (26.8)	6 (21.1)	10 (32.3)	4 (11.7)	4 (10.6)	5 (9.0)
All ages	11.3 (6.6–16.1)	23.6 (16.9–30.3)	21.3 (15.2–27.4)	27.2 (20.4–34.0)	27.9 (21.3–34.5)	30.5 (23.7–37.3)	18.8 (14.2–23.4)
Male							
0–5 yr	1 (5.5)	1 (5.1)	2 (9.4)	2 (9.3)	3 (14.2)	2 (9.6)	5 (18.8)
6–10 yr	2 (13.7)	1 (6.9)	3 (20.4)	6 (38.9)	6 (35.5)	8 (47.0)	8 (36.7)
11–17 yr	1 (4.7)	3 (13.9)	3 (14.4)	3 (14.9)	4 (19.7)	4 (18.6)	4 (13.1)
18–64 yr	7 (5.8)	22 (17.5)	15 (11.5)	19 (14.4)	12 (8.9)	30 (21.8)	20 (10.8)
⩾ 65 yr	2 (11.6)	2 (10.5)	7 (32.5)	10 (41.8)	5 (18.8)	2 (6.8)	2 (4.5)
All ages	7.2 (3.0–11.3)	14.5 (9.1–20.0)	15.9 (9.9–21.9)	20.4 (13.8–27.0)	13.5 (8.5–18.5)	19.4 (13.8–25.1)	11.9 (8.1–15.7)
Total							
0–5 yr	2 (5.7)	3 (7.9)	4 (9.7)	8 (19.1)	9 (21.9)	8 (19.6)	8 (15.2)
6–10 yr	5 (18.0)	3 (10.7)	8 (27.9)	13 (42.7)	12 (36.8)	19 (57.9)	18 (42.9)
11–17 yr	1 (2.4)	6 (14.4)	7 (17.2)	10 (25.2)	10 (24.9)	11 (25.9)	14 (23.4)
18–64 yr	23 (9.1)	58 (22.0)	46 (16.6)	52 (18.5)	59 (20.7)	80 (27.4)	56 (14.2)
⩾ 65 yr	5 (12.0)	9 (19.9)	13 (26.0)	20 (36.4)	9 (14.8)	6 (8.9)	7 (7.0)
All ages	9.2 (6.1–12.4)	19.1 (14.8–23.5)	18.4 (14.2–22.6)	23.6 (19.0–28.3)	20.5 (16.4–24.6)	24.9 (20.5–29.4)	15.3 (12.3–18.3)

[a]Age group–specific results are presented as number of patients (unadjusted incidence rate per 100,000 person-years). Results for "all ages" are incidence rates age-adjusted to the 2020 US White population (95% CI)

the pediatric population, however, adult incidence not only plateaued over the later decade of the study but also began to downtrend, especially in adults 65 years or older (Figure 2). This older adult population was the only age group to exhibit clear signs of decreasing incidence, with a final incidence rate of 7.0 per 100,000 person-years, nearly half the initial rate (12.0 per 100,000 person-years).

Sex differences in CD incidence

The incidence rates for the 395 female and 227 male patients, averaged over time, were 23.1 and 14.5 per 100,000 person-years, respectively (Table 2). The incidence trends overall by sex are shown in Figure 3. The CD incidence for females of all ages was consistently greater than males (23 *vs.* 14.4 per 100,000 person-years; $P < 0.001$), and there was no significant interaction with age or time ($P = 0.61$). Despite overall sex differences, longitudinal incidence trends indicate increasing rates of CD in both male and female persons younger than 65 years (Table 1). Men and women older than 64 years had a decreasing incidence of CD since 2000, after simultaneous peaks in 2009 through 2011.

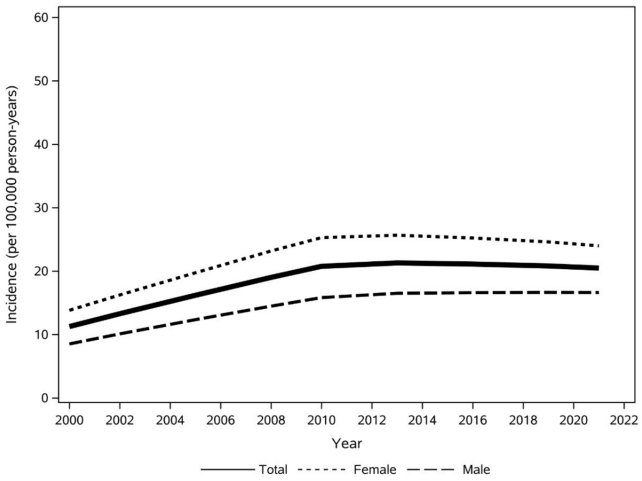

Figure 3. Loess smooth of calendar-year trends of incidence by sex.

