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ORIGINAL RESEARCH

Regional Trends in Inflammatory Bowel Disease-Related Mortality in the US from 1999 to 2022

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Purpose: Inflammatory bowel disease (IBD) is a grouping of chronic inflammatory diseases of the gastrointestinal tract that affects upwards of 2.4 million Americans. Despite its prevalence, the exact cause remains unknown. This study aims to identify geographical differences in IBD-related mortality.

Patients and Methods: We utilized Centers for Disease Control and Prevention Wide-ranging Online Data for Epidemiologic Research (CDC WONDER) database. IBD-related death and population size data over the span of 1999 to 2022 was extracted. Data was stratified by United States census regions, place of death, and gender. Crude and age-adjusted mortality rates (AAMR) were calculated and trends in mortality were modeled using the Join-point Regression Program, with statistically significant outcomes (p-value ≤ 0.05) denoted via an asterisk (*).

Results: During the interval from 1999 to 2022, there were a total of 71,628 deaths due to Inflammatory Bowel Disease (IBD) in the United States. All census regions showed an increase in AAMR over the study period. The Midwest had the highest AAMRs with 1.54 (95% CI 1.42 to 1.65) in 1999 and rising to 1.99 (95% CI 1.87 to 2.11) in 2022 with an AAPC of 1.57 (95% CI 0.75 to 2.14)* and an APC of 9.83 (95% CI 3.43 to 21.10)* from 2018 to 2022. More specifically, Midwestern males displayed the highest AAMR with 1.74 (95% CI 1.54 to 1.94) in 1999 and 2.09 (95% CI 1.9 to 2.27) in 2022, and an APC of 8.50 (95% CI 2.254 to 19.40)* between 2018 and 2022.

Conclusion: Persistent regional differences were seen in IBD mortality, with the Midwest having the highest AAMR and Southern states exhibiting the greatest regional increase in AAMR over the past two decades. IBD mortality worsened across all regions during the period of the COVID-19 pandemic.

Keywords: Crohn's, ulcerative colitis, regional, disparities

Introduction

Inflammatory bowel disease (IBD) is defined as a chronic inflammatory disease of the gastrointestinal tract that is a result of an autoimmune response to gut microflora within both the small and large intestines. IBD can be further classified into two main subsets: ulcerative colitis and Crohn's disease. Both subsets appear to affect men and women equally and affect both adolescents and adults within the U.S.[1] Although there appears to be a genetic component, the exact cause of IBD is not yet known. Therefore, it is important to explore trends in incidence and mortality of the disease to better understand the disease. Previous studies have explored the incidence, prevalence, and mortality rate of IBD in the United States and how these factors have increased in the last twenty years, however, any evidence of geographical differences in IBD-related mortality remains largely unknown.[2]

Prior studies have shown that the prevalence of IBD within the US is steadily increasing, particularly since the COVID-19 pandemic.[3] IBD affects approximately one percent of the US adult population, with numbers continuing to rise.[4] In the US, biological agents used to treat autoimmune diseases, specifically IBD, are becoming one of the fastest-

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growing sectors of the pharmaceutical market.[5] However, these drugs are a significant financial burden to both patients and the US healthcare system. Considering costs beyond pharmaceuticals alone, annual US healthcare spending on IBD has been shown to have increased from $6.4 billion in 1996 to $25.4 billion in 2016.[6]

Additionally, there has been an observed increase in morbidity and mortality in patients with IBD during the recent COVID-19 pandemic. The significance of this finding in part relates to recent meta-analysis studies conducted in patients who presented with IBD, which in turn revealed a trend in increased risk for oncologic transformations leading to the development of colorectal cancer, among others.[7]

To gain a clearer understanding of the burden of inflammatory bowel disease (IBD) on both patients and the US healthcare system, it is crucial to examine the relationship between mortality rates in IBD patients and various epidemiologic factors, including geographic location within the US. This study analyzes trends using data from the Centers for Disease Control and Prevention's Wide-ranging Online Data for Epidemiologic Research (CDC WONDER) database, aiming to provide the US healthcare system with valuable insights to regional trend and disparities in IBD mortality in US.

Materials and Methods

To identify Inflammatory Bowel Disease (IBD) related deaths occurring within the United States, we utilized Centers for Disease Control and Prevention Wide-ranging Online Data for Epidemiologic Research (CDC WONDER) database. Institutional Review Board (IRB) approval was not required, as the CDC WONDER database is comprised only of publicly available, depersonalized data. Death certificate records from the CDC WONDER database and Multiple Cause-of-Death Public Use Record were analyzed to find certificates with IBD listed as a contributing cause. This technique has been utilized in prior research that utilized CDC WONDER to analyze mortality trends in Inflammatory Bowel Disease. Identification of IBD-related mortality was achieved using the International Classification of Diseases, 10th revision, Clinical Modification Codes K50.0, K50.1, K50.8, K50.9, K51.0, K51.1, K51.2, K51.3, K51.4, K51.5, K51.8, K51.9 with an age restriction of ≥25 years of age due to the infrequent occurrence of IBD pathology in patients below this cutoff. As the CDC WONDER database contains anonymized, publicly available data, this study is exempt from institutional review board approval.

