U.PORTO

FACULDADE DE MEDICINA
UNIVERSIDADE DO PORTO

MESTRADO INTEGRADO EM MEDICINA

2021/2022

Francisco Stocker Ferreira de Castro

Incidence trends of Inflammatory Bowel Disease in a Southern-European country: a mirror of the western world?

MARÇO, 2022

Francisco Stocker Ferreira de Castro

Incidence trends of Inflammatory Bowel Disease in a Southern-European country: a mirror of the western world?

Mestrado Integrado em Medicina

Área: Medicina Clínica - Gastrenterologia

Tipologia: Dissertação

Trabalho efetuado sob a Orientação de:

Doutora Mafalda Santiago Alves Pereira

sob a Coorientação de:

Dr. Fernando José Magro Dias

Trabalho organizado de acordo com as normas da revista:
Clinical and Translational Gastroenterology (CTG)

MARÇO, 2022

U.PORTO
FMUP FACULDADE DE MEDICINA UNIVERSIDADE DO PORTO

UC Dissertação/Projeto (6º Ano) - DECLARAÇÃO DE INTEGRIDADE

Eu, Francisco Stocker Ferreira de Castro, abaixo assinado, nº mecanográfico 201603440, estudante do 6º ano do Ciclo de Estudos Integrado em Medicina, na Faculdade de Medicina da Universidade do Porto, declaro ter atuado com absoluta integridade na elaboração deste projeto de opção.

Neste sentido, confirmo que **NÃO** incorri em plágio (ato pelo qual um indivíduo, mesmo por omissão, assume a autoria de um determinado trabalho intelectual, ou partes dele). Mais declaro que todas as frases que retirei de trabalhos anteriores pertencentes a outros autores, foram referenciadas, ou redigidas com novas palavras, tendo colocado, neste caso, a citação da fonte bibliográfica.

Faculdade de Medicina da Universidade do Porto, 21/02/2022

Assinatura conforme cartão de identificação:
Francisco Stocker Ferreira de Castro

U.PORTO
FMUP FACULDADE DE MEDICINA UNIVERSIDADE DO PORTO

UC Dissertação/Projeto (6º Ano) – DECLARAÇÃO DE REPRODUÇÃO

NOME

Francisco Stocker Ferreira de Castro

NÚMERO DE ESTUDANTE	E-MAIL
201603440	franciscostocker@hotmail.com

DESIGNAÇÃO DA ÁREA DO PROJECTO

Medicina clínica - Gastrenterologia

TÍTULO DISSERTAÇÃO/~~MONOGRAFIA~~ (riscar o que não interessa)

Incidence trends of Inflammatory Bowel Disease in a Southern-European country: a mirror of the western world?

ORIENTADOR

Mafalda Santiago Alves Pereira

COORIENTADOR (se aplicável)

Fernando José Magro Dias

ASSINALE APENAS UMA DAS OPÇÕES:

É AUTORIZADA A REPRODUÇÃO INTEGRAL DESTE TRABALHO APENAS PARA EFEITOS DE INVESTIGAÇÃO, MEDIANTE DECLARAÇÃO ESCRITA DO INTERESSADO, QUE A TAL SE COMPROMETE.	☐
É AUTORIZADA A REPRODUÇÃO PARCIAL DESTE TRABALHO (INDICAR, CASO TAL SEJA NECESSÁRIO, Nº MÁXIMO DE PÁGINAS, ILUSTRAÇÕES, GRÁFICOS, ETC.) APENAS PARA EFEITOS DE INVESTIGAÇÃO, MEDIANTE DECLARAÇÃO ESCRITA DO INTERESSADO, QUE A TAL SE COMPROMETE.	☐
DE ACORDO COM A LEGISLAÇÃO EM VIGOR, (INDICAR, CASO TAL SEJA NECESSÁRIO, Nº MÁXIMO DE PÁGINAS, ILUSTRAÇÕES, GRÁFICOS, ETC.) NÃO É PERMITIDA A REPRODUÇÃO DE QUALQUER PARTE DESTE TRABALHO.	☒

Faculdade de Medicina da Universidade do Porto, 07/03/2022

Assinatura conforme cartão de identificação: Francisco Stocker Ferreira de Castro

Dedicatória

À minha orientadora, Mafalda Santiago Alves Pereira, agradeço o apoio desde o primeiro dia, pela sua dedicação e disponibilidade nos momentos atravessados. Um suporte fulcral para a concretização deste trabalho de investigação.

Ao meu coorientador, Sr. Professor Fernando Magro, agradeço o convite para desenvolver a Tese de Mestrado, assim como a oportunidade de integrar o seu grupo de investigação.

À Sra. Professora Dulce Madeira, enquanto diretora da Unidade de Anatomia onde me encontro contratado como Monitor, agradeço o estímulo e apoio para ultrapassar as adversidades encontradas em todas as fases do meu percurso académico.

Aos Professores, Colegas, e Amigos, com quem tive o privilégio de percorrer esta jornada, agradeço o estímulo e a partilha.

Aos meus familiares, agradeço pelos valores incutidos, pelo exemplo e pela confiança em mim depositada.

Por último, mas não menos importante, um agradecimento muito especial a três pessoas.
À Rita Vieira, companheira de todas as horas, pelo amor, carinho, alento e ainda pela ajuda técnica para a elaboração da Tese de Mestrado.
À Carolina Verde, amiga de longa data, pela paciência em escutar os meus desabafos e pelos melhores conselhos nos momentos certos.
Ao Pedro Silva, amigo de longa data, pelo suporte e amizade nos vários momentos.

TITLE: Incidence trends of Inflammatory Bowel Disease in a Southern-European country: a mirror of the western world?

Authors: Mafalda Santiago[1,2], Francisco Stocker[3], Paula Ministro[2,4], Raquel Gonçalves[2,5], Diana Carvalho[2,6], Francisco Portela[2,7], Luís Correia[2,8], Paula Lago[2,9], Eunice Trindade[2,10], Cláudia Camila Dias[1,11], Fernando Magro[1,2,3,12,13]

[1]Center for Health Technology and Services Research (CINTESIS), Porto, Portugal

[2]Portuguese Inflammatory Bowel Disease Study Group (GEDII), Portugal

[3]Department of Biomedicine, Unit of Pharmacology and Therapeutics, Faculty of Medicine, University of Porto, Porto, Portugal

[4]Department of Gastroenterology, Tondela-Viseu Hospital Center, Viseu, Portugal

[5]Department of Gastroenterology, Braga Hospital, Braga, Portugal

[6]Department of Gastroenterology, Central Lisbon Hospital Center, Lisbon, Portugal

[7]Department of Gastroenterology, Coimbra University Hospital Center, Coimbra, Portugal

[8]Department of Gastroenterology and Hepatology, Northern Lisbon Hospital Center, Lisbon, Portugal

[9]Department of Gastroenterology, Porto University Hospital Center, Porto, Portugal

[10]Department of Pediatrics, São João University Hospital Center, Porto, Portugal

[11]Department of Community Medicine, Information and Health Decision Sciences (MEDCIDS), Faculty of Medicine, University of Porto, Portugal

[12]Department of Gastroenterology, São João University Hospital Center, Porto, Portugal

[13]Clinical Pharmacology Unit, São João University Hospital Center, Porto, Portugal

Authors in bold share first co-authorship.

Corresponding author/Guarantor of the article

Fernando Magro (MD, PhD), Department of Biomedicine, Unit of Pharmacology and Therapeutics, Faculty of Medicine, University of Porto, Rua Plácido Costa, 4200-450, Porto, Portugal.

Tel.: +351 225513600; email: fm@med.up.pt

Specific author contributions

MS and FS were involved in data analysis, interpretation, and manuscript drafting; CCD was involved in data interpretation and manuscript revision; FM coordinated the study's conception, design and was involved in data interpretation and manuscript revision. PM, RG, DC, FP, and LC were involved in data interpretation and manuscript revision. All authors approved the final version of the manuscript.

Financial support

This work was supported by the Portuguese Study Group of Inflammatory Bowel Disease (GEDII).

Potential Competing Interests

FM 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 conflict of interest to disclose.

Word count: 2397 words

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 due to 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 to 39 years old, as well as 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.
- Additionally, it was predicted that, in December 2023, IBD incidence would reach 305.4 new cases [95% Prediction Interval (PI) 156.6 – 454.3], a similar result to the values forecasted for December 2021 (305.4, 95% PI 197.3 – 413.6).

Translational impact

- The presented data, along with the forecasting analysis, is of the utmost importance not only for the characterization of IBD in a Southern-European country but 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.

ABSTRACT

Background: Inflammatory Bowel Disease (IBD) affects people from all age categories worldwide. While the incidence of the disease is stabilizing or decreasing in most western world countries, its prevalence is still increasing due to 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. The 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 (PI) 156.6 – 454.3], a similar result to the values forecasted for December 2021 (305.4, 95% PI 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 is 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.

Keywords: IBD; epidemiology; incidence; forecasting; time series

INTRODUCTION

Crohn's disease (CD) and Ulcerative Colitis (UC) are the two 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 decade 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 countries increased in the following years [4,5,9]. On the other hand, IBD incidence in Western countries is reaching a plateau, following its growth in the 20th century [9]. Even though the prevalence of the disease is still increasing due to 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 this data with forecast models will deliver valuable information for adapting healthcare systems to the future reality, resulting in improved healthcare resources 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 pharmaco-epidemiologic 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 this data, we intend to evaluate the future incidence of IBD in Portugal, until 2024, through 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 (incidence rate for 2020 was not estimated since 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: 1) 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 1000; and 2) forecasted incidence, based on the estimation 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 two 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 (four categories: 0-19, 20-39, 40-59, ≥ 60 years old; three categories according to the Montreal classification: 0-16, 17-40, >40), and region according to the Nomenclature of Territorial Units for Statistics (NUTS) II (North, Center, Lisbon, Alentejo, Algarve).

Additionally, 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. Since stationarity was not observed, differencing was 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 (**Supplementary Table 1**). 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 via 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, 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 non-detection of correlated residuals (assessed visually and by the Ljung-Box test).

The observed incidence, using incident cases from 01/01/2017 to 30/04/2020, at monthly intervals, were imputed into R and forecasted to December 2023, with 95% prediction intervals.

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

Statistical analysis was performed using SPSS (version 27.0.1.0) and 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, Supplementary Table 2**). Moreover, new cases were more common among females than males (F vs. M, 2017-2019: 57.1 – 51.1 vs. 52.5 – 45.9) (**Figure 1, Supplementary Table 2**).

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, Supplementary Table 2**). Incidence trends over time are distinct in Alentejo and Algarve; in Algarve, the incidence in 2019 was lower than 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 three years in 2017 (24.6), having had increased since then (2017-2019: 24.6 – 47.7) (**Figure 2, Supplementary Table 2**).

As observed in **Figure 3A**, the incidence per 100,000 inhabitants was about five times higher in older patients (≥ 20 years old) when compared to younger ones. Nevertheless, the incidence rates were similar among older age categories. Patients aged between 20 and 39 years presented the highest incidence values during the study period. Accordingly, patients aged 17 to 40 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 the sensitivity analyses, as confidence intervals overlapped (**Supplementary Table 2**). Likewise, visual inspection of both analyses showed similar incidence patterns (**Supplementary**

Figures 1 – 4).

In December 2021, IBD incidence was forecasted to reach 305.4 (95% PI 197.3 – 413.6) new diagnoses, whereas, by December 2023, it is predicted to reach similar values (305.4, 95% PI 156.6 – 454.3). Hence, IBD incidence is projected to stabilize in the near future (**Figure 5, Supplementary Table 3**).

DISCUSSION

This study is a retrospective analysis of IBD first consultation data provided by official state sources (SPMS) regarding patients in 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, 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, two 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/1000person-year) can be considered high and is in line with the numbers registered in other European countries [17]. High incidence values are pointed as a result 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 non-linear variations in the analyzed period. Despite the observed decrease tendency between 2017 and 2019, some authors are still reporting distinct trends among European countries and regions due to 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 females [20]. The discussion around gender incidence has not reached a consensus so far as 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 UK and the USA 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 Portuguese population. Second, from 2017 to 2019, the declining incidence in patients above 60 years of age 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) that showed the highest incidence values in 2019. Similar distributions were reported for other countries in Europe but 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, as we speculate the youngest and oldest IBD patient population may be more commonly diagnosed in tertiary care settings, at least in Portugal.

