

# Incidence Trends of Inflammatory Bowel Disease in a Southern European Country: A Mirror of the Western World?

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**INTRODUCTION:** Inflammatory bowel disease (IBD) affects people from all age categories worldwide. Although the incidence of the disease is stabilizing or decreasing in most Western world countries, its prevalence is still increasing because of the rise in life expectancy and better disease management. This work intends to identify the trends related to IBD incidence nationwide, analyzing regional, sex, and age distributions.

**METHODS:** Data were provided by the Portuguese Shared Services of the Ministry of Health. This study consisted of a retrospective analysis of all first consultations coded for “Chronic enteritis/ulcerative colitis” (D94) in a primary healthcare setting, between 2017 and 2020, in Portugal. The primary outcome measure was the IBD incidence rate per 100,000 inhabitants. We also calculated the incidence rate per person-year and forecasted incidence until 2024.

**RESULTS:** Between 2017 and 2019, the incidence rate of IBD in Portugal decreased from 54.9 to 48.6 per 100,000 inhabitants. The average incidence was 20 new cases of IBD per 1,000 person-year. It was predicted that, in December 2023, IBD incidence would reach 305.4 new cases (95% Prediction Interval 156.6–454.3), a similar result to the values forecasted for December 2021 (305.4, 95% Prediction Interval 197.3–413.6).

**DISCUSSION:** The incidence of IBD slightly declined from 2017 to 2019, and it is posed to stabilize in the future. The presented data are of the utmost importance for the characterization of IBD in Southern European countries and the establishment of future health policies in the setting of compounding prevalence in the Western world.

**SUPPLEMENTARY MATERIAL** accompanies this paper at <http://links.lww.com/CTG/A786>, <http://links.lww.com/CTG/A787>

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## INTRODUCTION

Crohn disease (CD) and ulcerative colitis (UC) are the 2 main diseases of the spectrum of inflammatory bowel disease (IBD). The etiology of IBD is still under evaluation, and multiple factors, including environmental ones, have been associated with its appearance and development (1). IBD affects mainly people between the second and fourth decades of life (2). The chronic nature of these conditions demands continuous care, including hospitalization and surgery, and expensive treatments such as

biological therapies. Thus, IBD is a significant burden for most healthcare systems (3).

Although data from developing countries are scarce, several reports indicate that IBD prevalence is increasing worldwide (4). IBD has increased with industrialization and has the highest incidence and prevalence in Western Europe and North America (5). However, the incidence rates in newly industrialized countries, such as Africa, Asia, and Southern America, accelerated at the turn of the century (6–8). In consequence, the prevalence in those

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countries increased in the following years (4,5,9). On the other hand, IBD incidence in Western countries is reaching a plateau after its growth in the 20th century (9). Although the prevalence of the disease is still increasing because of the rising number of patients living with the disease owing to the reduction of mortality caused by recent innovative therapies (10), it is estimated that, in the next decade, more than 10 million people will be living with IBD, with more than 3.48 million people in the United States alone (10,11).

In this context, it is essential to understand and predict the evolution trends of IBD incidence and prevalence in the upcoming years, particularly in the Western world. An effective means to better understand and manage IBD is by collecting official statistics data that may also provide information regarding environmental risk factors. Studying these data with forecast models will deliver valuable information for adapting healthcare systems to the future reality, resulting in improved healthcare resource management and the development of cost-effective health policies in the setting of IBD increasing prevalence (11,12).

In Portugal, statistics on IBD epidemiology are sparse. In 2017, Azevedo and colleagues demonstrated through a pharmacoepidemiologic approach that Portugal was between countries with the highest and lowest IBD prevalence. The prevalence was similar for both CD and UC, increasing since 2003 (13).

Our study aims to identify the trends of IBD incidence in Portugal, with region, sex, and age-specific distributions. In addition, based on these data, we intend to evaluate the future incidence of IBD in Portugal until 2024 using forecasting models. This can be useful to establish incidence behavior and define policies, guidelines, and milestones for prevalence stabilization.