DISCUSSION

CD has emerged as a major global disease process, necessitating epidemiologic evaluation of populations worldwide to more accurately quantify increasing incidence.[1] Within a well-defined US population in Olmsted County, Minnesota, our epidemiology study identified 622 patients and showed an increase in CD incidence from 2000 through 2021. Our primary goal

Table 2: Incidence of celiac disease in Olmsted County, Minnesota, 2000–2021 overall by age group and sex[a], *n* (%)

Sex	0–5 yr	6–10 yr	11–17 yr	18–64 yr	⩾ 65 yr	All ages
Female	26 (18.2)	44 (41.0)	37 (24.7)	249 (23.1)	39 (16.4)	395 (23.1)
Male	16 (10.7)	34 (29.6)	22 (14.1)	125 (12.9)	30 (16.5)	227 (14.5)
Total	42 (14.4)	78 (35.1)	59 (19.3)	374 (18.3)	69 (16.5)	622 (18.9)

[a]Results are presented as number of patients (incidence rate per 100,000 person-years)

was to update the CD incidence trends reported in a previous study querying data from 2000 to 2010 using the REP.[27] The overall incidence peaked around 2015 and decreased thereafter, although it was still higher at the end of the study than the start. We identified different incidence trends by age group. The pediatric population consistently increased over time with a later plateau, whereas the adult incidence showed an early peak followed by a substantial decrease. Furthermore, CD incidence among females was consistently higher than males, regardless of age. Our results are comparable to other epidemiologic studies in the US indicating CD incidence among children under 10 years has continued to rise, despite slight regional differences.[28]

These results are consistent with a recent study in Israel that queried hospital records for patients with new CD autoimmunity and showed CD incidence increased from 25.4 per 100,000 person-years in 2007 to 52.3 per 100,000 person-years in 2015.[14] This increase was influenced entirely by the pediatric population, with incidence rates 4 times greater in children younger than 5 years than adults aged 26 to 55 years. The incidence was also significantly higher for females than males. Although showing similar demographic trends, our results are not directly comparable because the inclusion criteria by Lechtman *et al.*[14] only required anti-TTG IgA to be greater than 1 time the upper limit of normal,[14] whereas our study included confirmed CD cases. Autoimmunity is nondiagnostic for CD at lower antibody titers. Regardless, using autoimmunity as a surrogate for CD development, the similarity between these 2 demographically distinct populations suggests the possibility of a common underlying risk factor inherent to young children and women.

Generalizable epidemiologic trends have been difficult to establish based on the available worldwide data. Studies from the Netherlands and Scotland indicate increasing rates of CD across all age groups, whereas reports from Finland and South Wales demonstrate recent stabilization and a possible decrease in CD incidence.[20–22,29,30] Further complicating the uncertainty is a paucity of data from large population centers including Africa, Asia, and Latin America.[1] Despite this limitation, a global meta-analysis suggests CD incidence is highest in children and females with an overall annual increase of 7.5% over the past several decades, adding to a global prevalence already disproportioantely affecting females and children.[6]

The underlying reason for this increase is unknown. Suggested explanations include increased awareness among patients and providers, testing of high-risk groups, improved ease and accessibility of testing, and a possible time-based environmental condition losing its effect on older patients but impacting children as new arrivals to the risk environment.[14,15] A shift to earlier diagnosis may account for the overall increase in population incidence despite plateauing and even decreased incidence in older adults.