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, to 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 since 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, as well as by occasional underreporting. Also, we could not verify this aspect as 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, even though 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 last years, and is poised to stabilize in the near future. However, IBD incidence is still high nationwide, mainly in the North and Lisbon region. The presented data, along with the forecasting analysis, is of the utmost importance not only for the

characterization of IBD in a Southern-European country but 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.

DATA AVAILABILITY STATEMENT

The data underlying this article will be shared at reasonable request to the corresponding author.

ACKNOWLEDGMENTS

The authors thank the Portuguese Shared Services of the Ministry of Health (SPMS) for yielding the data and Paula Pinto, PharmD, PhD (PMA – Pharmaceutical Medicine Academy) for providing medical writing and editorial assistance.
The authors also thank the valuable help of Pedro Pereira Rodrigues, PhD, and Francisco Bischoff, MD, on the time series and forecasting analysis.
MS acknowledges 'Fundação para a Ciência e Tecnologia (FCT)', Portugal under grant number PD/BD/142890/2018; PhD Program in Clinical and Health Services Research (PDICSS). This work is integrated into the MD thesis of FS.

REFERENCES

1. Piovani D, Danese S, Peyrin-Biroulet L, Nikolopoulos GK, Lytras T, Bonovas S. Environmental Risk Factors for Inflammatory Bowel Diseases: An Umbrella Review of Meta-analyses. Gastroenterology. 2019;157:647-659.e4.
2. Molodecky NA, Soon IS, Rabi DM, Ghali WA, Ferris M, Chernoff G, et al. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. Gastroenterology. 2012;142:46-54.e42.
3. Burisch J, Vardi H, Schwartz D, Friger M, Kiudelis G, Kupčinskas J, et al. Health-care costs of inflammatory bowel disease in a pan-European, community-based, inception cohort during 5 years of follow-up: a population-based study. Lancet Gastroenterol Hepatol. 2020;5:454–464.
4. Ng SC, Shi HY, Hamidi N, Underwood FE, Tang W, Benchimol EI, et al. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. Lancet. 2017;390:2769–2778.
5. Windsor JW, Kaplan GG. Evolving Epidemiology of IBD. Curr Gastroenterol Rep. 2019;21:40.
6. Quaresma AB, Kaplan GG, Kotze PG. The globalization of inflammatory bowel disease. Curr Opin Gastroenterol. 2019;35:259–264.
7. Ng SC, Kaplan GG, Tang W, Banerjee R, Adigopula B, Underwood FE, et al. Population Density and Risk of Inflammatory Bowel Disease: A Prospective Population-Based Study in 13 Countries or Regions in Asia-Pacific. Am J Gastroenterol. 2019;114:107–115.
8. Hodges P, Kelly P. Inflammatory bowel disease in Africa: what is the current state of knowledge? Int Health. 2020;12:222–230.
9. Khalili H. The Changing Epidemiology of Inflammatory Bowel Disease: What Goes Up May Come Down. Inflamm Bowel Dis. 2020;26:591–592.

10. Kaplan GG, Windsor JW. The four epidemiological stages in the global evolution of inflammatory bowel disease. Nat Rev Gastroenterol Hepatol. 2020. 2020. https://doi.org/10.1038/s41575-020-00360-x.
11. Coward S, Clement F, Benchimol EI, Bernstein CN, Avina-Zubieta JA, Bitton A, et al. Past and Future Burden of Inflammatory Bowel Diseases Based on Modeling of Population-Based Data. Gastroenterology. 2019;156:1345-1353.e4.
12. Santiago M, Magro F, Correia L, Portela F, Ministro P, Lago P, et al. What forecasting the prevalence of inflammatory bowel disease may tell us about its evolution on a national scale. Therap Adv Gastroenterol. 2019;12:175628481986004.
13. Azevedo LF, Magro F, Portela F, Lago P, Deus J, Cotter J, et al. Estimating the prevalence of inflammatory bowel disease in Portugal using a pharmaco-epidemiological approach. Pharmacoepidemiol Drug Saf. 2010;19:499–510.
14. Cleveland, R, Cleveland, W, McRae, J and Terpenning I. STL: A Seasonal-Trend Decomposition Procedure Based on Loess. J Off Stat. 1990;6:3–73.
15. Torabi M, Bernstein CN, Yu BN, Wickramasinghe L, Blanchard JF, Singh H. Geographical Variation and Factors Associated with Inflammatory Bowel Disease in a Central Canadian Province. Inflamm Bowel Dis. 2020;26:581–590.
16. Osei JA, Peña-sánchez JN. Population-Based Evidence From a Western Canadian Province of the Decreasing Incidence Rates and Trends of Inflammatory Bowel Disease Among Adults. 2021;4:186–193.
17. Chaparro M, Garre A, Núñez Ortiz A, Diz-Lois Palomares M, Rodríguez C, Riestra S, et al. Incidence, Clinical Characteristics and Management of Inflammatory Bowel Disease in Spain: Large-Scale Epidemiological Study. J Clin Med. 2021;10:2885.
18. Ananthakrishnan AN, Bernstein CN, Iliopoulos D, Macpherson A, Neurath MF, Ali RAR, et al. Environmental triggers in IBD: a review of progress and evidence. Nat Rev Gastroenterol Hepatol. 2018;15:39–49.

19. Olalde I, Mallick S, Patterson N, Rohland N, Villalba-Mouco V, Silva M, et al. The genomic history of the Iberian Peninsula over the past 8000 years. Science (80-). 2019;363:1230–1234.
20. Barreiro-de Acosta M, Magro F, Carpio D, Lago P, Echarri A, Cotter J, et al. Ulcerative colitis in northern Portugal and Galicia in Spain. Inflamm Bowel Dis. 2010;16:1227–1238.
21. Shah SC, Khalili H, Gower-Rousseau C, Olen O, Benchimol EI, Lynge E, et al. Sex-Based Differences in Incidence of Inflammatory Bowel Diseases—Pooled Analysis of Population-Based Studies From Western Countries. Gastroenterology. 2018;155:1079-1089.e3.
22. Shivashankar R, Tremaine WJ, Harmsen WS, Loftus E V. Incidence and Prevalence of Crohn's Disease and Ulcerative Colitis in Olmsted County, Minnesota From 1970 Through 2010. Clin Gastroenterol Hepatol. 2017;15:857–863.
23. Mak WY, Zhao M, Ng SC, Burisch J. The epidemiology of inflammatory bowel disease: East meets west. J Gastroenterol Hepatol. 2020;35:380–389.
24. Benchimol EI, Mack DR, Nguyen GC, Snapper SB, Li W, Mojaverian N, et al. Incidence, Outcomes, and Health Services Burden of Very Early Onset Inflammatory Bowel Disease. Gastroenterology. 2014;147:803-813.e7.
25. Roberts SE, Thorne K, Thapar N, Broekaert I, Benninga MA, Dolinsek J, et al. A Systematic Review and Meta-analysis of Paediatric Inflammatory Bowel Disease Incidence and Prevalence Across Europe. J Crohn's Colitis. 2020;14:1119–1148.
26. Keyashian K, Dehghan M, Sceats L, Kin C. Comparative Incidence of Inflammatory Bowel Disease in Different Age Groups in the United States. 2019;25:1983–1989.
27. Pasvol TJ, Horsfall L, Bloom S, Segal AW, Sabin C, Field N, et al. Incidence and prevalence of inflammatory bowel disease in UK based primary care : a

population- - cohort study. 2020:1–10.

28. Benchimol EI, Bernstein CN, Bitton A, Murthy SK, Nguyen GC, Lee K, et al. The Impact of Inflammatory Bowel Disease in Canada 2018: A Scientific Report from the Canadian Gastro-Intestinal Epidemiology Consortium to Crohn's and Colitis Canada. J Can Assoc Gastroenterol. 2019;2:S1–S5.

29. Vegh Z, Burisch J, Pedersen N, Kaimakliotis I, Duricova D, Bortlik M, et al. Incidence and initial disease course of inflammatory bowel diseases in 2011 in Europe and Australia: Results of the 2011 ECCO-EpiCom inception cohort. J Crohn's Colitis. 2014;8:1506–1515.

30. Su HY, Gupta V, Day AS, Gearry RB. Rising Incidence of Inflammatory Bowel Disease in Canterbury, New Zealand. Inflamm Bowel Dis. 2016;22:2238–2244.

31. Jones G-R, Lyons M, Plevris N, Jenkinson PW, Bisset C, Burgess C, et al. IBD prevalence in Lothian, Scotland, derived by capture–recapture methodology. Gut. 2019;68:1953–1960.

FIGURE CAPTIONS

Figure 1. Inflammatory Bowel Disease incidence rate per 100,000 inhabitants.

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.

Figure 4. Inflammatory Bowel Disease incidence per 1000 person-years.

Figure 5. Inflammatory Bowel Disease incidence forecast until 2024.

SUPPLEMENTARY MATERIAL

Table S1. Mean square error (MSE), and root mean square error (RMSE) of the tested forecasting models.

Table S2. Inflammatory Bowel Disease incidence per 100,000 habitants and per person-year.

Table S3. Forecasted incidence of Inflammatory Bowel Disease between April 2020 and December 2023.

Figure S1. Inflammatory Bowel Disease incidence rate per 100,000 inhabitants (only cases presenting more than one consultation coded with D94).

Figure S2. Regional distribution of Inflammatory Bowel Disease, in Portugal, between 2017 and 2019 (only cases presenting more than one consultation coded with D94).

Figure S3. Inflammatory Bowel Disease incidence rate per 100,000 inhabitants per age category (only cases presenting more than one consultation coded with D94). A: Four age categories; B: age categories according to the Montreal Classification.

Figure S4. Inflammatory Bowel Disease incidence per 1000 person-years (only cases presenting more than one consultation coded with D94).

Figure 1. Inflammatory Bowel Disease incidence rate per 100,000 inhabitants.

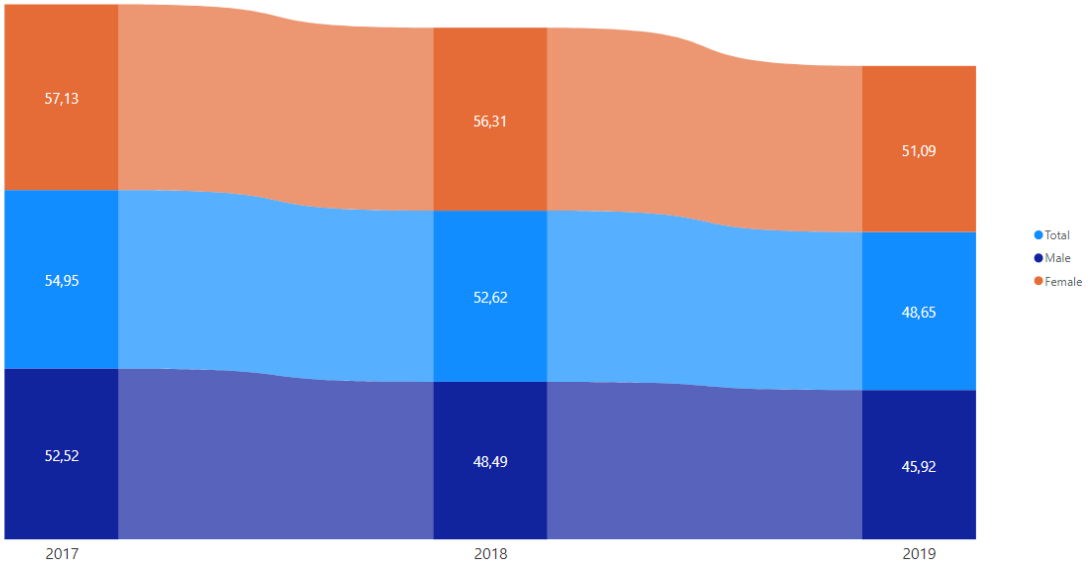


Figure 2. Regional distribution of Inflammatory Bowel Disease, in Portugal, between 2017 and 2019.