## METHODS

### Study design and data source

This study consisted of a retrospective analysis of all first consultations coded for “Chronic enteritis/ulcerative colitis” (International Classification of Primary Care-2 code: D94) in a primary healthcare setting between January 2015 and April 2020 in mainland Portugal. Data were provided by the Portuguese Shared Services of the Ministry of Health (SPMS). All possible patient identifiers were encrypted to ensure patients’ confidentiality.

For each consultation, the following data were provided: patient identifier (encrypted), age at diagnosis, sex, institution identifier (encrypted), region, and diagnosis date. All study procedures were approved by the São João Hospital Center Ethics Committee on 14 September 2018 and conducted following the Declaration of Helsinki.

### Outcomes

The primary outcome measure was IBD incidence rate per 100,000 inhabitants, which was calculated by dividing the number of new diagnoses during the study period (numerator) by the total number of inhabitants (denominator) multiplied by a factor of 100,000 each year (the incidence rate for 2020 was not estimated because only data from January until April were available). The total number of inhabitants in mainland Portugal in the years under study considered for the computation of the rates was obtained from the National Institute of Statistics.

Other outcome measures included (i) incidence rate per person-year, which was calculated by dividing the number of new diagnoses during the study period (numerator) by the sum of each patient’s age at diagnosis (denominator), multiplied by a factor of

1,000; and (ii) forecasted incidence, based on the estimation of the number of new diagnoses per month during the study period and application of several forecasting models to predict incidence values until 2024.

### Statistical analysis

To prevent prevalence mixing with incidence cases, we performed a washout period of 2 years. Therefore, we analyzed data from January 2017 to April 2020.

Incidence rates per 100,000 inhabitants were analyzed by year and stratified by sex (male and female), age (4 categories: 0–19, 20–39, 40–59, and  $\geq 60$  years and 3 categories according to the Montreal classification: 0–16, 17–40, and  $> 40$  years), and region according to the Nomenclature of Territorial Units for Statistics II (North, Center, Lisbon, Alentejo, and Algarve).

In addition, we performed a sensitivity analysis by including solely the cases presenting more than one consultation with the D94 code. Confidence intervals were used to assess statistical differences between the primary and sensitivity analyses.

We used several forecasting models to estimate future incidence. First, data outliers and anomalies were removed from the time series. Second, the stationarity of the time series was assessed. When stationarity is not observed, differencing is used to achieve it. To choose the best forecasting model, we applied time series cross-validation to identify the one presenting the smallest forecasting error, such as mean square error and root mean square error (see Supplementary Table 1, <http://links.lww.com/CTG/A787>). We selected the model based on Seasonal and Trend decomposition with Loess (STL) and AutoRegressive Integrated Moving Average (ARIMA), according to which forecasts are produced by subtracting the seasonality estimated using STL and, then, forecasting the deseasonalized data by using the ARIMA model. STL uses the Loess (Local regrESSion) method to decompose the time series into its trend and seasonal components using polynomial regression (14); then, an ARIMA model is applied to the remainder element generating the final forecast after summation of all components. ARIMA models are defined by the parameters ( $p$ ,  $d$ , and  $q$ ), where  $p$  corresponds to the order of autoregression,  $d$  is the degree of differencing, and  $q$  refers to the order of the moving average segment. We applied an ARIMA (0, 1, 1) model, chosen due to its lower corrected Akaike information criteria and nondetection of correlated residuals (assessed visually and by the Ljung-Box test).