We extracted IBD-related death and population size data over the span of 1999 to 2022. We further extracted demographical and regional group data including the United States census regions, place of death, and gender. Regional data was classified via the United States Census Bureau Definitions as Northeast, Midwest, South and West. Location of death was categorized as within medical facilities (outpatient/ER, inpatient), outside of medical facilities (hospice facility, nursing home/long-term care facility, home), or unknown.

Inflammatory Bowel Disease related crude mortality rates and age-adjusted mortality rates (AAMR) were calculated. To calculate the crude mortality rates, the number of IBD-related deaths was divided by the corresponding United States population. AAMR values were standardized using the 2000 United States standard population as previously described in the National Vital Statistics Report by the Center for Disease Control and Prevention. Trends in mortality over the study period were modeled using the Join-point Regression Program. Specifically, this program utilizes Join-point regression modeling to find statistically significant changes in annual mortality trends. Join-point modeling connects several linear segments at inflection points (join points), starting with the simplest model (a single linear trend) and adding additional join points to break the data temporally and demonstrate distinct periods in which variation occurred. For each line segment linking join points the annual percentage change (APC) in AAMR was calculated along with 95% confidence intervals (CI) via the Monte Carlo permutation test. The weighted average of the APCs was also calculated and reported as the average annual percentage change (AAPC) with 95% CIs as a representation of the reported mortality trend over the entire study period. Increases or decreases in APC and AAPC were determined if the value was found to be significantly different from zero via 2-tailed *t* test. A p value of ≤0.05 was utilized in determining statistical significance, with statistically significant values denoted by an asterisk (*).

Results

Overall

During the interval from 1999 to 2022, there were 71,628 deaths associated with Inflammatory Bowel Disease (IBD) in the United States.

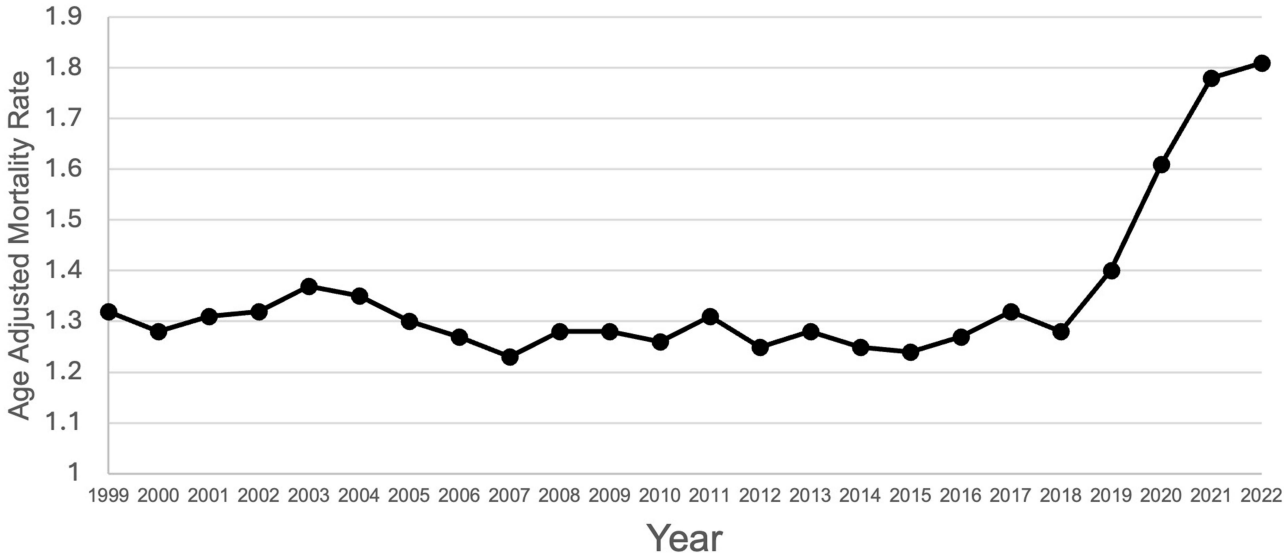

Figure 1 Overall Age Adjusted Mortality Rate of deaths related to Inflammatory Bowel Disease from 1999 to 2022.

During this period, overall age-adjusted mortality rates (AAMR) increased from 1.32 (95% CI 1.27 to 1.38) in 1999 to 1.81 (95% CI 1.76 to 1.86) in 2022, with an average annual percentage change (AAPC) of 1.63 (95% CI 1.34 to 1.88) * (Figure 1, Table 1). Join point analysis revealed that over the period of 1999 to 2018, there was no statistically significant

Table 1 Overall Age Adjusted Mortality Rate of Deaths Related to Inflammatory Bowel Disease from 1999 to 2022

Year	Overall Age Adjusted Mortality Rate
1999	1.32
2000	1.28
2001	1.31
2002	1.32
2003	1.37
2004	1.35
2005	1.30
2006	1.27
2007	1.23
2008	1.28
2009	1.28
2010	1.26
2011	1.31
2012	1.25
2013	1.28
2014	1.25
2015	1.24
2016	1.27
2017	1.32
2018	1.28
2019	1.40
2020	1.61
2021	1.78
2022	1.81