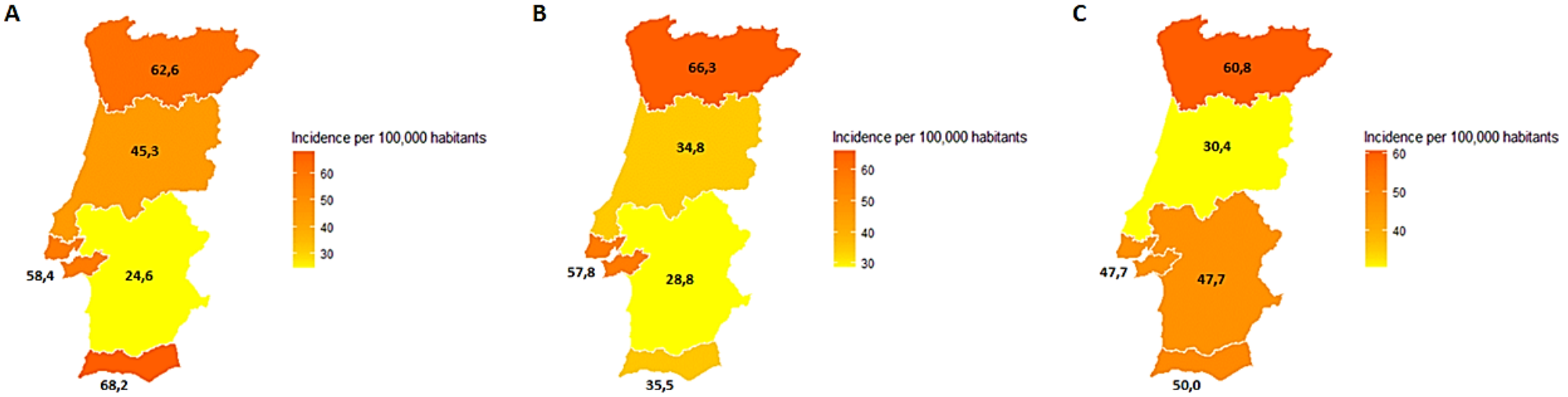
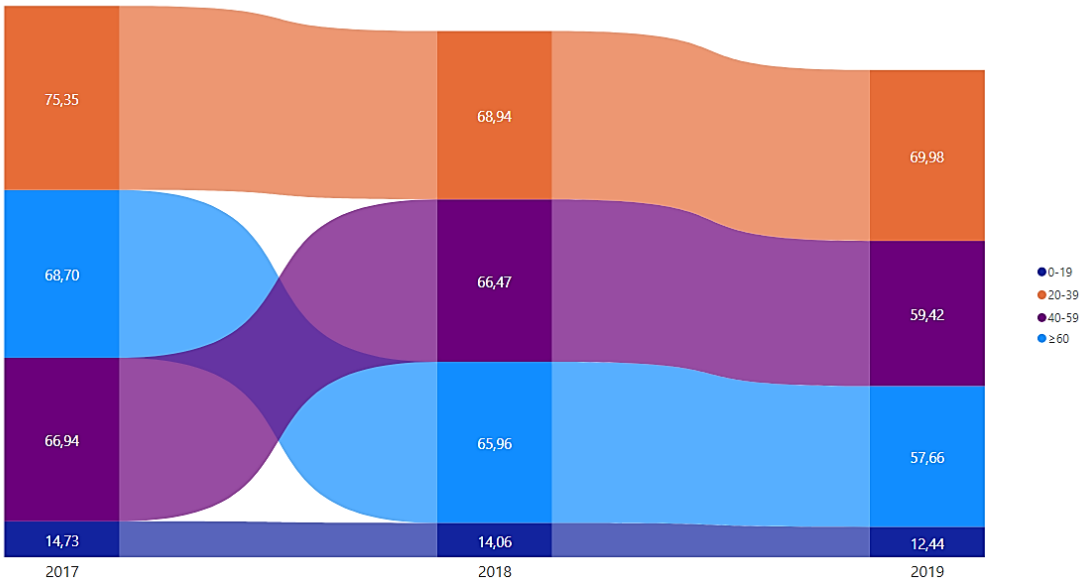


Figure 3. Inflammatory Bowel Disease incidence rate per 100,000 inhabitants per age category. A: Four age categories; B: age categories according to the Montreal Classification.

A



B

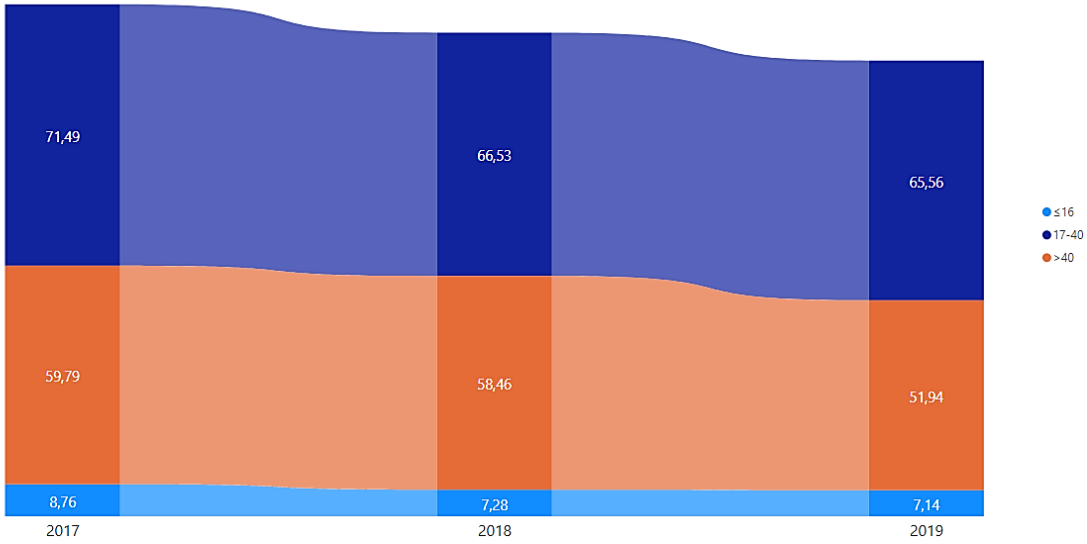


Figure 4. Inflammatory Bowel Disease incidence per 1000 person-years.

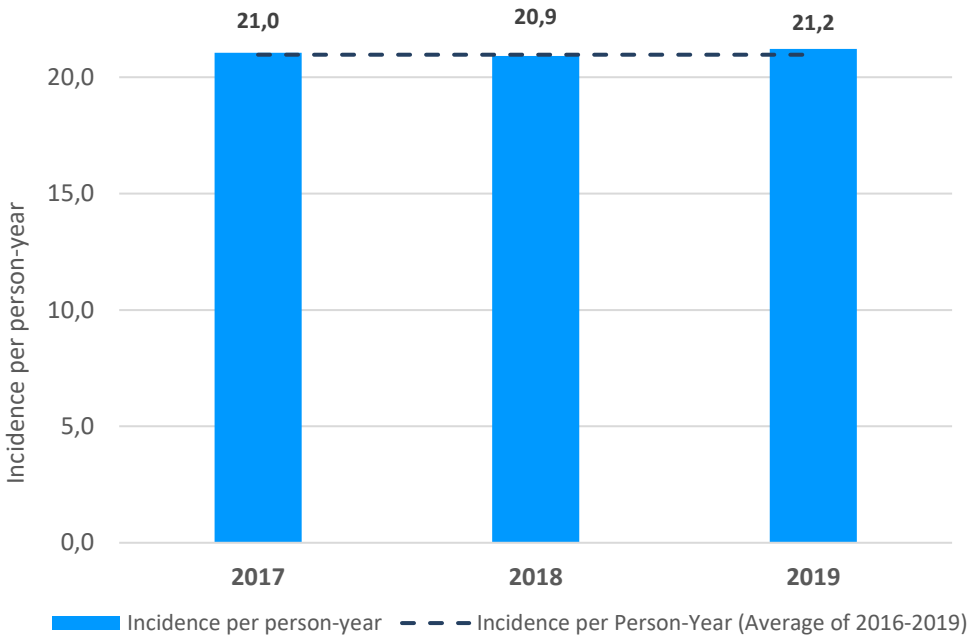
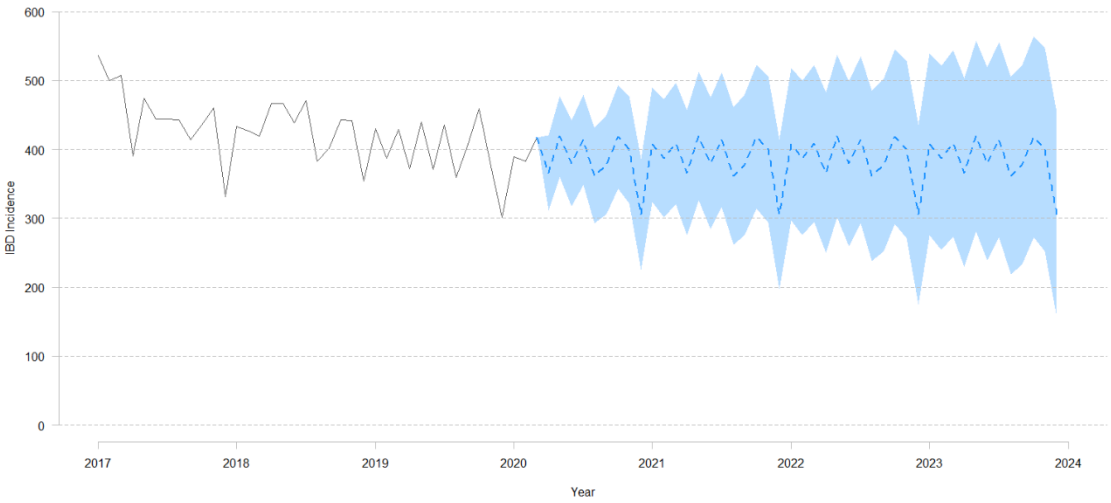


Figure 5. Inflammatory Bowel Disease incidence forecast until December 2023.



Supplementary Table 1. Mean square error (MSE) and root mean square error (RMSE) of the tested forecasting models.

Model	MSE*	RMSE*
STL + ARIMA	1310.374	36.199
STL + ETS	1767.841	42.046
ARIMA	2772.987	52.659
ETS	3790.935	61.571
MA	3520.605	59.334
TBATS	4734.804	68.810
HW	3498.414	59.147
STL	4851.092	69.650
SNAIVE	6496.324	80.600

ARIMA: Auto Regressive Integrated Moving Average; ETS: Error Trend Seasonal model; HW: Holt-Winters model; MA: Moving Average; MSE: Mean Squared Error; RMSE: Root Mean Squared Error; STL: Seasonal and Trend decomposition using Loess model; SNAIVE: Seasonal Naive model; TBATS: Exponential smoothing state space model with Box-Cox transformation, ARMA errors, Trend and Seasonal components.
*The lower the number, the better the model.

Supplementary Table 2. Inflammatory Bowel Disease incidence rate per 100,000 habitants and per person-year.

