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ORIGINAL REPORT

Estimating the prevalence of inflammatory bowel disease in Portugal using a pharmaco-epidemiological approach†

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SUMMARY

Purpose To estimate inflammatory bowel disease (IBD) prevalence in Portugal from 2003 to 2007, and to obtain disease, sex and age specific estimates.

Methods A pharmaco-epidemiological approach based on intestinal anti-inflammatory (IAI) drugs consumption was used. Proportion of patients taking IAI drugs and mean prescribed daily dose (PDD) were estimated from a sample of 513 IBD patients. Assumptions were made about unknown parameters and sensitivity analysis performed: drug compliance (80% in base case; range 70–85%) and proportion of sulphasalazine used in IBD (52%; range 40–80%). Sex and age specific estimates were based on a proposed methodological extension and results from a nationwide ($n = 5893$) cross-sectional study.

Results IBD prevalence increased from 86 patients per 100 000 in 2003 to 146 in 2007. Regions more affected were Lisboa and Porto (173 and 163 per 100 000 in 2007, respectively). Prevalence increased from 42 and 43 per 100 000 in 2003 to 71 and 73 in 2007, respectively for ulcerative colitis (UC) and Crohn's disease (CD). In 2007, prevalence was higher in the 40–64 age stratum for UC (99 per 100 000) and in the 17–39 stratum for CD (121). Prevalence was consistently higher in females.

Conclusions Portugal is half way between countries with the highest and lowest IBD prevalence, but is steeply making the road to the highest-level group. Despite limitations of the proposed methods, assumptions were reasonable and estimates seem to be valid. Feasibility and comparability of this methodology makes it an interesting tool for future studies on IBD epidemiology. Copyright © 2010 John Wiley & Sons, Ltd.

KEY WORDS — drug-consumption data; epidemiologic methods; inflammatory bowel disease; intestinal anti-inflammatory drugs; pharmacoepidemiology; prevalence

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INTRODUCTION

Inflammatory bowel disease (IBD) comprises two distinct pathologic entities, Crohn's Disease (CD) and Ulcerative Colitis (UC), and is one of the most serious conditions of the gastrointestinal tract. Availability of adequate statistics allows proper planning and distribution of healthcare resources and a better understanding of diseases aetiology and prognosis.[1–3] In Portugal statistics on IBD epidemiology are scarce.

Generally the estimation of epidemiological frequency measures comes from population surveys or disease registries.[1–3] Given the fact that IBD is not a particularly frequent occurrence, population studies are organizationally and financially difficult to implement and hard to update along time. Therefore, alternative and less demanding methods could have great importance in this context.

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Treatment and management of IBD (CD and UC) heavily depends on drugs. The most typically used drugs for this indication are:[4] intestinal anti-inflammatory (IAI) drugs, systemic corticosteroids, imunossupressors, biologic therapy and antibiotics. One of these drug groups—IAI drugs—is quite specific to IBD, and since their consumption depends on the number of affected subjects in the population, relaying on some plausible assumptions it is possible to obtain good estimates of IBD prevalence from drug consumption data.[5–7] This methodology is of course much less organizationally and financially demanding, and gives estimates with acceptable precision and validity.[5–8]

The aim of this study was to estimate IBD prevalence in Portugal and to obtain disease (UC and CD), sex and age specific prevalence estimates, using a pharmacoepidemiological approach based on IAI drugs consumption.

METHODS

In this study IBD prevalence in Portugal was estimated according to the method proposed by Sartor and Walkiers.[7] This method requires data on national drug sales of tracer drugs, estimates of daily drug consumption and demographic data. Tracer drugs should ideally be taken only by patients suffering from the disease and regularly all year long.[7] IAI drugs (sulphasalazine and mesalazine) are indicated for the treatment of IBD, and in Portugal nearly all patients in the country are currently taking one of these two drugs on a daily basis.[9]

IBD prevalence estimates

The method proposed by Sartor and Walkiers[7] defines the following estimator for the disease prevalence ($\hat{P}$):

$$\hat{P} = \frac{\hat{n}_e}{N} = \frac{\sum_{i=1}^{k} \hat{n}_i \cdot \hat{w}}{N} = \frac{\sum_{i=1}^{k} \frac{V_i}{\hat{c}_i} \cdot \hat{w}}{N}$$