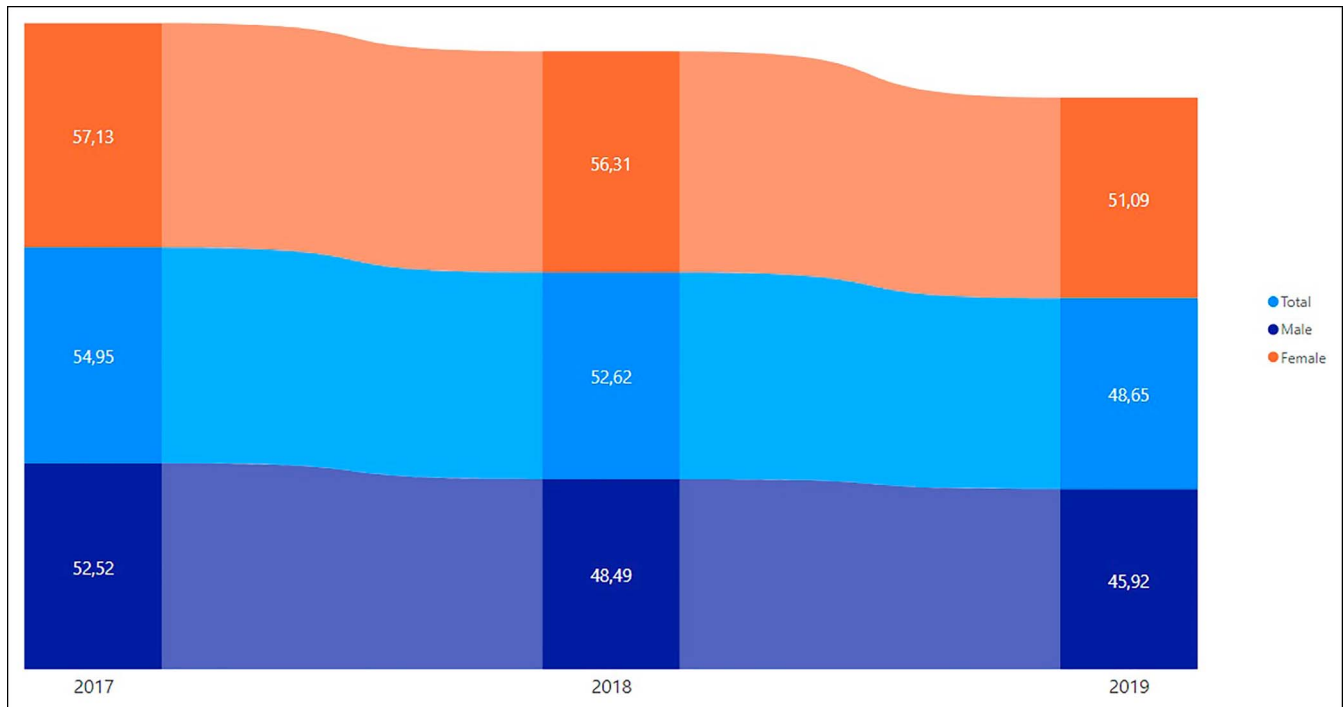
The observed incidence, using incident cases from January 1, 2017, to April 30, 2020, at monthly intervals, were imputed into R and forecasted to December 2023, with 95% prediction intervals (PIs).

PIs depend on the analysis period. The longer the forecasted time, the higher the uncertainty, and thus, the broader the PIs. Therefore, we have decided to forecast only a short period in the future.

Statistical analysis was performed using SPSS (version 27.0.1.0), R statistical software (version 3.6.1), and RStudio (version 1.2.1335).

## RESULTS

The incidence rate of IBD in Portugal between 2017 and 2019 was 54.9 and 48.6 per 100,000 inhabitants, respectively, with a slight reduction in disease incidence throughout the study period of about 12% (Figure 1; see Supplementary Table 2, <http://links.lww.com/CTG/A787>). Moreover, new cases were more common among female patients than male patients (F vs M, 2017–2019:



**Figure 1.** Inflammatory bowel disease incidence rate per 100,000 inhabitants.

57.1–51.1 vs 52.5–45.9) (Figure 1; see Supplementary Table 2, <http://links.lww.com/CTG/A787>).