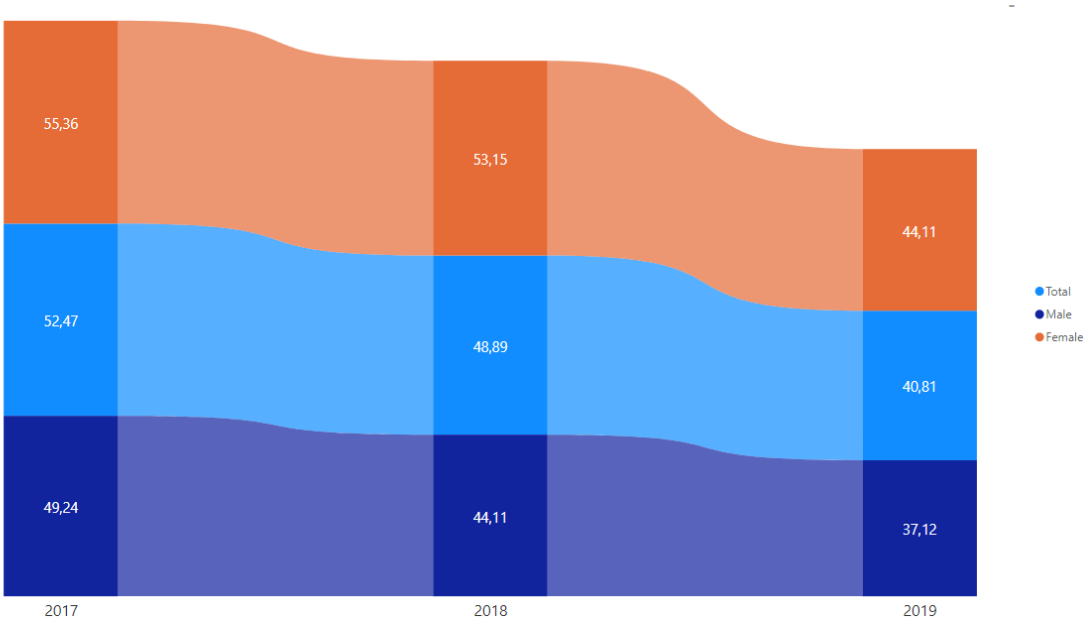
	Year	Total	Sex		Age				Age according to the Montreal classification			Portuguese Region (NUTS II)					Incidence per person-year
			Male	Female	0-19	20-39	40-59	≥60	0-16	17-40	>40	North	Center	Lisbon	Alentejo	Algarve	
Primary analysis	**2017**	54.9	52.5	57.1	14.7	75.3	66.9	68.7	8.8	71.5	59.8	62.6	45.3	58.4	24.6	68.2	21.0
	2018	52.6	48.5	56.3	14.1	68.9	66.5	66.0	7.3	66.5	58.5	66.3	34.8	57.8	28.8	35.5	20.9
	2019	48.6	45.9	51.1	12.4	70.0	59.4	57.7	7.1	65.6	51.9	60.8	30.4	47.7	47.7	50.0	21.2
	Mean (95% CI)	52.0 (44.1-60.0)	49.0 (40.7-57.2)	54.8 (46.7-62.9)	13.7 (10.8-16.7)	71.4 (62.9-79.9)	64.3 (53.8-74.7)	64.3 (53.8-74.7)	7.7 (5.4-10.0)	67.9 (60.0-75.8)	56.7 (46.2-67.3)	63.2 (56.3-70.2)	36.8 (17.8-55.9)	54.6 (39.7-69.6)	33.7 (3.1-64.3)	51.2 (10.5-91.9)	21.0 (20.7-21.4)
Sensitivity analysis	**2017**	52.5	49.2	55.4	13.3	70.5	64.4	67.1	7.7	66.9	57.9	59.9	43.0	55.9	23.3	65.3	20.9
	2018	48.9	44.2	53.2	12.4	62.0	62.1	63.5	6.6	59.7	55.4	61.5	32.9	53.6	25.9	32.6	20.7
	2019	40.8	37.1	44.1	9.6	55.7	49.5	52.5	5.3	52.0	45.2	50.6	26.1	40.2	40.3	40.6	20.7
	Mean (95% CI)	47.4 (32.6-62.2)	43.5 (28.4-58.6)	50.9 (36.1-65.7)	11.8 (7.0-16.5)	62.7 (44.3-81.1)	58.7 (38.7-78.7)	61.0 (42.2-79.9)	6.5 (3.5-9.5)	59.5 (41.0-78.0)	52.8 (36.0-69.6)	57.3 (42.7-72.0)	34.0 (12.9-55.1)	49.9 (28.8-71.0)	29.8 (7.1-52.6)	46.2 (3.8-88.5)	20.8 (20.5-21.1)

NUTS II: Nomenclature of Territorial Units for Statistics; Statistical significance assessed through Mann-Whitney U tests.

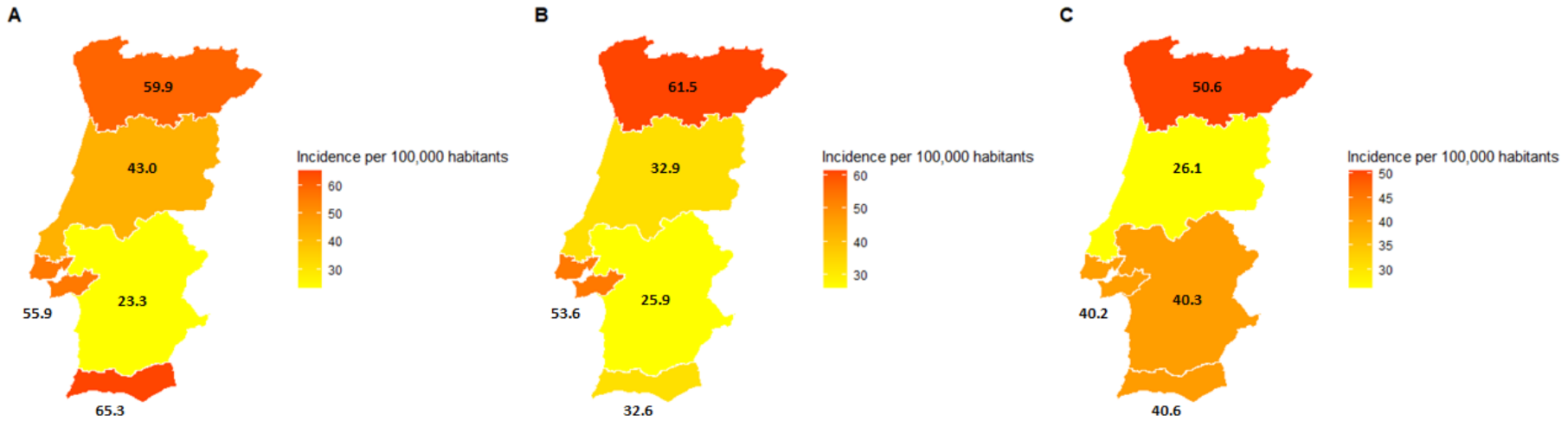
Supplementary Table 3. Forecasted incidence between April 2020 and December 2023 (PI, Prediction Interval).

Month	Year	Point Forecast	Lower PI 95%	Higher PI 95%
Apr	2020	366.3431	311.6530	421.0333
May	2020	419.2920	360.7560	477.8281
Jun	2020	379.5429	317.3985	441.6874
Jul	2020	414.1271	348.5726	479.6816
Aug	2020	361.9390	293.1433	430.7348
Sep	2020	377.4176	305.5266	449.3086
Oct	2020	418.0765	343.2181	492.9349
Nov	2020	400.0688	322.3563	477.7813
Dec	2020	305.4325	224.9670	385.8980
Jan	2021	407.5060	324.3787	490.6334
Feb	2021	387.3768	301.6702	473.0834
Mar	2021	408.7475	320.5370	496.9579
Apr	2021	366.3431	275.6980	456.9883
May	2021	419.2920	326.2759	512.3082
Jun	2021	379.5429	284.2147	474.8711
Jul	2021	414.1271	316.5416	511.7126
Aug	2021	361.9390	262.1473	461.7307
Sep	2021	377.4176	275.4674	479.3678
Oct	2021	418.0765	314.0126	522.1405
Nov	2021	400.0688	293.9332	506.2044
Dec	2021	305.4325	197.2649	413.6001
Jan	2022	407.5060	297.3439	517.6682
Feb	2022	387.3768	275.2556	499.4979
Mar	2022	408.7475	294.7009	522.7940
Apr	2022	366.3431	250.4032	482.2831
May	2022	419.2920	301.4891	537.0950
Jun	2022	379.5429	259.9060	499.1799
Jul	2022	414.1271	292.6839	535.5704
Aug	2022	361.9390	238.7160	485.1621
Sep	2022	377.4176	252.4401	502.3951
Oct	2022	418.0765	291.3688	544.7842
Nov	2022	400.0688	271.6542	528.4834
Dec	2022	305.4325	175.3334	435.5315
Jan	2023	407.5060	275.7440	539.2680
Feb	2023	387.3768	253.9725	520.7810
Mar	2023	408.7475	273.7210	543.7740
Apr	2023	366.3431	229.7137	502.9726
May	2023	419.2920	281.0782	557.5059
Jun	2023	379.5429	239.7626	519.3232
Jul	2023	414.1271	272.7977	555.4565
Aug	2023	361.9390	219.0773	504.8007
Sep	2023	377.4176	233.0399	521.7953
Oct	2023	418.0765	272.1986	563.9545
Nov	2023	400.0688	252.7059	547.4318
Dec	2023	305.4325	156.5994	454.2656

Supplementary Figure 1. Inflammatory Bowel Disease incidence rate per 100,000 inhabitants (only cases presenting more than one consultation coded with D94).

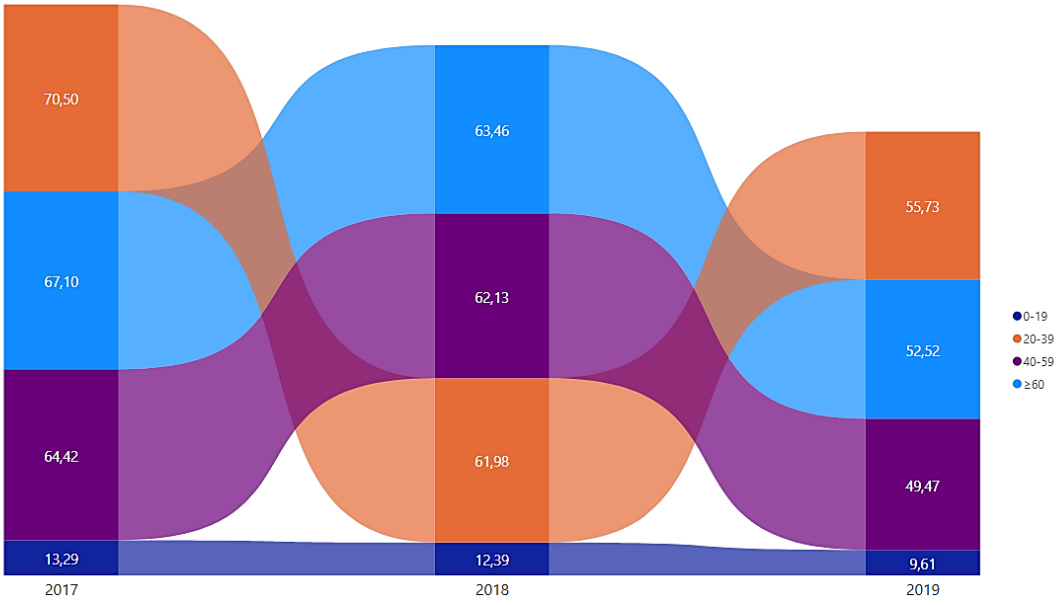


Supplementary Figure 2. Regional distribution of Inflammatory Bowel Disease, in Portugal, between 2017 and 2019 (only cases presenting more than one consultation coded with D94).

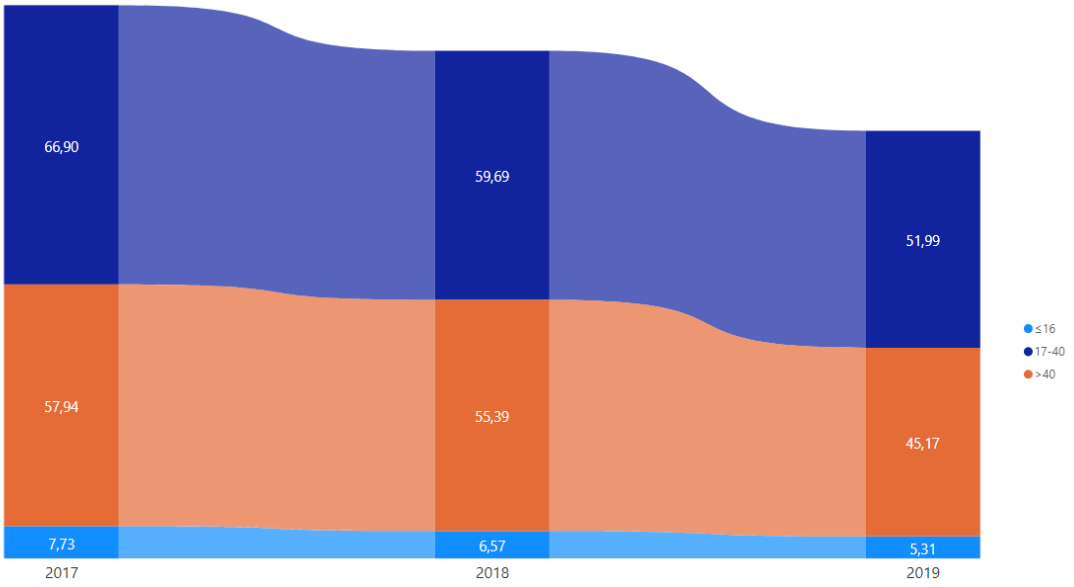


Supplementary Figure 3. Inflammatory Bowel Disease incidence rate per 100,000 inhabitants per age category (only cases presenting more than one consultation coded with D94). A: Four age categories; B: age categories according to the Montreal Classification.