Where $\hat{n}_e$ is the estimated number of patients with the disease and taking drugs, $\hat{n}_i$ is the estimated number of patients taking the ith class of drugs, V_i is the total amount of the ith class of drugs sold in 1 year, $\hat{c}_i$ is the estimated mean intake of the ith drug class by patients in 1 year, N is the total population living in this region and $\hat{w}$ is a weighting factor that corrects for the proportion of patients taking combinations of two or more classes of drugs, avoiding double counting. To estimate c_i we should preferably have the mean intake of the ith class of drugs in 1 year, given by a cross-sectional survey on patients with the disease.

In this study, the IAI drugs sulphasalazine and mesalazine were included in the analysis. Direct estimates of the proportion of IBD patients taking these two drugs and their mean yearly intake (c_i) were obtained from a cross-sectional study on IBD patients. Based on these direct estimates and the yearly national total amount of IAI drugs consumed (V_i), it was possible to obtain an estimate of the disease prevalence ($\hat{P}$). Sulphasalazine and mesalazine have the same therapeutic goal and mechanism in IBD treatment and are not taken concurrently. Thus the weighting factor $\hat{w}$ was assumed to be equal to 1, implicitly assuming that none of the patients were taking combinations of the included drugs.

In order to further correct the prevalence estimation model and obtain more valid estimates, three additional adjustment factors were considered important and included in the model.

First, because some of the sulphasalazine sold is used for other indications than IBD, an adjustment was introduced based on the proportion of the total amount of sulphasalazine sold specifically for IBD indication. In the Portuguese Formulary, mesalazine is only indicated for IBD treatment, whereas sulphasalazine is also indicated as a second line therapy for the treatment of rheumatoid arthritis (RA). There are no records of other indications or off-label use of these drugs in Portugal. It is then safe to assume that the total amount of mesalazine sold was used by IBD patients, but in contrast only a certain proportion of the total amount of sulphasalazine was actually prescribed to IBD patients. Thus an adjustment was introduced in order to take into account the proportion of sulphasalazine for other indications than IBD. The limited evidence about the proportion of IBD patients among sulphasalazine users comes from prescription-monitoring studies,[10–12] and indicates estimates between 52 and 63%. In the base case scenario of our prevalence estimation model a value of 52% was assumed, but sensitivity analysis was performed and estimates assuming proportions of 40, 52, 60, 70 and 80% are presented.

Second, because drug non-compliance could affect the proposed prevalence estimation, as this is based on total amount of drugs sold, an adjustment for drug non-compliance was introduced. Non-compliers are not taken into account when total drug sales are used to estimate disease prevalence, thus a more adequate prevalence estimate was obtained adjusting for the proportion of patients actually complying with the drug regimen. Estimates of IAI drugs compliance in IBD patients come from several clinical trials evaluating these drugs and is generally around 80%, but in some cases it may be as low as 50%.[13–15] In the base case scenario of our prevalence estimation model a value of 80% was assumed, but sensitivity analysis was performed and estimates assuming proportions of 70, 75, 80 and 85% are presented.

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Third, because some of the IBD patients may not be using IAI drugs, proportions of UC and CD patients actually using IAI drugs were estimated from a national cross-sectional study and adjustment factors were introduced in the prevalence estimation model. This adjustment allowed us to account for some of the CD and UC patients that, for some reason, are not taking IAI drugs (for example, some UC patients with isolated proctitis or some patients on immunosuppressant or biologic therapies).