Incidence distribution was heterogeneous nationwide, with more new cases in the Northern region of Portugal and the Lisbon Metropolitan Area. We observed a decreasing trend in the North (2017–2019: 62.6–60.8) and Lisbon (2017–2019: 58.4–47.7). On the other hand, the Center region presented lower rates (2017–2019: 45.3–30.4) (Figure 2; see Supplementary Table 2, <http://links.lww.com/CTG/A787>). Incidence trends over time are distinct in Alentejo and Algarve; in Algarve, the incidence in 2019 was lower than that in 2017 (2017–2019: 68.2–50.0), but the variation was not linear over time; in Alentejo, the incidence presented the lowest national rate over 3 years in 2017 (24.6), having had increased since then (2017–2019: 24.6–47.7) (Figure 2; see Supplementary Table 2, <http://links.lww.com/CTG/A787>).

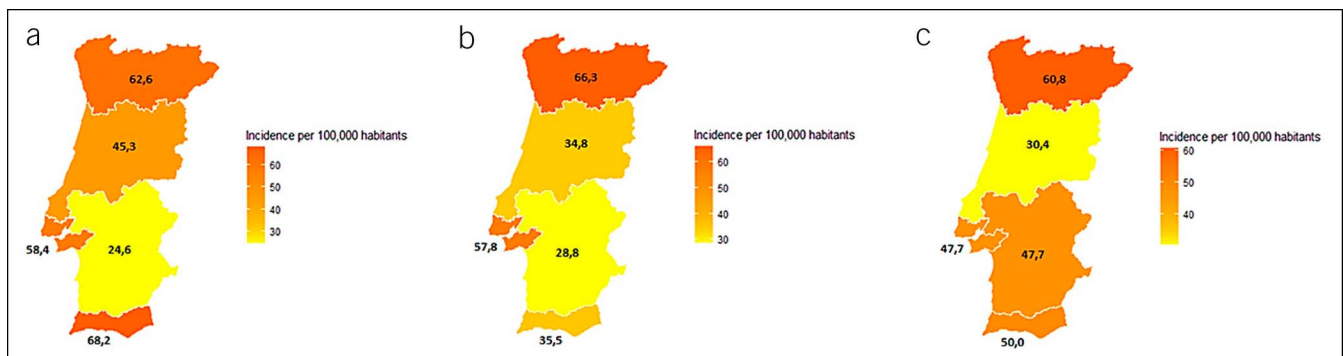
As observed in Figure 3A, the incidence per 100,000 inhabitants was about 5 times higher in older patients ( $\geq 20$  years) when compared with younger ones. Nevertheless, the incidence rates

were similar among older age categories. For example, patients aged between 20 and 39 years presented the highest incidence values during the study period. Accordingly, patients aged 17 to 40 years presented higher incidence rates when categorizing age according to the Montreal classification (Figure 3B).