Furthermore, the rise in CD incidence among those under 5 years may reflect more symptomatic presentations compared to older ages, resulting in a higher rate of diagnosis in this age group. Early diagnosis of children also places first-degree relatives as new additions to the "at risk" population, theoretically prompting household adoption of GFD practices out of shopping/food preparation convenience or perceived universal harm of gluten. The disproportionate increase in the prevalence of GFD compared to CD diagnosis has implications on the sensitivity of future testing for individuals already on theraputic diets.[1,31,32]

A substantial limitation of the existing literature is that the available data are primarily from Europe and North America where increased public access to medical services could skew testing and impact incidence estimates. This same limitation applies to the current study due to availability of excellent health care and high awareness of CD in Olmsted County. In a previous study in Olmsted County between 2000 and 2014, diagnoses based on high-risk testing accounted for only 23% of CD incident cases.[15] Additionally, a population-based study in Olmstead County indicated CD incidence was unaffected by increased amount of serologic testing, implying increased testing alone may not explain rising incidence.[33]

Instead, incidence trends are likely reflective of a genuine increase in CD influenced by environmental conditions. The proliferation of gluten containing foods in Western diet and reliance of wheat as a dietary staple

is certainly an environmental risk factor, especially for socioeconomic classes less able to afford the often-pricier gluten-free alternatives. Though largely outside of the scope of this study, we are unaware of significant changes in local environmental risk factors, including trends in childhood intestinal infections, indications for antibiotic therapy in infants that may alter the gut microbiome, or statistically significant association between peripartum antibiotics and development of CD.[34] We are also unaware of shifts in food processing techniques or early gluten introduction practices.[1,35]

Regarding the impacts of racial and ethnic diversity on overall incidence trends, we did not see any definite drift in terms of ethnicity distribution or age distribution that would have impacted incidence trends. Despite an increase in population over the study period, the vast majority remained White with only a modest increase in minority groups according to local school enrollment and US census data.[24]

Although it theoretically seems plausible that a time-based environmental condition is disproportionately affecting children, this does not explain incidence trends in females. Sex-differences might simply represent an imbalance in healthcare utilization, evidenced by data suggesting that screening studies yield similar occurrence of CD in men and women.[1] Perhaps females are disproportionally diagnosed as part of medical evaluations for comorbid conditions more commonly diagnosed in women, such as hypothyroidism.[1] Similarly, the current recommendation for frequent, routine well-child visits might disproportionately provide children with access to medical evaluations and testing for potentially less symptomatic cases. A multifactorial explanation is most likely and will require additional population-based studies to evaluate further.

Increased CD incidence has prompted debate regarding implementation of mass screening to identify asymptomatic disease. Though universal testing could potentially reduce morbidity from diagnostic delay, it will also increase false positive results as well as the cost and morbidity associated with unnecessary, invasive confirmatory procedures.[36] With a global prevalence of about 1%, the positive predictive value of mass screening is lower, hence, universal mass screening has not been adopted in North America.[37] Furthermore, universal screening is limited by a lack of innovative changes in CD diagnosis over the past decade and continued failure to precisely identify hidden disease within the general population.[38,39]

In addition to the inherent limitations of retrospective studies, our study had a few notable limitations, including the demographics of Olmsted County, where more than 80% of the population is White. Relative underrepresentation of minority racial or ethnic groups compared to 2020 census data of the general US population may limit cultural differences in dietary practices. Furthermore, poverty rates in Olmstead County have consistently been well below the national average (most recently 7.61% *vs.* 12.6% in 2021) and may have implications in the ability for families to empirically start a more expensive GFD without first undergoing medical evaluation. Strengths include being a population-based study in a setting with unique epidemiologic advantages for retrospective population-based studies. Such advantages include a self-contained health care environment and medical record linkage system through the REP for almost the entire Olmsted County population. Additionally, our case ascertainment was based on clinical criteria and pathologic confirmation. Regardless of study limitations, our results draw attention to increasing CD incidence and reminds medical providers to consider CD in the differential for their patients, especially within the at-risk age group of 6- to 10-year-olds.

CD incidence fluctuated in Olmsted County, Minnesota over the past 2 decades with increasing rates in children aged 6 to 10 years, stabilization in adults between 18 and 64 years, and a marked decrease among adults aged 65 years and older. This may reflect a shift to earlier diagnosis. CD incidence has continued to increase and should remain in the differential, especially for young children presenting with new abdominal complaints.

DECLARATIONS

Author contributions

VanNess GH, Ismail Y, Lee AT, King KS, Choung RS, Murray JA, and Absa I designed the study and write the article. All authors reviewed the manuscript and approved its submission.

Informed consent

Informed consent was obtained from all subjects involved in the study.

Ethical approval

Not applicable.

Conflict of interest

The authors declare no conflicts of interest.

Data availability statement

The authors confirm that the data supporting the findings of this study are available within the article.

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