Sartor and Walkiers[7] also defined an estimator for the variance of $\hat{P}$ using the delta method:[16–18]

$$\mathrm{Var}(\hat{P}) \approx \sum_{i=1}^{k} \left[\frac{\partial P}{\partial c_i}\right]^2 \cdot \mathrm{Var}(c_i) + 2 \cdot \sum_{i \neq j} \left[\frac{\partial P}{\partial c_i}\right] \cdot \left[\frac{\partial P}{\partial c_j}\right] \cdot \mathrm{Cov}(c_i, c_j) + \sum_{j=2}^{k} \left[\frac{\partial P}{\partial p_j}\right]^2 \cdot \mathrm{Var}(p_j)$$

Where $\hat{p}_j$ represents the estimate of the proportion of patients taking a combination of $j = \{2, 3, \ldots, k\}$ drug classes concurrently, used to calculate the weighting factor $\hat{w}$, and $(\partial P/\partial c_i)$, $(\partial P/\partial c_j)$ and $(\partial P/\partial p_j)$ are the partial derivatives of P with respect to c_i, c_j and p_j, evaluated at their expected values, and $\mathrm{Cov}(c_i, c_j)$ is the covariance between c_i and c_j. The 95% confidence interval (95%CI) may be derived assuming the asymptotic normality of this estimator.[17]

In this case, values for c_i were estimated in a cross-sectional study on a sample of IBD patients and were used to calculate the variance of the prevalence estimate and 95%CI.

Disease, sex and age specific prevalence estimates

IBD is a heterogeneous pathologic entity, therefore it would be important to have prevalence estimates specific for CD and UC. Moreover, it would be important to have estimates specific for the different sex and age strata. These may not be directly obtained from the previous method. So we propose an extension to Sartor and Walkiers' approach based on the fact that the disease specific prevalence (P_i) for disease $i = \{1, 2, \ldots, p\}$ and the sex and age specific prevalence (P_{ijk}) are calculated as:

$$P_i = \frac{n_i}{N} \quad P_{ijk} = \frac{n_{ijk}}{N_{jk}}$$

Where n_i is the number affected by the disease i, N is the total number of individuals in the population, n_{ijk} is the number affected by the disease i and pertaining to stratum $j = \{1, 2, \ldots, q\}$ of sex and $k = \{1, 2, \ldots, r\}$ of age and N_{jk} is the total number in the population pertaining to stratum $j = \{1, 2, \ldots, q\}$ of sex and $k = \{1, 2, \ldots, r\}$ of age.

It is easy to see that, if there is a set of mutually exclusive and jointly exhaustive disease, sex and age strata, the total number of patients is equal to

$$n_e = \sum_{i,j,k} (\pi_{ijk} \cdot n_e)$$

Where π_{ijk} are the proportions of patients pertaining to each stratum.

Given that π_{ijk} are calculated as

$$\pi_{ijk} = \frac{n_{ijk}}{n_e}$$

If there are adequate estimates of π_{ijk} available (for example, from a representative sample, preferably large, of all national IBD patients in the considered time period), it is possible to estimate n_{ijk} and P_{ijk} as follows:

$$\hat{n}_{ijk} = \hat{\pi}_{ijk} \cdot \hat{n}_e \quad \text{and} \quad \hat{P}_{ijk} = \frac{\hat{n}_{ijk}}{N_{ijk}} = \frac{\hat{\pi}_{ijk} \cdot \hat{n}_e}{N_{ijk}}$$

The Portuguese IBD Study Group (Grupo de Estudos de Doença Inflamatória Intestinal—GEDII—www.gedi.med.up.pt), performed, in 2006, a large national cross-sectional study on IBD patients ($n = 5893$).[19,20] Using the results of this study we obtained estimates for the proportions of patients in each disease, sex and age specific stratum ($\hat{\pi}_{ijk}$) in our country, and estimates of $\hat{n}_{ijk}$ and $\hat{P}_{ijk}$.

To complement the inference procedure, the variance of the prevalence estimators—$Var(\hat{P}_{ijk})$—may be derived using the delta method:[16–18]

$$\mathrm{Var}(\hat{P}_{ijk}) \approx \left[\frac{\partial P_{ijk}}{\partial n_e}\right]^2 \cdot \mathrm{Var}(n_e) + \left[\frac{\partial P_{ijk}}{\partial \pi_{ijk}}\right]^2 \cdot \mathrm{Var}(\pi_{ijk})$$

Where $(\partial P_{ijk}/\partial n_e)$ and $(\partial P_{ijk}/\partial \pi_{ijk})$ are the partial derivatives of P_{ijk} with respect to n_e and π_{ijk}, evaluated at their expected values. Covariance terms were dropped because n_e and π_{ijk} are independently estimated and assumed independent. The 95%CI may be derived assuming the asymptotic normality of these estimators.[17]

Statistical analysis was performed using the software program SPSS® 15.0.