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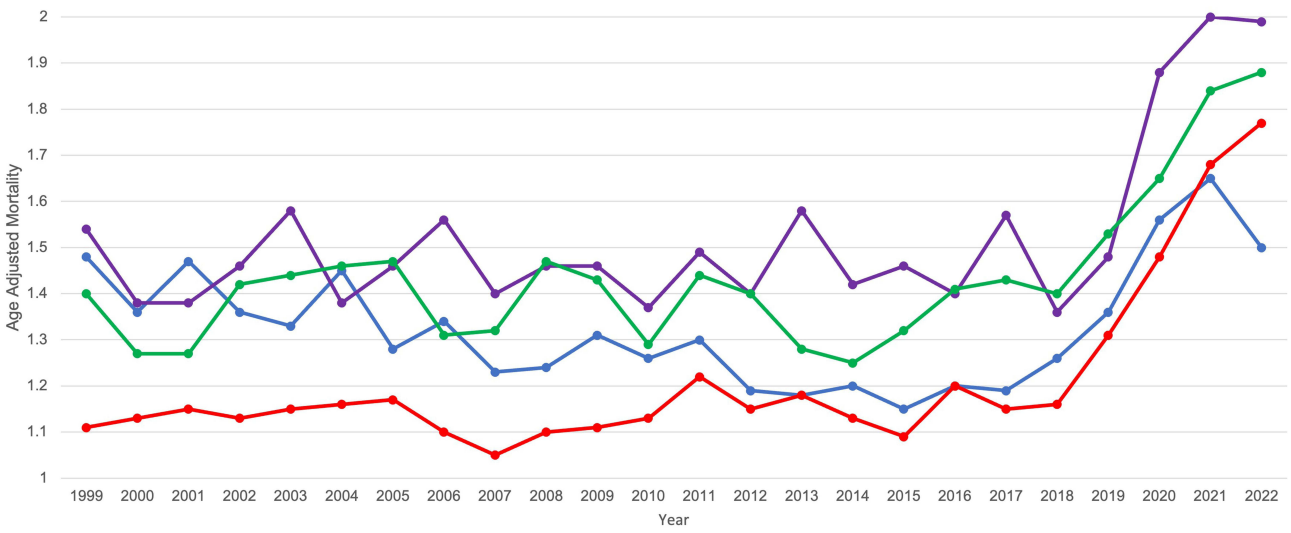

Figure 2 Age-Adjusted Mortality Rate of Deaths related to Inflammatory Bowel Disease from 1999 to 2022, stratified by census region. Blue: Northeast, Purple: Midwest, Red: South, Green West.

change in AAMR, with the annual percentage change (APC) in overall AAMR being −0.14 (95% CI −0.42 to 0.15). However, from 2018 to 2022 there was a statistically significant increase in AAMR, with the APC increasing to 10.44 (95% CI 7.89 to 14.0)*.

Regional Variation

Census Region Stratified

All census regions showed an increase in AAMR over the period of the study.

The Midwest had the highest AAMRs with 1.54 (95% CI 1.42 to 1.65) in 1999 and rising to 1.99 (95% CI 1.87 to 2.11) in 2022 with an AAPC of 1.57 (95% CI 0.75 to 2.14)* (Figure 2, Table 2). Joinpoint analysis showed two distinct

Table 2 Age Adjusted Mortality Rate from 1999 to 2022 Stratified by Census Region

Year	Age Adjusted Mortality Rate			
	Northeast	Midwest	South	West
1999	1.48	1.54	1.11	1.40
2000	1.36	1.38	1.13	1.27
2001	1.47	1.38	1.15	1.27
2002	1.36	1.46	1.13	1.42
2003	1.33	1.58	1.15	1.44
2004	1.45	1.38	1.16	1.46
2005	1.28	1.46	1.17	1.47
2006	1.34	1.56	1.10	1.31
2007	1.23	1.40	1.05	1.32
2008	1.24	1.46	1.10	1.47
2009	1.31	1.46	1.11	1.43
2010	1.26	1.37	1.13	1.29
2011	1.30	1.49	1.22	1.44
2012	1.19	1.40	1.15	1.40
2013	1.18	1.58	1.18	1.28

(*Continued*)

Table 2 (Continued).

Year	Age Adjusted Mortality Rate			
	Northeast	Midwest	South	West
2014	1.20	1.42	1.13	1.25
2015	1.15	1.46	1.09	1.32
2016	1.20	1.40	1.20	1.41
2017	1.19	1.57	1.15	1.43
2018	1.26	1.36	1.16	1.40
2019	1.36	1.48	1.31	1.53
2020	1.56	1.88	1.48	1.65
2021	1.65	2.00	1.68	1.84
2022	1.50	1.99	1.77	1.88

periods in AAMR trends. The APC increased from −0.09 (95% CI −1.47 to 0.62) between 1999 and 2018 up to 9.83 (95% CI 3.43 to 21.10)* from 2018 to 2022.

The South showed the greatest change in AAMR from 1.11 (95% CI 1.03 to 1.19) in 1999 to 1.77 (95% CI 1.69 to 1.86) in 2022 with an AAPC of 2.1312 (95% CI 1.86 to 2.39)*. Joinpoint analysis found that the APC increased from 0.20 (95% CI −0.16 to 0.53) between 1999 and 2018 up to 11.81 (95% CI 9.05 to 16.30)* between 2018 and 2022 (Figure 3).