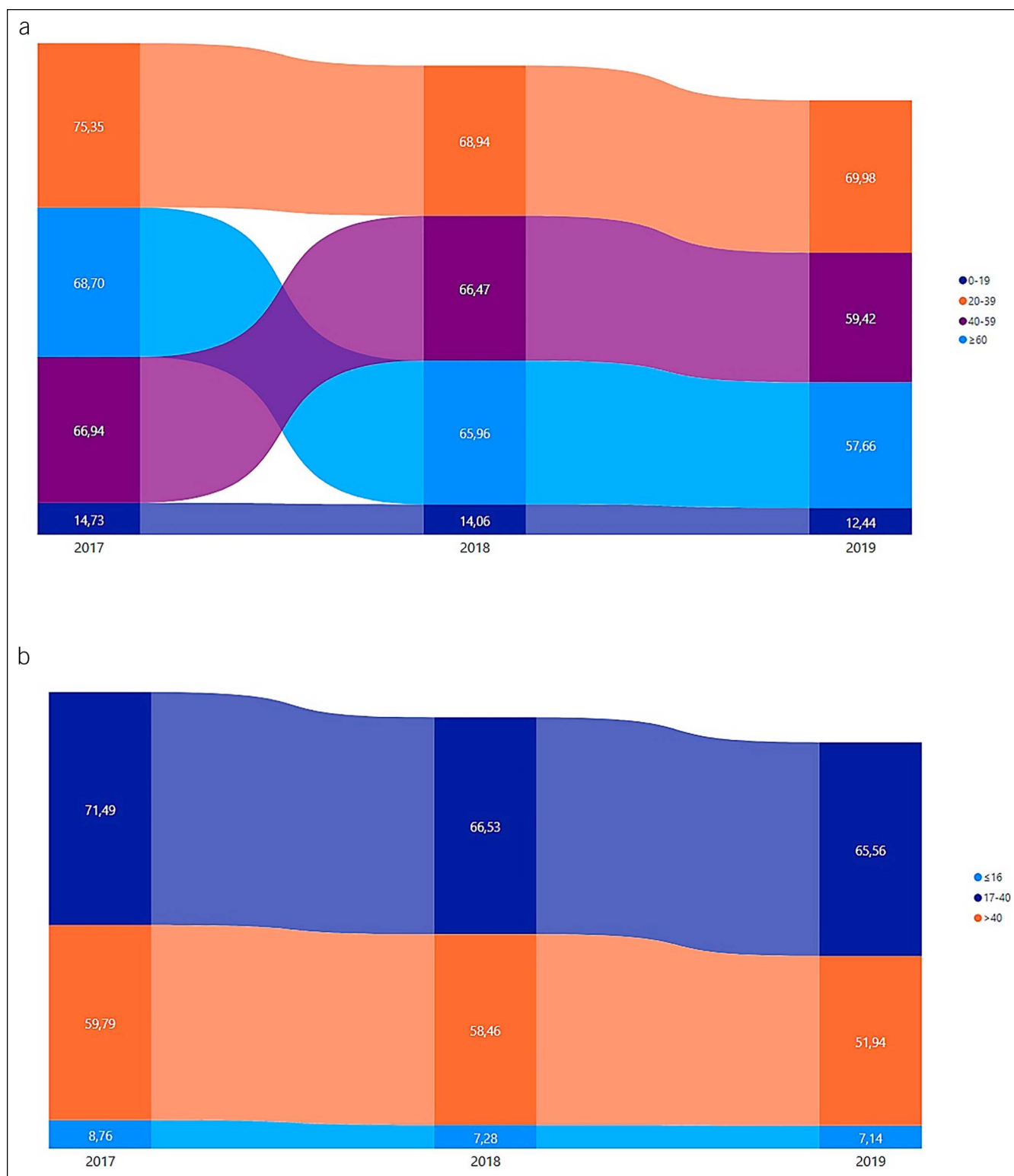
Figure 4 shows that, from 2017 to 2019, there has been an average incidence of 20 new cases of IBD per 1,000 people per year in mainland Portugal. This value has remained constant throughout the study period.

Ultimately, no statistical differences were found between the primary and sensitivity analyses because confidence intervals overlapped (see Supplementary Table 2, <http://links.lww.com/CTG/A787>). Similarly, visual inspection of both analyses showed comparable incidence patterns (see Supplementary Figures 1–4, <http://links.lww.com/CTG/A786>).

In December 2021, IBD incidence is forecasted to have reached (95% PI 197.3–413.6) new diagnoses, whereas, by December 2023, it is predicted to reach similar values (305.4, 95% PI



**Figure 2.** Regional distribution of inflammatory bowel disease in Portugal between 2017 and 2019.



**Figure 3.** Inflammatory bowel disease incidence rate per 100,000 inhabitants per age category: (a) four age categories and (b) age categories according to the Montreal classification.