Sources of data

Drug sales data. Yearly total national sales, for all drugs included in the ATC group A07E—IAI Agents—were obtained, from 2003 to 2007, from IMS Health (an international consulting company in the area of pharmaceutical marketing), corresponding to the total amount sold from wholesalers to

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community pharmacies. Only formulations for systemic use were considered in the analysis.

Drug use and dosage data and IBD epidemiology data. The Portuguese IBD Study Group (GEDII- www.gedi.med.up.pt), as previously mentioned, performed, between 2005 and 2006, a large national cross-sectional study on IBD patients, that included almost half of the estimated number of patients nationally ($n = 5893$). This study has been previously described.[19,20] In brief, from September 2005 until December 2006, all medical doctors in Portugal seeing IBD patients (gastroenterologists, paediatricians, surgeons, and general practioners) were invited to include patients in a national IBD database registry. In this initial cross-sectional study 77 Portuguese MDs coming from 33 medical centres, distributed all over Portugal, from north to south, including the islands of Madeira and Azores, participated in the study and recruited 5893 IBD patients. Patient registration was carried out through a Web-based system. The patients were from quaternary and tertiary referral hospitals (48.6%) and regional hospitals plus private practice (50.7%). A small percentage (0.5%) was included by paediatricians working in referral paediatric centres. All participating MDs had at least three meetings per year to discuss and review inclusion criteria. All patients were included according to strict international diagnostic criteria for IBD.[21–23] Data on date of onset of symptoms and diagnosis, type of clinical onset, extent of disease, familial occurrence of IBD, presence of extra-intestinal manifestations, type of colonic, anal and rectal involvement, previous history of abdominal abscesses and/or fistulas, clinical course, Montreal classification categories, response to steroids, immunosuppression and/or biologic treatment, as well as previous abdominal or anal surgery were systematically collected for every recruited patient.

In order to estimate the proportion of IBD patients in Portugal taking IAI drugs and their mean yearly intake (c_i) data from the national cross-sectional study were used. A subsample of IBD patients, part of the large national cross-sectional study, were specifically asked about IAI drug use, daily drug doses and consumption frequency. This subsample included patients, from the larger initial sample, willing and already recruited to participate in an ongoing prospective follow-up study. Data were available on IAI drugs use for 3587 IBD patients (1936 UC and 1651 CD patients). Seventy five per cent of the patients ($n = 2698$) were using regularly IAI drugs—1460 (75%) of UC patients and 1238 (75%) of CD patients. For 513 IBD patients, data on daily dose and drug use pattern were available, allowing the estimation of mean yearly intake (c_i) for mesalazine and sulphasalazine.

Demographic data. Demographic data including total national population by age, sex and district of residence were obtained from the national official statistics agency.[24]

RESULTS

In Table 1 the total amount of IAI drugs sold in the 20 Portuguese Districts and national totals are shown from 2003 to 2007. An increase in the amount of drugs sold is evident in the period analysed.

Drug use and mean yearly drug intake

Data on IAI drugs consumption were available for 3587 IBD patients. Seventy five per cent of the patients ($n = 2698$) reported regular use of systemic formulations of IAI drugs. There were 1936 UC patients and 1651 CD patients in the sample and regular IAI drug use was reported by 74.6% ($n = 1460$) of UC patients and 75.0% ($n = 1238$) of CD patients. These observed proportions of patients actually using IAI drugs among UC and CD patients were introduced as adjustment factors in the prevalence estimation model, in order to take into account IBD patients that, for some reason, were not taking IAI drugs.