The Northeast showed an overall slight increase in AAMR from 1.48 (95% CI 1.35 to 1.60) in 1999 to 1.50 (95% CI 1.39 to 1.61) in 2022 with an AAPC of 0.55 (95% CI 0.11 to 0.97)*. Joinpoint analysis, however, found that there was an

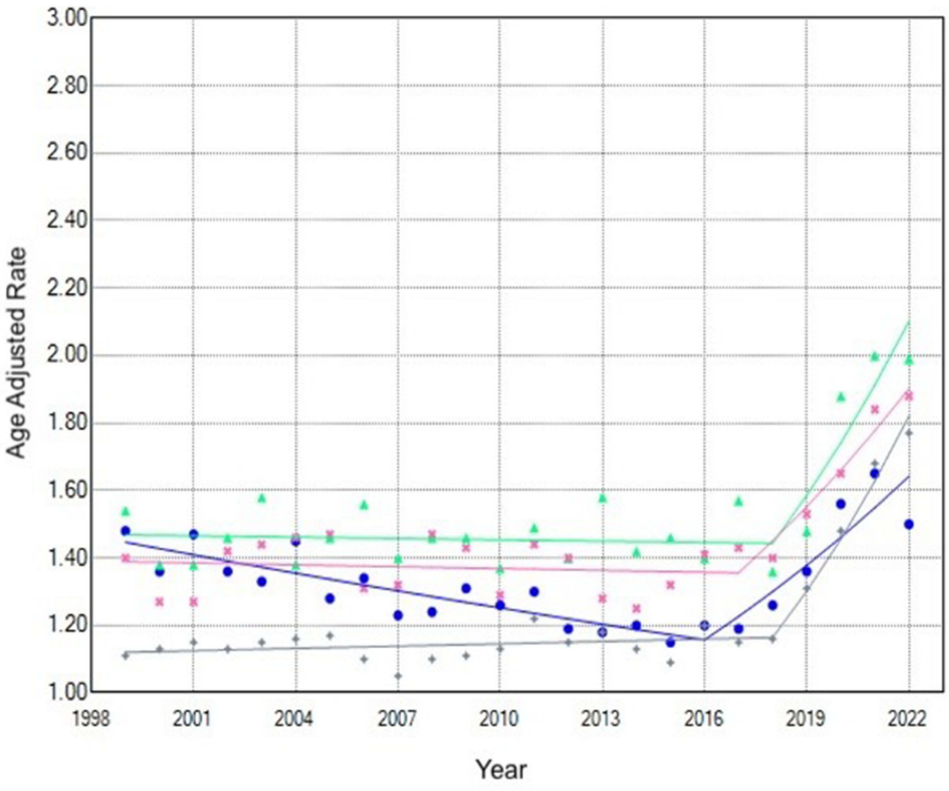

Figure 3 Joinpoint showing Annual Percent Change in Age Adjusted Mortality Rate of deaths related to Inflammatory Bowel Disease from 1999 to 2022, stratified by census region. Blue: Northeast, Green: Midwest, Black: South, Pink: West.

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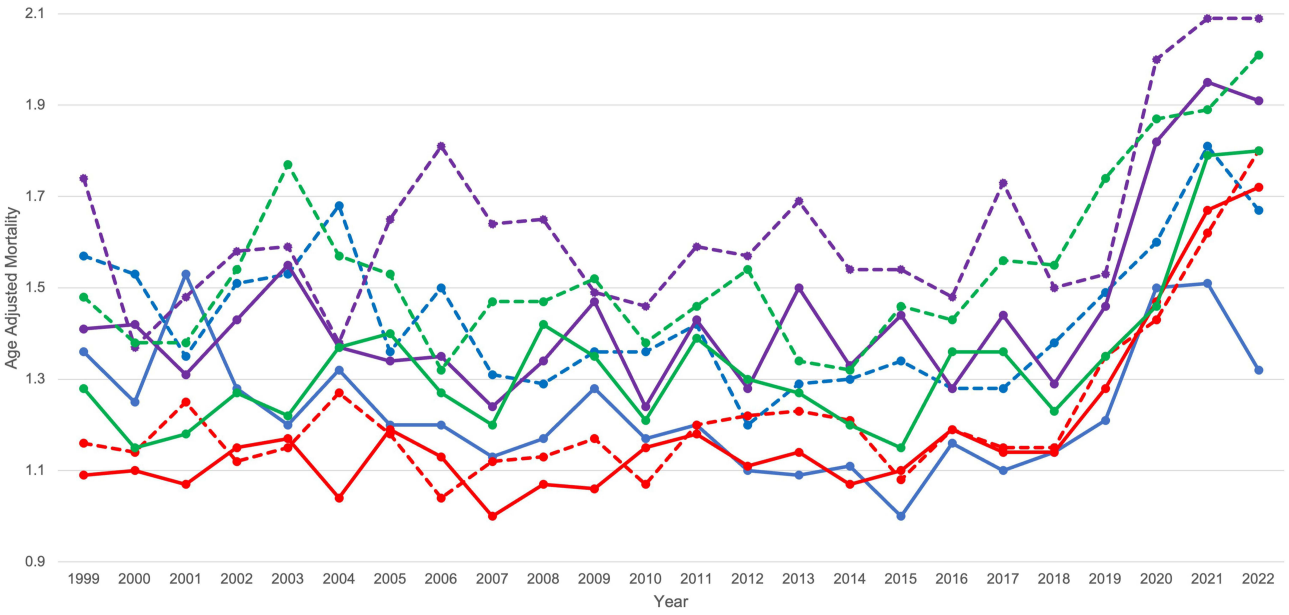

Figure 4 Age Adjusted Mortality Rate of deaths related to Inflammatory Bowel Disease from 1999 to 2022, stratified by gender and region. Blue solid line: Northeast Female, Blue dashed line: Northeast Male, Purple solid line: Midwest Female, Purple dashed line: Midwest Male, Red solid line: South Female, Red dashed line: South Male, Green solid line: West Female, Green dotted line: West Male.

initial decrease in AAMR, with an APC of −1.30 (95% CI −1.99 to −0.77)* from 1999 to 2016. From 2016 to 2022, conversely, there was an increase in AAMR, with an APC of 6.00 (95% CI 3.61 to 11.00)*.