156.6–454.3). Hence, IBD incidence is projected to stabilize in the near future (Figure 5; see Supplementary Table 3, <http://links.lww.com/CTG/A787>).

## DISCUSSION

This study is a retrospective analysis of IBD first consultation data provided by official state sources (SPMS) regarding patients in

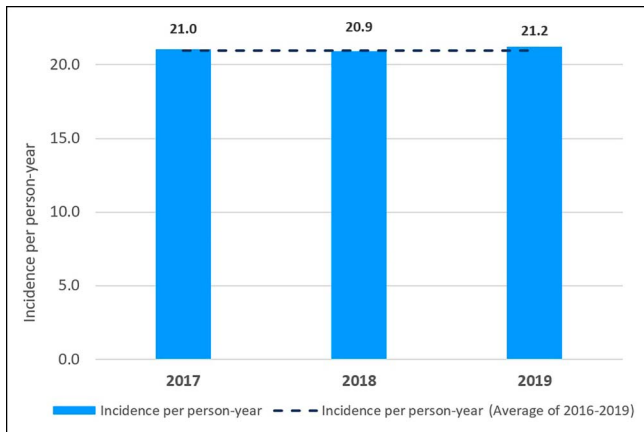


Figure 4. Inflammatory bowel disease incidence per 1,000 person-years.

mainland Portugal between 2017 and 2019. As a result, we report, for the first time, IBD incidence trends nationwide.

The obtained results indicate that IBD incidence slightly decreased in the analyzed period, with heterogeneous trends in the distinct regions (Figure 1 and Figure 2). This tendency is in good agreement with recent epidemiological reports that evidence a stabilization or decrease of IBD incidence in Europe and North America in recent years (4,9,10). In 2017, Ng and colleagues published a systematic review of population-based studies where IBD incidence was reported to have shifted considerably in the Western world such that more than 70% of the studies, pertaining to countries such as the Netherlands, France, or the United Kingdom, presented stable or decreasing incidence (4). More recently, 2 population-based studies from different regions of Canada published results on IBD incidence, showing similar declining rates (15,16).

In addition, the average incidence between 2017 and 2019 (20 cases/1,000 person-year) can be considered high and is in line with the numbers registered in other European countries (17).

High incidence values are pointed because of the Western lifestyle and have been linked to environmental factors associated with westernization (9,18). This justifies the increasing incidence trend that is still observed in newly industrialized countries (4,5). In our study, the North region presented the highest IBD incidence during the whole analyzed period (Figure 5). This tendency became more notorious with time and seemed to agree with that registered in Spain, where the cumulative incidence of IBD in 2017 was higher in the Central and North regions of the country (17). We anticipate that this predisposition might be related to the genetic heritage of the northern populations that partially results from movements entering the Iberian Peninsula from Northern and Central Europe in the Iron Age (19). Still, this hypothesis needs confirmation through structured studies that could further enhance the understanding of IBD epidemiology in this region.

Regarding regional trends within Portugal, it seems that the South regions (Alentejo and Algarve) can still be on the stabilization phase, showing nonlinear variations in the analyzed period. Despite the observed decreasing tendency between 2017 and 2019, some authors are still reporting distinct trends among European countries and regions because of the stabilization process of IBD incidence (10).

Concerning gender distribution, our results relate to those reported in a study in northern Portugal and Galicia (Spain), in which UC was more predominant in female patients (20). The discussion around gender incidence has not reached a consensus so far because we were able to find distinct reports with equal distribution or higher incidence in both women and men (21–23).