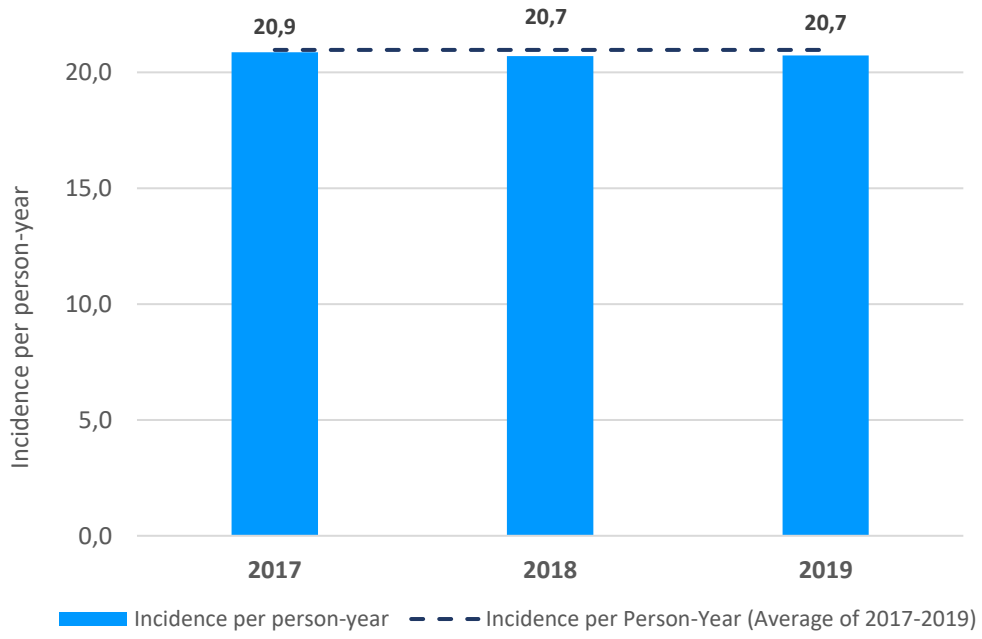
A



B



Supplementary Figure 4. Inflammatory Bowel Disease incidence per 1000 person-years (only cases presenting more than one consultation coded with D94).



ANEXO

APPENDIX

1. Recomendações Internacionais | Reporting guidelines

2. Normas da revista | Author information

3. Parecer da Comissão de Ética | Approval of the Ethics Committee

4. Componente de Disseminação | Dissemination Component

1. Normas Internacionais | Reporting guidelines

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract 'The 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.'	9
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found 'This work intends to identify the trends related to IBD incidence nationwide, analyzing regional, sex, and age distributions.' 'The incidence of IBD slightly declined from 2017 to 2019, and it is posed to stabilize in the future.'	9
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported 'IBD affects mainly people between the second and fourth decade 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].'	10
Objectives	3	State specific objectives, including any prespecified hypotheses 'Our study aims to identify the trends of IBD incidence in Portugal, with region, sex, and age-specific distributions. In addition, based on this data, we intend to evaluate the future incidence of IBD in Portugal, until 2024, through forecasting models. This can be useful to establish incidence behavior and define policies, guidelines, and milestones for prevalence stabilization.'	11
Methods			
Study design	4	Present key elements of study design early in the paper 'This study consisted of a retrospective analysis'	12
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection '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	12

		(SPMS). All possible patient identifiers were encrypted to ensure patients' confidentiality.'	
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up '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.' *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	12
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable 'The primary outcome measure was IBD incidence rate per 100,000 inhabitants (…) Other outcome measures included: 1) 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 1000; and 2) forecasted incidence, based on the estimation the number of new diagnoses per month during the study period and application of several forecasting models to predict incidence values until 2024.'	12
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group 'Data were provided by the Portuguese Shared Services of the Ministry of Health (SPMS).' '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 (four categories: 0-19, 20-39, 40-59, ≥ 60 years old; three categories according to the Montreal classification: 0-16, 17-40, >40), and region according to the Nomenclature of Territorial Units for Statistics (NUTS) II (North, Center, Lisbon, Alentejo, Algarve).'	12,13
Bias	9	Describe any efforts to address potential sources of bias	13

		‘To prevent prevalence mixing with incidence cases, we performed a washout period of two years. Therefore, we analyzed data from January 2017 to April 2020.’	
Study size	10	Explain how the study size was arrived at	NA
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why ‘Incidence rates per 100,000 inhabitants were analyzed by year and stratified by sex (male and female), age (four categories: 0-19, 20-39, 40-59, ≥ 60 years old; three categories according to the Montreal classification: 0-16, 17-40, >40), and region according to the Nomenclature of Territorial Units for Statistics (NUTS) II (North, Center, Lisbon, Alentejo, Algarve).’	13
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding ‘To prevent prevalence mixing with incidence cases (…) software (version 3.6.1) and RStudio (version 1.2.1335).’	13,14
		(*b*) Describe any methods used to examine subgroups and interactions ‘Incidence rates per 100,000 inhabitants were analyzed by year and stratified by sex (male and female), age (four categories: 0-19, 20-39, 40-59, ≥ 60 years old; three categories according to the Montreal classification: 0-16, 17-40, >40), and region according to the Nomenclature of Territorial Units for Statistics (NUTS) II (North, Center, Lisbon, Alentejo, Algarve).’	13
		(*c*) Explain how missing data were addressed	NA
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses ‘Additionally, 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.’	13

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	NA
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	NA
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount) 'The incidence rate of IBD in Portugal, between 2017 and 2019'	15
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time '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%.'	15
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included '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%. Moreover, new cases were more common among females than males (F vs. M, 2017-2019: 57.1 – 51.1 vs. 52.5 – 45.9) (Figure 1, Supplementary Table 2). Incidence distribution was heterogeneous nationwide, with more new cases in the Northern region of Portugal and the Lisbon Metropolitan Area' 'As observed in Figure 3A, the incidence per 100,000 inhabitants was about five times higher in older patients (≥ 20 years old) when compared to younger ones.' '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.' 'In December 2021, IBD incidence was forecasted to reach 305.4 (95% PI 197.3 – 413.6) new diagnoses, whereas, by December 2023, it is predicted to reach similar values (305.4, 95% PI 156.6 – 454.3).'	15, 16
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses 'Ultimately, no statistical differences were found between the primary and the sensitivity analyses, as confidence intervals overlapped (**Supplementary Table 2**).'	15
Discussion			
Key results	18	Summarise key results with reference to study objectives 'The obtained results indicate that IBD incidence slightly decreased in the analyzed period, with heterogeneous trends in the distinct regions (**Figure 1, 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' 'In conclusion, our study showed that IBD incidence decreased slightly in mainland Portugal in the last years, and is poised to stabilize in the near future. However, IBD incidence is still high nationwide, mainly in the North and Lisbon region. The presented data, along with the forecasting analysis, is of the utmost importance not only for the characterization of IBD in a Southern-European country but 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.'	17, 19-20
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias '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 since 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, as well as by occasional underreporting. Also, we could not verify this aspect as 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, even though the prediction is in good agreement with estimations performed by other authors. Nevertheless, further research of larger datasets is necessary to confirm these findings.'	19
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence 'The obtained results indicate that IBD incidence slightly decreased in the analyzed period (…)that anticipate the stabilization or decrease of IBD incidence at least until 2050, as part of a compounding prevalence stage [10].'	17-19
Generalisability	21	Discuss the generalisability (external validity) of the study results	19, 20

		‘The presented data, along with the forecasting analysis, is of the utmost importance not only for the characterization of IBD in a Southern-European country but as a potential mirror of disease behavior in the western world.’	
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based ‘This work was supported by the Portuguese Study Group of Inflammatory Bowel Disease (GEDII).’	6

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

2. Normas da revista | Author information

Clinical and Translational Gastroenterology (CTG)

Author Resources

Instructions for Authors (this page)

MISSION

To improve the health and well-being of individuals worldwide impacted by digestive disorders.

AIMS AND SCOPE

Clinical and Translational Gastroenterology (CTG), published on behalf of the American College of Gastroenterology (ACG), is a double-blind peer-reviewed, open access, online journal dedicated to innovative clinical work in the field of gastroenterology, pancreatology, and hepatology. CTG seeks to promptly publish and broadly disseminate important clinical care insights and significant scientific discoveries that impact the prevention, diagnosis, and treatment of digestive disorders. CTG hopes to fulfill an unmet need for clinicians and scientists by welcoming novel cohort studies, early-phase clinical trials, qualitative and quantitative epidemiologic research, hypothesis-generating research, and studies of novel mechanisms and methodologies including public health interventions. CTG also welcomes hypothesis-generating studies, methods papers, and translational research with clear applications to human physiological processes or diseases involving the gastrointestinal system. CTG adopts the National Institutes of Health's (NIH) definition of translational research:

> Translational research includes two areas of translation. One is the process of applying discoveries generated during research in the laboratory, and in preclinical studies, to the development of trials and studies in humans. The second area of translation concerns research aimed at enhancing the adoption of best practices in the community. Cost-effectiveness of prevention and treatment strategies is also an important part of translational science[1].

This definition therefore requires the application of findings to human subjects, either directly or indirectly. Basic science research, particularly research involving animal models or *in-vitro* work, is best reported elsewhere. CTG expands the scope of translational research to include public health dimensions that impact the human experience. CTG devotes itself to publishing timely medical research in gastroenterology, pancreatology and hepatology with:

- Original Research Articles
- Review Articles
- Brief Report
- The Clinician's Toolbox: Understanding our Tests (a structured assessment of individual diagnostic tests used in gastroenterology, pancreatology and hepatology)
- Editorials
- Correspondence

MANUSCRIPT SUBMISSION

Submissions are not accepted via email. Manuscripts must be submitted online at https://www.editorialmanager.com/ctg

First-time Users: Please click the Register button in the main menu and enter the requested information. Upon successful registration, you will be sent an email indicating your username and password. Save a copy of this information for future reference. Note: If you have received an email from us with an assigned user ID and password, or if you are a repeat user, do not register again. Once you have an assigned ID and password, you do not need to re-register, even if your role changes (that is, author, reviewer, or editor). Authors please click the login button from the menu at the top of the page and log in to the system as an Author. Submit your manuscript according to the system instructions. You will be able to

track the progress of your manuscript through the system. If you experience any problems, please contact the Editorial Office (or click on the 'Contact Us' link in the header menu).

ETHICAL AND LEGAL CONSIDERATIONS

A submitted manuscript must be an original contribution not previously published (except as an abstract), must not be under consideration for publication elsewhere, and, if accepted, it must not be published elsewhere in similar form, in any language, without the consent of Wolters Kluwer. The *Journal follows* the ICJME recommendations for authorship. Any person listed as an author is expected to have participated in the study to a significant extent. Although editors and reviewers make every effort to ensure the validity of published manuscripts, the final responsibility rests with the authors, not with the *Journal*, its editors, or the publisher.

Documented review and approval from a formally constituted review board (Institutional Review Board or Ethics committee) is required for all studies involving people, medical records, and human tissues, and for all animal studies. For authors or investigators that do not have access to formal ethics review committees, the principles outlined in the Declaration of Helsinki should be followed. If the study is judged exempt from review, a statement from the committee should be provided. Informed consent by participants should always be sought and documented in the Methods section. If not possible, an institutional review board must decide if this is ethically acceptable, and documentation of this decision must be included with the submission. In the main manuscript, a general IRB approval statement should be included. A more detailed statement that includes the name of the approving institution must be included on the title page.

Plagiarism Detection: *CTG* is a member of CrossCheck by CrossRef and iThenticate. iThenticate is a plagiarism screening service that verifies the originality of content submitted before publication. iThenticate checks submissions against millions of published research papers, and billions of web content. Authors, researchers, and freelancers can also use iThenticate to screen their work before submission by visiting www.ithenticate.com. If a case of plagiarism comes to light after a paper is published, the Journal will conduct a preliminary investigation, utilizing the guidelines of the Committee on Publication Ethics. If plagiarism is proven, the journal will contact the author's institute and funding agencies as appropriate. The paper containing the plagiarism may also be formally retracted or subject to correction.

Patient Anonymity and Informed Consent: Authors should remove patients' names and other identifying information from figures. If any identifying details appear in text, tables, and/or figures, the author must provide proof of informed consent obtained from the patient (i.e., a signed permission form). Photographs with bars placed over eyes of patients should NOT be used in publication. If they are used, permission from the patient is required. If the parents or guardian were unable to be located for their consent, a signed statement from the Chair of the Department or from the Institutional Review Board may be accepted. The statement must read: all attempts have been exhausted in trying to contact the parents or guardian for the purpose of attaining their consent to publish their information.

Conflicts of Interest: Authors must state all possible conflicts of interest in the manuscript, including financial, consultant, institutional and other relationships that might lead to bias or a conflict of interest. If there is no conflict of interest, this should also be explicitly stated as none declared. All sources of funding should be acknowledged in the manuscript. All relevant conflicts of interest and sources of funding should be included on the title page of the manuscript with the heading "Conflicts of Interest" and via the submission form in Editorial Manager.