The West also saw an increase in AAMR, from 1.40 (95% CI 1.28 to 1.53) in 1999 to 1.88 (95% CI 1.77 to 1.99) in 2022 with an AAPC of 1.37 (95% CI 0.75 to 1.90)*. Join point analysis showed the APC increasing from −0.14 (95% CI −1.27 to 0.54) between 1999 and 2017 up to 6.99 (95% CI 3.25 to 15.95)* from 2017 to 2022.

Census Region and Gender Stratified

Overall, when stratified by census region and gender, the AAMR for males was higher than that of females in the same census region over the period studied. Midwestern males displayed the highest AAMR while southern and northeastern females had the lowest (Figure 4, Tables 3 and 4).

Table 3 Age Adjusted Mortality Rate from 1999 to 2022 Stratified by Census Region and Male Gender

Year	Age Adjusted Mortality Rates			
	Northeast Male	Midwest Male	South Male	West Male
1999	1.57	1.74	1.16	1.48
2000	1.53	1.37	1.14	1.38
2001	1.35	1.48	1.25	1.38
2002	1.51	1.58	1.12	1.54
2003	1.53	1.59	1.15	1.77
2004	1.68	1.38	1.27	1.57
2005	1.36	1.65	1.18	1.53
2006	1.50	1.81	1.04	1.32
2007	1.31	1.64	1.12	1.47
2008	1.29	1.65	1.13	1.47
2009	1.36	1.49	1.17	1.52

(*Continued*)

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Table 3 (Continued).

Year	Age Adjusted Mortality Rates			
	Northeast Male	Midwest Male	South Male	West Male
2010	1.36	1.46	1.07	1.38
2011	1.42	1.59	1.20	1.46
2012	1.20	1.57	1.22	1.54
2013	1.29	1.69	1.23	1.34
2014	1.30	1.54	1.21	1.32
2015	1.34	1.54	1.08	1.46
2016	1.28	1.48	1.19	1.43
2017	1.28	1.73	1.15	1.56
2018	1.38	1.5	1.15	1.55
2019	1.49	1.53	1.35	1.74
2020	1.60	2.00	1.43	1.87
2021	1.81	2.09	1.62	1.89
2022	1.67	2.09	1.80	2.01

Table 4 Age Adjusted Mortality Rate from 1999 to 2022, Stratified by Census Region and Female Gender

Year	Age Adjusted Mortality Rates			
	Northeast Female	Midwest Female	South Female	West Female
1999	1.36	1.41	1.09	1.28
2000	1.25	1.42	1.10	1.15
2001	1.53	1.31	1.07	1.18
2002	1.28	1.43	1.15	1.27
2003	1.20	1.55	1.17	1.22
2004	1.32	1.37	1.04	1.37
2005	1.20	1.34	1.19	1.40
2006	1.20	1.35	1.13	1.27
2007	1.13	1.24	1.00	1.20
2008	1.17	1.34	1.07	1.42
2009	1.28	1.47	1.06	1.35
2010	1.17	1.24	1.15	1.21
2011	1.20	1.43	1.18	1.39
2012	1.10	1.28	1.11	1.30
2013	1.09	1.50	1.14	1.27
2014	1.11	1.33	1.07	1.20
2015	1.00	1.44	1.10	1.15
2016	1.16	1.28	1.19	1.36
2017	1.10	1.44	1.14	1.36
2018	1.14	1.29	1.14	1.23
2019	1.21	1.46	1.28	1.35
2020	1.50	1.82	1.47	1.46
2021	1.51	1.95	1.67	1.79
2022	1.32	1.91	1.72	1.80

More specifically, Midwestern males displayed the highest AAMR with 1.74 (95% CI 1.54 to 1.94) in 1999 and 2.09 (95% CI 1.9 to 2.27) in 2022. Their overall AAPC during this period was 1.40 (95% CI 0.52 to 2.04)*with an APC of −0.04 (95% CI −1.83 to 0.71) from 1999 to 2018 which then increased to 8.50 (95% CI 2.254 to 19.40)* between 2018 and 2022 (Figure 5).