Several details regarding the distribution of IBD incidence by age categories deserve attention. First, the low incidence values in young children over time do not resemble those of recent studies, including a meta-analysis that reported an increasing trend of IBD incidence in this age category in the Western world (24,25). On the other hand, incidence reports from the United Kingdom and the United States presented similar age distributions as those observed in this study (26,27). These results might suggest that IBD onset occurs more often after childhood among the

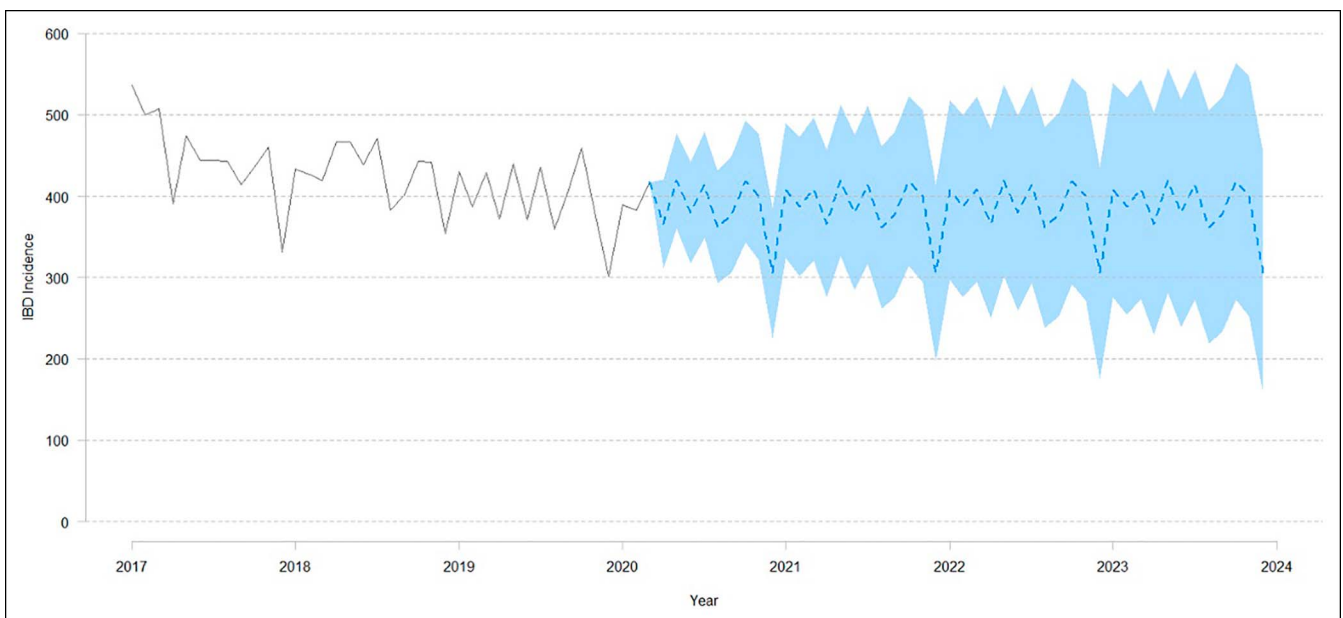


Figure 5. Inflammatory bowel disease incidence forecast until 2024.



Portuguese population. Second, from 2017 to 2019, the declining incidence in patients older than 60 years seems to contradict the tendency induced by the rise of life expectancy and described by several authors (5,10,28). Third, we highlight the increase of IBD incidence in young adults (20–39 years) who showed the highest incidence values in 2019. Similar distributions were reported for other countries in Europe and also in North America and Australia (23,29,30), reopening the discussion around the influence of environmental factors in IBD, which are particularly evident in this socially and professionally active age category. However, further research is warranted to confirm these findings because we speculate that the youngest and oldest IBD patient population may be more commonly diagnosed in tertiary care settings at the national level.