Declaration of Funding Source: Acknowledgment of grants or financial support must be declared for all manuscripts. In addition, authors of all articles in which the effect of a drug, appliance, or treatment is evaluated must also acknowledge all support from the manufacturer of such drug, appliance, or treatment or its competitor. Authors of all articles, including review articles, editorials, and

correspondence, must disclose any financial interests that might have an impact on the views expressed in the submission. The funding declaration must be included on the title page of the manuscript and via the submission form in Editorial Manager. Authors with nothing to declare should provide a statement to that effect. Manuscripts submitted without the required disclosures will be returned to the authors.

Permissions: Authors must submit written permission from the copyright owner (usually the publisher) to use direct quotations, tables, or illustrations that have appeared in copyrighted form elsewhere, along with complete details about the source. Any permission fees that might be required by the copyright owner are the responsibility of the authors requesting use of the borrowed material, not the responsibility of Wolters Kluwer. Contact the publication's website of the content being reused and follow the instructions for contacting the permissions team. There is often a direct link to request permission through the online version of the article.

Clinical Trials: Original Research Articles of studies that prospectively assign human subjects to specific intervention or comparison groups and determine the relationship between an intervention and outcome are considered clinical trials. To ensure consistency with the guidelines of the Clinical Trial Registration Statement from the International Committee of Medical Journal Editors, all trials submitted to the Journal with patient enrollment commencing after January 1, 2009 **must** be registered in a public trials registry **prior** to enrollment of the first subject. The registry must incorporate free public access, and must be searchable, open to prospective registrants, and have not-for-profit management. The following information must be included in the registry: (1) unique identifying number, (2) statement of intervention(s), (3) hypothesis, definition of primary and secondary outcome measurements, eligibility criteria, target number of subjects, funding source, contact information for principal investigator, and dates of registration, start, and completion. Authors should provide the URL (website address) and trial identification number on the title page of the manuscript. This information will be published with the article.

Clinical trial reports should comply with the Consolidated Standards of Reporting Trials (CONSORT) and the checklist should be submitted at the end of the manuscript.

Reporting Clinical Trials Conducted by Pharmaceutical Companies: Please ensure that clinical trials sponsored by pharmaceutical companies follow the guidelines on Good Publication Practice (Committee on Publication Ethics). These guidelines aim to ensure that such trials are published in a responsible and ethical manner. The guidelines cover companies' responsibility to endeavor to publish results of all studies, companies' relations with investigators, measures to prevent redundant or premature publication, methods to improve trial identification, and the role of professional medical writers.

STAndards for the Reporting of Diagnostic accuracy studies (STARD checklist): If you are reporting a study that has assessed one or more diagnostic tests you must complete the STARD Statement, and paste it onto the end of your full manuscript.

STrengthening the Reporting of OBservational studies in Epidemiology (STROBE Statement): Reports of an observational cohort, case-control, or cross-sectional study must include the relevant STROBE Checklist at the end of the manuscript. Additional information can be found on the STROBE website.

Standards for QUality Improvement Reporting Excellence (SQUIRE statement): should be applied for quality improvement (QI) projects and those involving a detailed consensus process.

ARTICLE TYPES

Original Research Articles: Although the Editors do not impose page or word limits on articles, they reserve the right to request that any text and/or information deemed non-essential be published online as supplementary material to the main article. In general, limit full-length articles to 3,000 words, not including references, tables, or abstract. Include a structured abstract of 250 words or fewer and study highlights. All abstracts and main body of Original Research article manuscripts must include the following section headings:

- **Introduction**: the specific aim(s) and an a priori hypothesis must be stated.
- **Methods**: must include sufficient information by which to judge the quality of the research, including statistical analyses and study power where appropriate.
- **Results**: do not duplicate results presented in the text and tables.
- **Discussion**: consider including a brief statement of the principal findings, the strengths and weaknesses of the study, strengths and weaknesses in relation to other studies, a consideration of important differences in results, the meaning of the study, including possible explanations and implications for clinicians and policymakers, and a commentary considering unanswered questions and future research.

Review Article (Narrative): *CTG* publishes substantive reviews on clinical and translational topics with value to clinicians. Special priority is given to emerging or rapidly evolving topics. All articles will be peer reviewed prior to consideration. Include an unstructured abstract of no more than 250 words. The main article should be not more than 3,000 words excluding references, figures and tables. The review should contain at least 2 and not more than 8 figures or tables. Authors of either narrative reviews or systematic reviews (see below) with financial conflicts of interest relevant to the topic(s) should make every effort to present a fair and balanced review. In the setting of potential conflicts of interest, the Editorial Board may summarily reject reviews perceived as biased.

Review Article (Systematic Review and Meta Analysis): *CTG* publishes high-quality systematic reviews and meta-analyses in all topics of gastroenterology, pancreatology and hepatology. All articles will be peer reviewed prior to consideration. The literature search should be conducted in MEDLINE and EMBASE at minimum. If controlled trials are sought, the Cochrane Central Register of Controlled Trials should be searched as well. The risk of bias of included studies should be systematically assessed, reported and discussed. Include a structured abstract of not more than 250 words. The main article should be not more than 3,000 words excluding references, figures and tables. The review should contain at least 2 and not more than 8 figures or tables.

A Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Checklist should be included at the end of the manuscript. Alternatively, the MOOSE checklist should be applied for meta-analyses of observational studies. A full list and index of reporting guidelines can be found at www.equator-network.org/library/. All can be downloaded as Word documents that can then be included at the end of the manuscript.

The Clinician's Toolbox: Understanding our Tests: This article type explores a single diagnostic test used in gastroenterology, pancreatology or hepatology. The manuscript should include an overview of the test, its indication(s), how it is performed, the performance characteristics (sensitivity, specificity, positive- and negative-predictive values and likelihood ratios), conditions that make the test results inaccurate and how to manage such results, how clinicians should incorporate the testing into clinical care or research studies, a brief discussion of any alternative tests that may replace or complement the test, and relevant billing and cost information. Published literature should be cited to support the information provided and relevant studies that examined the test's utility and accuracy should be included. Figures are encouraged. **Authors should not have financial conflicts of interest related to the test.** In general,

limit the main text to 3,000 words, not including references, tables, or abstract. Please include an unstructured abstract summarizing the content of the article.

Brief Report: The Editors welcome brief reports of novel findings and/or highly-impactful preliminary data deemed likely to alter clinical care or foster a new direction in research. As such, CTG expects to publish only a very small number of these articles each year. Like with our Original Research format, only studies with human subjects or with human-derived samples are appropriate. Include the following sections: Introduction, Methods, Results, Discussion (see *Original Research Articles* above for more details). Manuscripts should be limited to 1000 words or less, excluding references and abstract. Include a structured abstract of 150 words or less, 15 references or less, and 3 or less total tables/figures/images. Include a title page with COI information, but no study highlights.

Editorial: Editorials will be paired with select articles and solicited at the provisional acceptance of an article. Unsolicited Editorials will not be considered. To submit a perspective for consideration, please see the Correspondence section. Editorials require an unstructured abstract of 100 words or less and limited to 1,000 words, excluding references.

Correspondence: Correspondence should regard published articles in *CTG*, or be a general comment about an issue relevant to the field. Peer review of letters will be at the discretion of the Editor. Correspondence must cite the article on which it comments, should be no more than 500 words, have 5 or less references, and no abstract. Please include a complete title page with full conflict of interest and funding disclosures as a separate file. This is not a forum for authors to publish their own original research or data, and *CTG* does not publish case reports. Note that article processing charges do not apply to Correspondence.

MANUSCRIPT PREPARATION

Manuscripts must be in English and typed double-spaced. *The American Medical Association Manual of Style* (10th ed.), *Stedman's Medical Dictionary* (28th ed.), and *Merriam-Webster's Collegiate Dictionary* (11th ed.) should be used as standard references. The journal follows the International Committee of Medical Journal Editors' Uniform Requirements for Manuscripts Submitted to Biomedical Journals. Manuscripts not prepared according to the Instructions to Authors will be returned to the author(s) without review.

English Language: Concise, clearly written articles are more likely to be accepted for publication in the *CTG*. **Authors whose first language is not English are strongly encouraged to ask a native English-speaking colleague or a professional author's editor, preferably with knowledge in the subject matter contained in the manuscript, to edit their manuscript before submission.** Please note that the use of a language editing service is not a requirement for publication in this journal and does not imply or guarantee that the article will be selected for peer review or accepted. A list of editing services is available at https://wkauthorservices.editage.com.

Human Data Requirement: *CTG* requires that manuscripts describe work involving humans or human samples. If the manuscript lacks a human research component, the work must have immediate and direct translational applicability, which should be clearly communicated in the manuscript.

Cover Letter: In the cover letter, provide a statement of whether the paper was previously published in any language, including the abstract, and whether the paper is currently under consideration elsewhere for publication.

Title Page: The journal conducts a double-blind peer review process. The title page must include following: 1) the article title (150 characters or less); 2) all authors' names, degrees, affiliations, and

locations; 3) the name and email address of the corresponding author; 4) the author(s) conflict of interest/study support items as noted below; 5) IRB approval statement

Author Conflict of Interest/Study Support: Authors submitting work for publication in the *Journal*, including those writing Correspondence, are required to submit a conflict of interest disclosure. Review of a submission for publication will not commence and publication will not be permitted unless and until disclosures are submitted. If there is no actual or potential conflict, the author must indicate such. On your title page, please include a section with the following headings:

- **Guarantor of the article:** Identify the author who is accepting full responsibility for the conduct of the study. He or she must have had access to the data and have control of the decision to publish.
- **Specific author contributions:** List the role played by each author, e.g., in planning and/or conducting the study, collecting and/or interpreting data, and/ or drafting the manuscript. For each author, there should also be a statement that he or she has approved the final draft submitted. Refer to the ICMJE guidelines for appropriate input for authorship.
- **Financial support:** Disclose funding sources for the publication. Describe the role of any study sponsors in the study design, collection, analysis, and interpretation of the data and in the writing of the report. If there was funding but the work was independent of it, this must be specifically stated. (Other types of assistance—i.e., non-financial—may be acknowledged in an Acknowledgments section in the text.)
- **Potential competing interests:** List all potential conflicts or if there is no conflict of interest, this should also be explicitly stated as none declared.

Study Highlights: Only authors of original research Articles are required to include a Study Highlights section in their manuscript. The section should contain two headings: 1) WHAT IS KNOWN and 2) WHAT IS NEW HERE. The items under each heading should be bullet points that are very short, i.e., up to about 15 words.

WHAT IS KNOWN

- Heartburn is common and costly.
- The impact of reflux symptoms on mortality is poorly documented.

WHAT IS NEW HERE

- Reflux symptoms appear not to be associated with a major increased risk of poorer survival.
- Those with intermediate frequencies of reflux symptoms had better survival.
- Gastroesophageal reflux symptoms are a benign condition in most sufferers.

Visual Abstracts: Visual abstracts summarize an article's main findings and may be published with the accepted article in the journal's online table of contents and/or used for promotion of your article. Authors of accepted articles should submit a visual abstract for publication with their manuscript. Please find a template with formatting instructions and some examples of previously published visual abstracts here.

Abbreviations: Write out the full term for each abbreviation at its first use in abstract, what is known, manuscript body, and in each table and figure legend unless it is a standard unit of measure. Write out the full term for each abbreviation at its first use unless it is a standard unit of measure.

Units: All measurements should be given in metric units.

Title Length: The manuscript title should have no more than 150 characters including spaces. Keywords for referencing should be included in the title. Please no abbreviations. Fancy or comical titles are inappropriate and will be asked to be revised. Trade names of drugs and other products must not appear in the article title.

Abstract: Please refer to the table below for abstract requirements for various article types. Do not cite references in the abstract. Limit the use of abbreviations and acronyms. At first mention, please write out the full term for abbreviations (e.g. celiac disease (CD)). Use the following subheads in your structured abstract: Introduction, Methods, Results, and Conclusions. A fifth subhead, Translational Impact, may be used if your manuscript is pre-clinical to briefly explain how the results may impact future clinical practice.

Keywords: List three to five keywords for your article.

Drugs, Devices, and Other Products: Use nonproprietary names of drugs, devices, and other products, unless the specific trade name is essential to the discussion. The trade name may appear once in the Abstract and once in the Introduction or Methods section, followed by the nonproprietary name, manufacturer, and manufacturer location in parentheses; all other mention of the product must use the generic name. Trade names of drugs and other products must not appear in the article title.