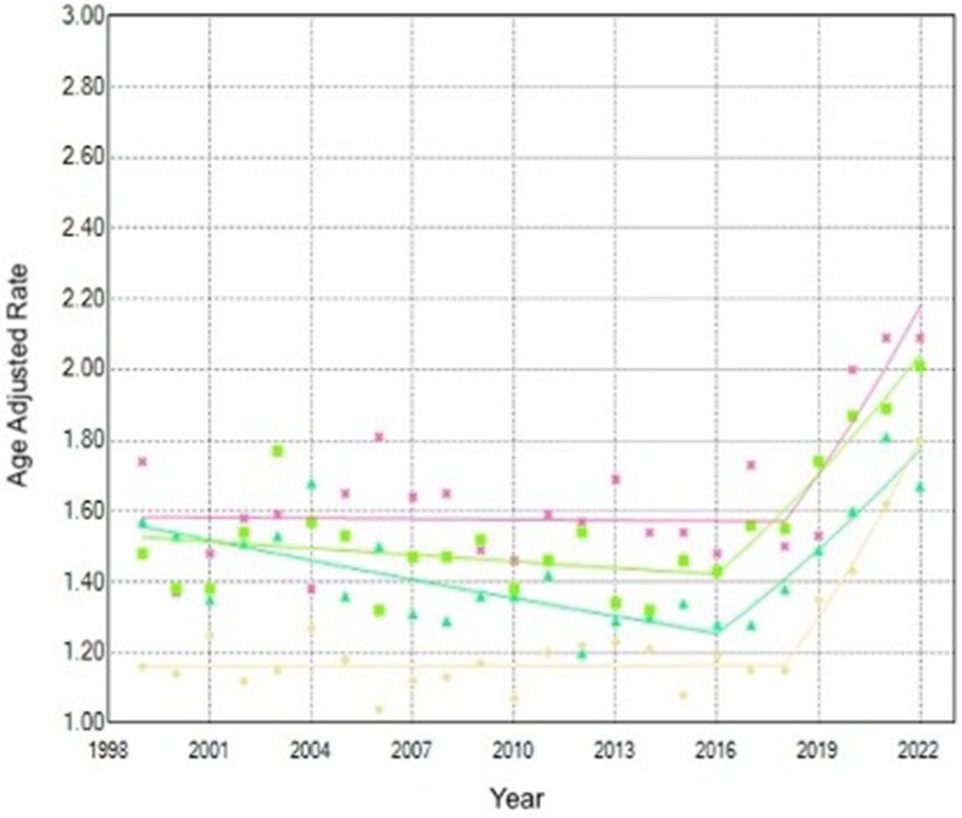

Figure 5 Annual Percent Change in Age Adjusted Mortality Rate of deaths related to Inflammatory Bowel Disease from 1999 to 2022, stratified by Male gender and census region. Teal: Northeast, Pink: Midwest, Yellow: South, Lime: West.

Southern females initially had the lowest AAMR with 1.09 (95% CI 0.99 to 1.20) in 1999 compared to northeastern females with an AAMR of 1.36 (95% CI 1.21 to 1.52) in the same year. However, by 2022 northeastern females had the lowest AAMR of 1.32 (95% CI 1.19 to 1.46) in contrast to the southern female AAMR of 1.72 (95% CI 1.61 to 1.83). Northeastern females had an AAPC of 0.25 (95% CI −0.48 to 0.90), however from 1999 to 2015 they had an APC of −1.63 (95% CI −3.46 to −0.74)* which then rose to 4.68 (95% CI 1.70 to 13.98)* between 2015 and 2022. In contrast, southern females had an AAPC of 2.20 (95% CI 1.71 to 2.65)*with an APC of 0.27 (95% CI −0.33 to 0.83) between 1999 and 2018 which then increased to 11.85 (95% CI 7.49 to 20.58)* from 2018 to 2022 (Figure 6).

Place of Death

Of the 71,628 deaths caused by IBD, 68,454 (95.6%) had known places of death, with 3,174 (4.4%) occurring in unknown or uncategorized places. A total of 32,589 (45.5%) took place in medical facilities (40.9% inpatient, 4.6% outpatient/ER), while 35,865 (50.1%) took place outside of medical facilities (27.8% home, 5.6% hospice, 16.6% nursing home/long-term care facility). Over the period of the study, Medical Facility Inpatient deaths saw a 29.9% increase from 1,278 in 1999 to 1,660 in 2022. Hospice facility deaths also saw a 3,554.5% increase from 11 in 2004 to 402 in 2022 (Figure 7, Table 5).