Based on consultations coded for D94, IBD incidence was estimated until 2024 by a monthly prediction of new cases. Forecasting models have been used extensively in the economic field and, in more recent years, in prevalence forecasting (11,12,31). This analysis is based on historical values at regular time intervals (time series), considering stationarity to model future values. In Figure 5, the lower peaks registered at the end of each year account for fewer consultations in that period (holidays). In this analysis, we have compared the yearly pattern of all consultations in primary care facilities on a national scale with the yearly patterns of our dataset, and they are a match. Thus, these fluctuations should be a consequence of the data provenance and not of IBD incidence. The estimated values are in line with the predictions of Kaplan and Windsor that anticipate the stabilization or decrease of IBD incidence at least until 2050, as part of a compounding prevalence stage (10).

This study presents some limitations that shall be addressed. First, data collection based on a D94 code does not guarantee that all identified patients have IBD because using a single code may lead to the identification of false-positive cases, thus potentially inflating incidence values. However, the D94 code encompasses both CD and UC and is the most accurate way to collect data to accomplish our purpose. Another critical point is the possibility of misclassification by inaccurate coding and validation and by occasional underreporting. Also, we could not verify this aspect because we worked with official data provided by the SPMS. Moreover, the forecast analysis does not include any other factors or predictors, relying only on the observed incidence and new diagnoses, although the prediction is in good agreement with estimations performed by other authors. Nevertheless, further research of larger datasets is necessary to confirm these findings.

In conclusion, our study showed that IBD incidence decreased slightly in mainland Portugal in the past few years and is poised to stabilize in the near future. However, IBD incidence is still high nationwide, mainly in the North and Lisbon regions. The presented data, along with the forecasting analysis, are of the utmost importance not only for the characterization of IBD in a Southern European country but also as a potential mirror of disease behavior in the Western world, ultimately, for establishing a plan of action to face the challenges of the disease in a setting of compounding prevalence.

## CONFLICTS OF INTEREST

**Guarantor of the article:** Fernando Magro, MD.

**Specific author contributions:** Mafalda Santiago, BSc, and Francisco Stocker, MSc, contributed equally to this work. M.S. and F.S. were involved in data analysis, interpretation, and manuscript drafting;

C.C.D. was involved in data interpretation and manuscript revision; F.M. coordinated the study's conception and design and was involved in data interpretation and manuscript revision. P.M., R.G., D.C., F.P., and L.C. were involved in data interpretation and manuscript revision. All authors approved the final version of the manuscript.

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**Potential competing interests:** F.M. served as a speaker and received honoraria from Merck Sharp & Dohme, AbbVie, Vifor, Falk, Laboratórios Vitória, Ferring, Hospira, and Biogen. The other authors have no conflicts of interest to disclose.

**Data availability statement:** The data underlying this article will be shared at reasonable request to the corresponding author.

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## Study Highlights

### WHAT IS KNOWN

- ✓ Inflammatory bowel disease (IBD) affects people from all age categories worldwide.
- ✓ The incidence of IBD is stabilizing or decreasing in most Western world countries; however, its prevalence is still increasing because of the increase of life expectancy and better disease management.

### WHAT IS NEW HERE

- ✓ This study is the first of its kind conducted in our country with nationwide coverage data from official state sources.
- ✓ During the study period, the incidence rate of IBD in Portugal decreased approximately 12%. New cases were more frequent in female patients in the age category of 20–39 years and in the North and the Lisbon Metropolitan Area regions.
- ✓ Between 2017 and 2019, the average incidence was 20 new cases of IBD per 1,000 person-year.
- ✓ In addition, it was predicted that, in December 2023, IBD incidence would reach 305.4 new cases (95% Prediction Interval 156.6–454.3), a similar result to the values forecasted for December 2021 (305.4, 95% Prediction Interval 197.3–413.6).

### TRANSLATIONAL IMPACT

- ✓ The presented data, along with the forecasting analysis, are of the utmost importance not only for the characterization of IBD in a Southern European country but also as a potential mirror of disease behavior in the Western world, ultimately, for establishing a plan of action to face the challenges of the disease in a setting of compounding prevalence.

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