References: The reference list should only include works that are cited in the text, should be listed consecutively as they appear in the text, and should follow the *AMA Manual of Style, 10th Edition*. The authors are responsible for the accuracy of the references. Cite the references in text in the order of appearance. Cite unpublished data—such as papers submitted but not yet accepted for publication and personal communications, including email communications—in parentheses in the text. If there are more than three authors, name only the first three authors and then use et al. Refer to the List of Journals Indexed in Index Medicus for abbreviations of journal names.

Sample References:

Journal Article

Rautava S, Lu L, Nanthakumar NN, et al. TGF-β2 induces maturation of immature human intestinal epithelial cells and inhibits inflammatory cytokine responses induced via the NF-κB pathway. J Pediatr Gastroenterol Nutr 2012;54:630-8.

Online Article

7. Sullivan D. Major search engines and directories. SearchEngineWatch Web site. [URL]. Published May 8, 2011. Accessed July 13, 2012.

Entire Book

Ming S-C, Goldman H. Pathology of the Gastrointestinal Tract. Philadelphia: Lippincott Williams & Wilkins; 2008.

Book Chapter

Todd VR. Visual information analysis: frame of reference for visual perception. In: Kramer P, Hinojosa J, eds. Frames of Reference for Pediatric Occupational Therapy. Philadelphia: Lippincott Williams & Wilkins; 2017:205–56.

Database

6. CANCERNET-PDQ [database online]. Bethesda, MD: National Cancer Institute; 2016. Updated March 29, 2016.

Figures:

Creating Digital Artwork

- Learn about the publication requirements for Digital Artwork: http://links.lww.com/ES/A42
- Create and Save your artwork and compare your final figure to the Digital Artwork Guideline Checklist below.
- Upload each figure to Editorial Manager as separate files with your manuscript text and tables. Figure legends should be included in the text and not in the image files.

Digital Artwork Guideline Checklist

- Artwork should be saved in TIFF, PPT, JPG, or EPS format (PDF is not recommended).
- Artwork is created as the actual size (or slightly larger) it will appear in the journal. (To get an idea of the size images should be when they print, study a copy of the journal. Measure the artwork typically shown and scale your image to match.)
- Crop out any white or black space surrounding the image.
- Diagrams, drawings, graphs, and other line art must be vector or saved at a resolution of at least 1200 dpi.
- Photographs, radiographs and other halftone images must be saved at a resolution of at least 300 dpi.
- Photographs and radiographs with text must be saved as postscript or at a resolution of at least 600 dpi.
- Each figure must be saved and submitted as a separate file. Figures should not be embedded in the manuscript Word file.

Remember

- Cite figures consecutively in your manuscript.
- Number figures in the figure legend in the order in which they are discussed.
- Each figure must have a legend. Legends should be brief (no more than 100 words) and should be typed in the manuscript document. Figure parts should be labelled a, b, c, etc.
- Use scale markers in the image for electron micrographs, and indicate the type of stain used.

Tables: Cite tables consecutively in the text and number them in that order. Provide tables in Word format, either as separately labeled files or at the end of your main manuscript document. Each table must have a title. Use footnotes to define abbreviations and for other explanatory detail in a legend below the Tables. Tables should be self-explanatory and must supplement, rather than duplicate, the material in the text.

Supplemental Digital Content (SDC): Authors may submit supplemental digital content with a submission to enhance their article's text or include text, tables, and figures outside of the specified limits. All supplemental digital content is posted online only. One advantage of including material as SDC is that SDC has no limitation of space or length. SDC may include the following types of content: text documents--including very detailed methods--graphs, tables, figures, graphics, illustrations, audio, and video. Authors are encouraged to submit related but not essential tables (e.g., large tables of articles cited in a meta-analysis, or a large demographic table of a study population) as SDC.

Notes: All online-only materials will be subject to peer review and published at the editor discretion. Supplemental figures, legends, and tables must not appear in the main manuscript file. All legends should be kept with the image or table it refers to for reader access. SDC text will not be copyedited nor typeset. Submit content exactly as intended to be displayed (including legends). No errata will be written for SDC content. No patient-identifying information should be used in SDC unless written consent from the patient,

the patient's parent/guardian has been obtained and is submitted with the manuscript. Copyright and Permission forms for article content including SDC must be provided at the time of submission.

Each piece of supplemental content should be uploaded in a separate file, labeled consecutively as Supplemental Digital Content, regardless of type. For example:

- Video, Supplemental Digital Content 1
- Supplemental Table, Supplemental Digital Content 2
- Supplemental Figure 1, Supplemental Digital Content 3

Cite all supplementary content consecutively in the text and independently from any figures or tables, including a sequential number, and provide a brief description of the supplementary content. For example:

- (See Video, Supplemental Digital Content 1, which demonstrates the statistical methods used)

To ensure a quality experience for those viewing supplemental digital content, it is suggested that authors submit supplemental digital files no larger than 10 MB each. Documents, graphs, and tables may be presented in any format. Figures, graphics, and illustrations should be submitted with the following file extensions: .tif, .eps, .ppt, .jpg, .pdf, .gif. Audio files should be submitted with the following file extensions: .mp3, .wma. Video files should be submitted with the following file extensions: .wmv, .mov, .mpg, .mpeg, .mp4. Video files should also be formatted with a 320 X 240 pixel minimum screen size. For more information, please review Wolters Kluwer's requirements for submitting supplemental digital content: http://links.lww.com/A142.

PEER REVIEW PROCESS

CTG currently utilizes the double-blind method of peer reviewing. The peer review process is handled entirely electronically through the Editorial Manager site. Peer reviewers are instructed to review the contents of the submission in a critical, unbiased, and timely fashion. They review all pieces of the submission, including the main text manuscript, as supplementary files, tables, and images. The title page with author names, affiliations, and IRB statement are blinded to the reviewers. The Editorial Board aims to have all Articles and Review Articles peer reviewed by two external reviewers in addition to one Associate Editor and the Editor-in-Chief. Editorials, and Correspondence are reviewed by an Associate Editor and the Editor in Chief, and are sent for external peer review if needed.

Editors are excluded from the review process for any manuscript on which they are an author. Other Editors perform these duties in these situations. Authors may suggest peer reviewers during the submission process, but the Editorial Office does not guarantee that those peer reviewers will be invited for review, and peer review invitations are at the sole discretion of the Editorial Office and Editorial Board. The Editorial Board has the freedom to assess the peer reviews and decide either with or against the recommendations. Peer reviews are rated after each decision, and these ratings are used to refine the peer reviewer pool for future use.

OPEN ACCESS

License to Publish: At submission, all authors must certify their understanding of the open access requirement for *CTG*. In addition, the corresponding author must complete a license to publish form on behalf of all authors at the time of submission. A copy of the license form is made available to the corresponding author during the Editorial Manager submission process, and can be uploaded with the manuscript files. Payment of article processing charges will be collected only upon acceptance of the manuscript.

Article Processing Charges: *CTG* is an open access, peer reviewed journal. For all accepted articles, the article processing charge (APC) will be required to allow perpetual unrestricted online access to the published article to readers globally, immediately upon publication. This fee is collected only upon acceptance of the manuscript. *CTG* uses a tiered APC system, where direct submissions by non-members of ACG are $2,800 USD, submissions by one or more members of ACG are $2,600 USD, and submissions transferred directly from the *American Journal of Gastroenterology* are $2,200 USD. Further instructions for payment will be provided by the editorial office upon acceptance, per your submission type. There are no submission, color, or page charges. Fees are collected through Wolters Kluwer's payment site at https://wolterskluwer.qconnect.com.

Authors Retain Copyright: Authors retain their copyright for all articles published open access. Authors grant Wolters Kluwer an exclusive license to publish the article and the article is made available under the terms of a Creative Commons user license.

Creative Commons License: Open access articles will be freely available to read, download and share from the time of publication. *CTG* provides authors the choice of applying one of the Creative Commons 4.0 licenses defined below. Questions regarding licenses can be directed to the Editorial Office.

- **Attribution-Noncommercial-NoDerivs (CC BY-NC-ND)**
  This license is the most restrictive of the six main licenses, only allowing others to download your works and share it with others as long as they credit you, but they cannot change the work in any way or use it commercially.
- **Attribution (CC-BY)**
  This license lets others distribute, remix, tweak, and build upon your work, even commercially, as long as they credit you for the original creation. This is the most accommodating of licenses offered, and is typically used when mandated by funders.

Compliance with NIH and Other Research Funding Agency Accessibility Requirements: A number of research funding agencies now require or request authors to submit the post-print (the article after peer review and acceptance but not the final published article) to a repository that is accessible online by all without charge. As a service to our authors, Wolters Kluwer identifies to the National Library of Medicine (NLM) articles that require deposit and transmits the post-print of an article based on research funded in whole or in part by the National Institutes of Health, Howard Hughes Medical Institute, or other funding agencies to PubMed Central. The License to Publish provides the mechanism. Wolters Kluwer ensures that authors can fully comply with the public access requirements of major funding bodies worldwide.

FAQ for Open Access: http://www.wkopenhealth.com/openaccessfaq.php

AFTER ACCEPTANCE

Accepted Article: The publisher will place the PDF of your accepted paper on the Latest Articles page with the label "Accepted Manuscript." After copyediting and typesetting, you'll be given the chance to view your paper one final time before publication. Once you approve the typeset version the editorial office will place the article into an upcoming issue.

Electronic Page Proofs and Corrections: Corresponding authors will receive electronic page proofs to check the copyedited and typeset article before publication. Portable document format (PDF) files of the typeset pages and support documents (e.g., reprint order form) will be sent to the corresponding author via e-mail. Complete instructions will be provided with the e-mail for downloading and marking the electronic page proofs. Corresponding author must provide an email address. The proof/correction process is done electronically.

It is the author's responsibility to ensure that there are no errors in the proofs. Changes that have been made to conform to journal style will stand if they do not alter the authors' meaning. Only the most critical changes to the accuracy of the content will be made. Changes that are stylistic or are a reworking of previously accepted material will be disallowed. The publisher reserves the right to deny any changes that do not affect the accuracy of the content. Authors may be charged for alterations to the proofs beyond those required to correct errors or to answer queries. Electronic proofs must be checked carefully and corrections returned within 24 to 48 hours of receipt, as requested in the cover letter accompanying the page proofs.

Reprints: Authors will receive an email notification with a link to the order form soon after their article publishes in the journal (https://shop.lww.com/author-reprint). Reprints are normally shipped 6 to 8 weeks after publication of the issue in which the item appears. Contact the Reprint Department, Lippincott Williams & Wilkins, 351 W. Camden Street, Baltimore, MD 21201; Fax: 410.558.6234; E-mail: authorreprints@wolterskluwer.com with any questions.

CTG Summary of Article Type Parameters

Article Type	Abstract	Study Highlights	Text Limit	Image/Table Limit	Reference Limit	COI Statement
Article	Structured 250 words	Required	3000 words	8 total	No limit	Required
Review Article (Narrative)	Unstructured 250 words	No	3000 words	8 total	No limit	Required
Review Article (SR/MA)	Structured 250 words	No	3000 words	8 total	No limit	Required
Clinician's Toolbox	Unstructured 250 Words	No	3000 words	8 total	No Limit	Required
Brief Report	Structured 150 Words	No	1000 words	3 total	15	Required
Editorial	Unstructured 100 words	No	1000 words	2 total	10	Required
Correspondence	None	No	500 words	2 total	5	Required

PRE-SUBMISSION CHECKLIST

Please use the following checklist to decrease the likelihood that your manuscript will be returned:

1. **Title page:** Provide details for all of the authors/co-authors and an email for the corresponding author on the title page. Verify that co-author names, titles, affiliations and degrees are accurate and current.

2. **Conflict of Interest:** Be sure to list all Conflicts of Interest on your title page in the format specified earlier in this guide, and enter into the Editorial Manager submission system where requested.

3. **Manuscript length and formatting:** Check that the length of the manuscript and abstract do not exceed the maximum word count and are formatted as per instructions to authors for each. See

the Article Type chart for length and abstract guidelines.

4. **Study highlights:** For Articles, be sure to include the study highlights section as described earlier in this guide.

5. **Figures:** Do not embed figures in manuscript. Cite the figures in the text of the manuscript andprovide figure legends at the end of your manuscript. Check that the figures and supplementary figures are formatted as indicated in the instructions to authors. Each figure should be in a separate file (uploaded individually).