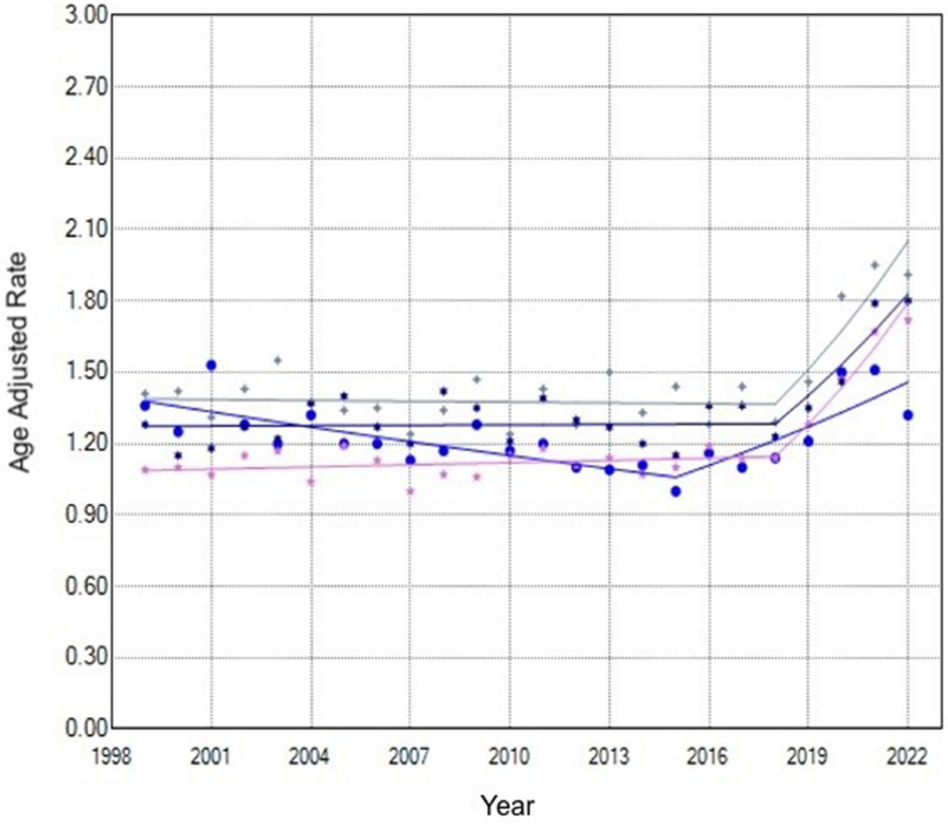

Figure 6 Annual Percent Change in Age Adjusted Mortality Rate of deaths related to Inflammatory Bowel Disease from 1999 to 2022, stratified by Female gender and census region. Blue: Northeast, Grey: Midwest, Pink: South, Indigo: West.

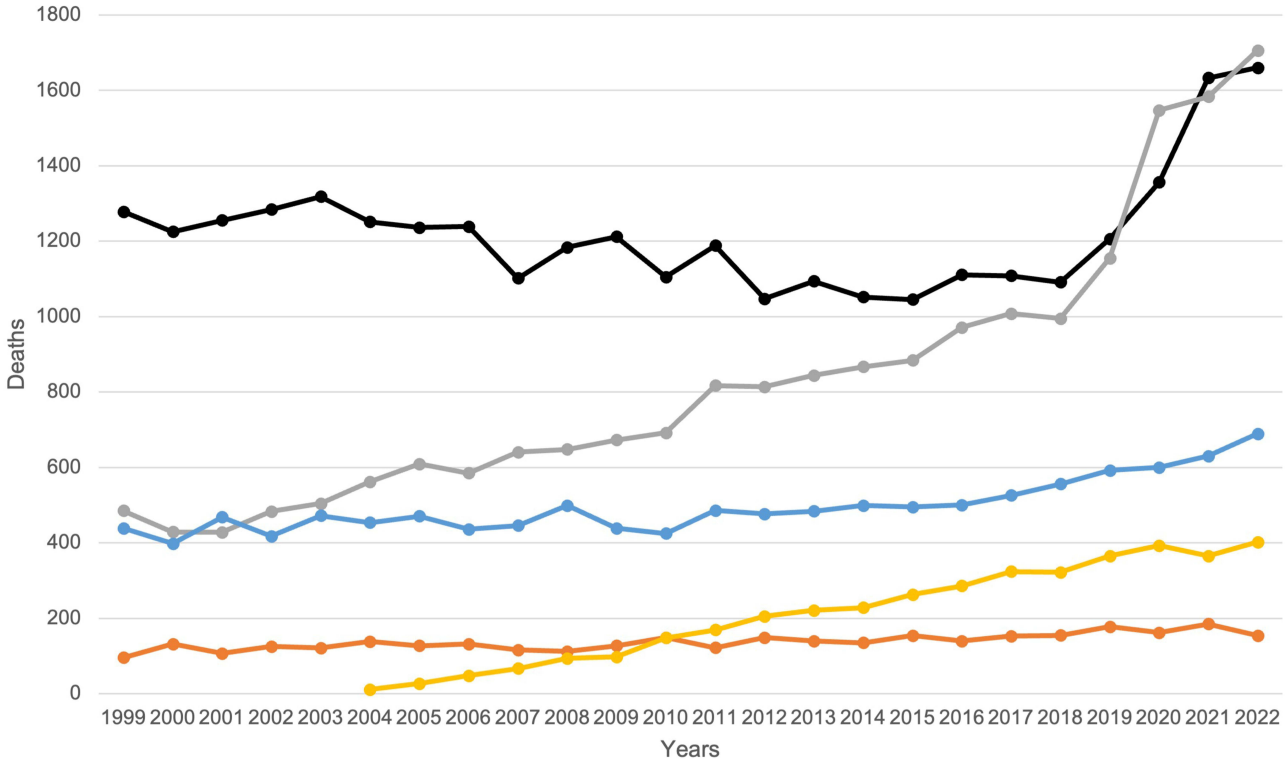

Figure 7 Crude Mortality Rate of deaths related to Inflammatory Bowel Disease from 1999 to 2022, stratified by place of death. Black: Medical Facility Inpatient, Orange: Medical Facility Outpatient or Emergency Room, Grey: Decedent's Home, Yellow: Hospice Facility, Blue: Nursing Home and Long-Term Care.

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Table 5 Number of Inflammatory Bowel Disease-Related Mortalities by Place of Death from 1999 to 2022

Year	Deaths				
	Medical Facility Inpatient	Medical Facility Outpatient or Emergency Room	Decedent's Home	Hospice Facility	Nursing Home and Hospice Care
1999	1278	96	485		439
2000	1225	132	429		398
2001	1255	107	428		468
2002	1284	125	483		418
2003	1318	121	504		472
2004	1251	138	562	11	454
2005	1236	127	609	27	471
2006	1239	132	585	48	436
2007	1102	116	641	67	446
2008	1184	112	648	94	499
2009	1212	127	673	98	439
2010	1105	149	692	148	425
2011	1188	122	817	169	486
2012	1047	149	814	205	477
2013	1094	140	844	221	484
2014	1052	135	867	228	499
2015	1045	154	884	263	495
2016	1111	140	971	286	500
2017	1108	153	1008	324	526
2018	1091	155	995	322	556
2019	1206	178	1155	365	592
2020	1356	162	1547	393	600
2021	1633	185	1583	365	630
2022	1660	154	1706	402	689

Discussion

Our study found significant regional differences in IBD mortality in the United States. The Midwest having the highest AAMR is consistent with previous literature that has found both higher incidence and prevalence rates of IBD in Midwestern states.[8] Considering that most of these states have a predominantly white demographic, this would potentially explain our results as there is an established association between greater incidence of IBD in White populations.[9] Southern states exhibited the greatest increase in AAMR. This could be potentially explained by the prevalent Black population that exists in the South. A previous study demonstrated an increased mortality rate in Black patients in this region.[10] This study also noted disparities in IBD disease understanding and literacy in African American patients as compared with other racial groups in this region. This points to racial disparities in both education and healthcare resources in the South as a potential culprit for this increase in AAMR, as other research has shown that when equal education and resources are available these differences decrease.[9] Our study did not control for education status amongst our patients, and a limitation of CDC Wonder is the inability to stratify patients by income. This provides a future area of inquiry in order to determine the impact of social determinants of health and differences between demographic groups in order to explain the differences observed in our study.

When stratified for both region and gender, males consistently had higher mortality rates across all census regions. Although females have been found to have higher rates of IBD, current literature shows no significant difference in IBD-related mortality between male and female patients.[11] Some literature has shown that COVID male patients have a greater incidence of complications and higher mortality.[12] Further research is needed to fully explain these changes. Midwestern males had the highest overall mortality. This is in line with overall census region trends and with prior research regarding IBD prevalence regionally.[12]

Our investigation of trends in IBD mortality over the period of 1999 to 2022 demonstrated an overall increase from 2018 to 2022. This change in mortality overlaps with the onset of the COVID-19 pandemic in 2020 and an increase in healthcare system demands. Our finding is consistent with prior research indicating that patients on immunosuppressive therapies, such as corticosteroids used in the management of IBD, had worse outcomes than the public despite similar rates of COVID in both populations.[13] Furthermore, patients with IBD were not found to have a higher likelihood of infection when compared to the public.[14,15] The overall increased mortality rate seen in the period in which this study was conducted could be attributed to multiple physical comorbidities that were not evaluated for this study. For example, prior research had shown that there is an increased association between IBD and other autoimmune diseases, including Type 1 Diabetes Mellitus, Granulomatosis with Polyangiitis and other systemic vasculitides, and antiphospholipid syndrome to name a few.[16] These comorbidities could explain a greater mortality rate both prior to and during the onset of the COVID pandemic as these diseases could increase both baseline mortality and patient susceptibility to COVID complications. A limitation of our study was an inability to explore the impacts of comorbidities on the IBD associated mortality rate, so this leaves a potential area for future inquiry. It is also worth noting that between 2005 and 2015, the rate of incidence of both ulcerative colitis and Crohn's Disease has increased.[17] This would also help to explain the overall increase in mortality seen across the entirety of the United States prior to the onset of the COVID pandemic. It was similarly found in previous literature that a statistically significant trend has emerged showing increased hospitalizations for ulcerative colitis, due to its potential to cause permanent fibrosis and tissue damage that may in turn require surgical management.[18] This increased need for surgery could possibly reflect the increase in hospitalizations that have been seen amongst IBD patients, and as a result, the greater mortality rate depicted in the results of this study.

Limitations

Limitations of the analysis discussed in this paper include a lack of individual-level risk factors or other possible comorbidities that may have contributed as important confounding variables in the results outlined previously. Because of the limitations associated with the use of the CDC-WONDER database, information relating to family history, treatments, and past medical history have not been included in this analysis and may have contributed to the trends that were noted above. It is therefore important to emphasize that causal conclusions cannot be reliably drawn from any of the results discussed. Further research into this topic could potentially benefit from the incorporation of additional factors that might have a notable influence on AMI-related mortality.

Conclusion

Our results showed that for all United States census regions there was an increase in IBD-related mortality over the period studied. While it is evident that all census regions experienced an increase in AAMR, the Midwest had the highest AAMR overall, while the South showed the greatest increase in AAMR. However, further exploration is needed in order to determine if there are significant disparities between the increases seen within different regions. In recent years, the advent of more effective and available immune modulators has led to better control of disease in patients with IBD, and the increase in endoscopic evaluation and surveillance has helped in identifying patients earlier in their disease course. In spite of this, there was an increase in overall IBD mortality over the period study. This study thereby provides an opportunity for further inquiry into the pathogenesis of this condition with the ultimate goal of eventually seeing a trending decrease in AAMR in the near future.

Disclosure

The author(s) report no conflicts of interest in this work.

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