6. **Tables:** Include tables at the end of the main text of your manuscript. Tables must be in text format and not images embedded into the document. Cite the tables in the text of the manuscript and provide table legends. Check that the tables and supplementary tables are formatted as indicated in instructions to authors.

7. **References:** Make sure each reference is cited in the text, references are formatted per instructions to authors and the quantity does not exceed maximum for the article type. Double check the accuracy of each reference (spelling of names, page numbers, proper journal abbreviation, etc.) as any errors are the authors' responsibility.

8. **Supplementary files and appendices:** Make sure files are formatted per instructions to authors and cited in main text. Legends to figure(s) and/or table legend(s) should appear in the same file, or can be uploaded as separate supplementary digital content as needed.

9. **Clinical trials:** Include documentation that the project was registered in a public trials registry prior to enrollment of the first subject. Be sure you have complied with one of the appropriate reporting guidelines endorsed by the EQUATOR Network (i.e., CONSORT, PRISMA, STARD, SQUIRE, and MOOSE). More information may be found at http://www.equator-network.org and http://www.equator-network.org/library/. For studies falling into the categories covered by these checklists, authors need to submit a formal checklist at the end of the manuscript at the time of submission. This ensures faster review turnaround since many of the points on the checklist ensure improved ease of review.

10. **Ethics:** Make sure the necessary ethical approval/clearance or informed consent was obtained and is noted on the title page where applicable.

11. **Permissions:** If using previously published materials, include permission to re-use the material obtained from the copyright holder as Supplemental Data and acknowledge the source in your legend as indicated by the permission reuse terms.

12. **Revised manuscripts:** Include a point-by-point response to the comments of each reviewer in one separate file. Submit both a final and marked up revision showing all changes made with

highlighting or track changes.

CONTACT INFORMATION

For all matters manuscript and peer review, contact:
Managing Editor
Clinical and Translational Gastroenterology
6400 Goldsboro Road, Suite 200
Bethesda, MD 20817
Tel: 301-263-9000
Fax: 301-263-9025
Email: journals@gi.org

References

(http://grants.nih.gov/grants/guide/rfa-files/RFA-RM-07-007.html.; accessed February 7, 2021).

http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html (Accessed 5/28/2021)

3. Parecer da Comissão de Ética | Approval of the Ethics Committee

EXARADO NA ATA Nº 2020_05
REUNIÃO DE 2020-02-14

Deliberado Autorizar atendendo ao parecer do DPO
2020-02-14

Carlos Nunes
Presidente do CD

Maria Clara Castro
Maria Clara Castro
Vice Presidente do CD

Paula Duarte
Vogal do CD

Ponciano Oliveira
Vogal do CD

☐ COMUNICAÇÃO ☒ INFORMAÇÃO ☐ PARECER

DATA : 2020/01/15
Nº 1 (P.1/20-DPO)

PARA .....: Conselho Diretivo

DE : Data Protection Officer (DPO)

ASSUNTO : **CES - Parecer nº074A/2019: *"Caracterização da doença inflamatória intestinal em Portugal"***

No âmbito do estudo em título, já apreciado pelo DPO (cfr. Informação nº26, junta), levantaram-se algumas questões atinentes à segurança da informação, designadamente se terceiros poderiam aceder à base de dados a criar, onde seria a mesma armazenada e em que condições de segurança e qual o prazo de armazenamento, afigurando-se também que, ao contrário do que é referido na pag.25 do protocolo, a informação sobre a qual recairá o estudo se afigurava vir a ser disponibilizada pseudonimizada[1].

E pese embora o tratamento dos dados seja efetuado pelos SPMS, por superiormente lhe ter sido solicitado, o DPO apreciou sucintamente os documentos do protocolo tendo concluido pela necessidade de esclarecimentos relativos àquelas questões, o que mereceu concordância superior.

Nesta conformidade, solicitada a colaboração da Comissão de Ética, veio a investigadora principal clarificar alguns aspetos em formato de "*Adenda*" (pese embora não assinado, encontra-se como anexo ao email por si enviado, sendo legitimo presumir ter sido elaborado pela mesma), e onde é referido que serão os SPMS a codificar os dados sem possibilidade de identificação do doente, não estando a base de dados acessível a terceiros (ainda que não seja referido como), sendo os dados armazenados pelo período ali melhor indicado.

Considerando que será outra entidade, que não a ARSN, o responsável pelo tratamento da informação, considerando ainda que é legítimo presumir que sobre esse tratamento se terá já pronunciado o DPO dos SPMS, tendo ainda presente que, na senda do que se vem experienciando junto dos mesmos, a segurança da informação é um dos seus corolários, somos de entendimento de que, obtido, como foi, parecer favorável da Comissão de Ética, se afigura defensável poder ser comunicado aos investigadores de que a ARSN nada tem a obstar à realização do estudo em apreço.

[1] Atento o vertido no item 5.b.iv do protocolo (onde é referida a possibilidade de reversão de identificação dos titulares dos dados).

☐ COMUNICAÇÃO ☒ INFORMAÇÃO ☐ PARECER DATA : 12.11.2019
Nº <Processo> <Registo>

PARA .....: Conselho Diretivo da ARS Norte

DE : Comissão de Ética para a Saúde

ASSUNTO ..:Parecer nº 074A/2019

Levo ao conhecimento do Conselho Diretivo o Parecer nº 074A/2019 sobre o Estudo "Caraterização da doença inflamatória intestinal em Portugal", aprovado na reunião de 30 de julho de 2019 por unanimidade que anexa uma adenda ao protocolo com os elementos em falta, conforme o solicitado pelo Data Protection Officer (DPO) na sua comunicação º 1 (P.26/19-DPO).

À consideração superior

Ana Paula Capela
Ana Paula Capela
(Assessoria CES/UIC)

Ao DPO
para análise
e parecer

09.12.2019

Paula Duarte
Paula Duarte
Vogal do CD

Recebido em 15/1/20

Rua Santa Catarina, 1288
4000-447 Porto
Tel 220 411 000
Fax 220 411 005
arsn@arsnorte.min-saude.pt
www.arsnorte.min-saude.pt

Comissão de Ética para a Saúde da Administração Regional de Saúde do Norte, I.P.

PARECER Nº 074/2019

Sobre o estudo T1093 – "Caracterização da Doença Inflamatória Intestinal em Portugal"

A – Relatório

1. A Comissão de Ética para a Saúde (CES), da Administração Regional de Saúde do Norte I.P. (ARSN), iniciou a apreciação do Processo n.º T1093, Mafalda Santiago Alves Pereira estudante de Doutoramento da FMUP, Fernando José Magro Dias Orientador do projeto de Doutoramento e Professor agregado do Departamento de Farmacologia e Terapêutica da FMUP, Assistente médico no Serviço de Gastrenterologia, Centro Hospitalar São João e membro da Direção do Grupo de Estudo da Doença Inflamatória Intestinal (GEDII), e Cláudia Camila Dias Investigador Pos-Doc no grupo NanoStima, Departamento de Medicina da Comunidade Informação e Decisão em Saúde da FMUP e Professora associada do Departamento de Medicina da Comunidade Informação e Decisão em Saúde da FMUP, na sequência do pedido de parecer dirigido a esta Comissão pelos investigadores, relativo ao estudo intitulado "Caracterização da Doença Inflamatória Intestinal em Portugal".
2. Fazem parte do processo de avaliação o requerimento e o protocolo de investigação.
3. Trata-se de um estudo que pretende dar resposta à seguinte questão: Qual o "burden" associado à Doença Inflamatória Intestinal em Portugal através da utilização de dados secundários de diversas bases de dados administrativas desde o ano 2000? O projeto tem ainda como objetivo a caracterização da DII através da estimação de tendências de internamento, reinternamento e cirurgia assim como os seus custos associados. Pretende-se finalmente estimar a prevalência da DII e estudar os efeitos da terapêutica biológica na doença.
4. Sendo um estudo faseado e de abrangência nacional, as atividades a realizar na ARS Norte darão resposta contribuirão concretamente para o objetivo de caracterizar a Prevalência da Doença Inflamatória Intestinal em Portugal.
5. Concretamente para execução do ponto A.4. pretende-se extrair e analisar dados do processo clínico dos utentes frequentadores dos cuidados de saúde primários que apresentem registo do problema Enterite crónica/Colite ulcerosa (D94) na ARS Norte. Serão colhidas exclusivamente as seguintes variáveis: Idade à data do diagnóstico; Sexo; Código unidade de saúde (região) ou outra que nos indique concelho ou distrito; Diagnostico; Data do diagnóstico de Enterite crónica/Colite ulcerosa (em casos de múltiplas consultas colocar a data mais antiga); Referenciação para consulta de especialidade hospitalar; Nº

Rua Santa Catarina, 1288
4000-447 Porto
Tel 220 411 000
Fax 220 411 005
arsn@arsnorte.min-saude.pt
www.arsnorte.min-saude.pt

total de consultas; número de consultas por doente após diagnóstico; Os dados colhidos serão desde o ano 2000 até ao presente.

6. Segundo os autores, foi dirigido um pedido de extração de dados aos Serviços Partilhados do Ministério da Saúde (SPMS) que realizarão o processo de extração de informação. Terá sido por indicação dos SPMS que foi solicitado o parecer da comissão de ética da ARS Norte relativamente ao estudo, antes de se proceder à extração dos dados indicados no ponto A.5.

B – Identificação das questões com eventuais implicações éticas:
B.1. Reconhece-se relevância e interesse no estudo e nos resultados esperados.
B.2. Os dados recolhidos são adequados à dimensão em estudo.
B.3. Não há intervenção direta sobre utentes ou profissionais.
B.4. A extração de dados será realizada pelos Serviços Partilhados do Ministério da Saúde.
B.5. Os dados serão tratados garantindo a confidencialidade e o anonimato dos utentes.

C – Conclusões:

1. A CES reconhece relevância e interesse na realização do estudo.
2. Face ao exposto, a CES delibera emitir parecer favorável à autorização deste estudo no que respeita concretamente a extração e análise de dados identificados no ponto A.5.

Aprovado em reunião do dia 30 de julho de 2019, por unanimidade.

O relator,

Doutor Tiago Taveira-Gomes

O Presidente da Comissão de Ética para a Saúde da ARS Norte IP

Professor Doutor Alberto Pinto Hespanhol

Rua Santa Catarina, 1288
4000-447 Porto
Tel 220 411 000 arsn@arsnorte.min-saude.pt
Fax 220 411 005 www.arsnorte.min-saude.pt

4. Componente de Disseminação | Dissemination Component

[redacted]

-------- Mensagem Original --------
Assunto: Clinical and Translational Gastroenterology Editorial Decision - [EMID:969f2c9e220f85e7]
Data: 2022-02-09 15:08
Remetente: "Clinical and Translational Gastroenterology" <em@editorialmanager.com>
Para: "Fernando Magro" [redacted]
Responder a: "Clinical and Translational Gastroenterology" <journals@gi.org>

CTG-21-0382R1
Incidence trends of Inflammatory Bowel Disease in a Southern-European country: a mirror of the western world?

Dr. Magro,

Thank you for submitting your manuscript to Clinical and Translational Gastroenterology. Your manuscript has been reviewed by the Editorial Board, and we are extremely pleased to accept it for publication. The publisher, Wolters Kluwer, will place the PDF of your accepted paper on the Latest Articles section of the journal site, labeled "Accepted Manuscript." After copyediting and typesetting, you'll be given the chance to view your paper one final time before issue publication.

You will be receiving an Open Access Publication Charge letter from the Journal's Publisher, Wolters Kluwer, and within instructions on how to submit any open access charges. The email will be from publicationservices@copyright.com with the subject line 'Please Submit Your Open Access Article Publication Charge(s)'. Please complete payment of the Open Access charges within 48 hours of receipt.

PRODUCTION AND SUBSEQUENT PUBLICATION OF YOUR ARTICLE WILL BEGIN IMMEDIATELY UPON RECEIPT OF YOUR PAYMENT.

The APC is charged on acceptance of the article and must be paid within 30 days by the author, funding agency or institution. Payment must be received in full for the article to be published.

We sincerely appreciate that you shared your manuscript with us and know that it will be of significant interest to the readers of Clinical and Translational Gastroenterology.

Yours sincerely,
Eugenia Shmidt, MD
Associate Editor

Brian C. Jacobson, MD, MPH
Editor-in-Chief
Clinical and Translational Gastroenterology

In compliance with data protection regulations, you may request that we remove your personal registration details at any time. (Use the following URL: https://www.editorialmanager.com/ctg/login.asp?a=r).
Please contact the publication office if you have any questions.