In a sub-sample of 513 IBD patients, data on IAI drugs daily dose and drug use pattern were available, allowing the estimation of mean yearly drug intake (c_i). This subsample had 317 UC and 196 CD patients, 57% were of female gender, had mean age of 44 years (SD = 15 years) and a median disease duration of 6 years (25th percentile = 3 years and 75th percentile = 11 years). Mesalazine systemic formulations were taken by 469 (91%) of the patients and sulphasalazine formulations by 44 (9%) patients. None of the patients was taking concurrently mesalazine and sulphasalazine systemic formulations. All patients reported taking the systemic IAI formulations on a daily basis, and the mean of reported daily doses was 2.899 g/day (SD = 0.303 g) for mesalazine and 2.946 g/day (SD = 0.329 g) for sulphasalazine. Thus the estimated mean yearly drug intake used in the prevalence estimation model was for mesalazine 1058.199 g/year (SD = 110.699 g) and for sulphasalazine 1075.270 g/year (SD = 120.011 g).

When comparing UC and CD patients, a significantly more frequent use of sulphasalazine among CD patients was observed (4.4% for UC and 15.3% for CD patients; $p < 0.001$). No statistically significant differences existed between means of reported daily doses in UC and CD patients for sulphasalazine (2.833 g/day and 3.000 g/day, respectively; $p = 0.205$). However, a small but significant difference in mean daily dose of mesalazine was observed between

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Table 1. Total amount of intestinal anti-inflammatory drugs (ATC group A07E) sold in the 20 Portuguese districts and national totals ($\times 10^3$ mg) from 2003 to 2007

District	Year														
	2003			2004			2005			2006			2007		
	Amount of drugs sold ($\times 10^3$ mg)			Amount of drugs sold ($\times 10^3$ mg)			Amount of drugs sold ($\times 10^3$ mg)			Amount of drugs sold ($\times 10^3$ mg)			Amount of drugs sold ($\times 10^3$ mg)		
	Mesalazine	Sulphasalazine	Total	Mesalazine	Sulphasalazine	Total	Mesalazine	Sulphasalazine	Total	Mesalazine	Sulphasalazine	Total	Mesalazine	Sulphasalazine	Total
Açores	119 595	41 490	161 085	99 615	55 920	155 535	99 090	49 830	148 920	161 610	72 720	234 330	195 024	105 000	300 024
Aveiro	359 490	100 800	460 290	396 050	112 740	508 790	444 085	122 390	566 475	480 288	136 240	616 528	495 980	160 860	656 840
Beja	48 665	15 570	64 235	65 530	17 340	82 870	77 201	24 150	101 351	106 692	25 960	132 652	141 707	28 500	170 207
Braga	393 070	70 260	463 330	473 230	74 340	547 570	600 346	81 760	682 106	687 032	85 920	772 952	700 965	92 880	793 845
Bragança	50 665	22 620	73 285	59 015	19 260	78 275	75 757	21 090	96 847	105 309	28 290	133 599	105 033	29 580	134 613
Castelo Branco	98 505	41 400	139 905	113 730	43 020	156 750	138 726	45 300	184 026	165 582	50 220	215 802	172 747	60 360	233 107
Coimbra	167 680	87 360	255 040	174 240	97 410	271 650	196 566	104 890	301 456	220 435	122 220	342 655	233 979	124 740	358 719
Évora	58 170	30 270	88 440	72 250	34 110	106 360	80 126	37 940	118 066	91 518	41 010	132 528	98 044	40 890	138 934
Faro	140 035	46 320	186 355	186 150	54 150	240 300	217 021	61 610	278 631	230 177	60 420	290 597	283 505	70 950	354 455
Guarda	54 390	29 250	83 640	61 490	32 040	93 530	72 555	31 120	103 675	88 137	29 910	118 047	96 501	40 140	136 641
Leiria	252 685	103 110	355 795	283 145	115 200	398 345	298 241	132 120	430 361	326 927	148 550	475 477	353 296	157 380	510 676
Lisboa	1 016 655	493 950	1 510 605	1 252 920	528 600	1 781 520	1 618 409	572 760	2 191 169	1 875 642	634 530	2 510 172	2 092 561	698 490	2 791 051
Madeira	97 070	32 670	129 740	112 250	32 280	144 530	144 074	36 000	180 074	154 783	29 670	184 453	199 169	26 520	225 689
Portalegre	45 975	23 010	68 985	51 660	26 220	77 880	57 560	29 910	87 470	72 438	33 090	105 528	78 416	37 740	116 156
Porto	1 046 760	227 640	1 274 400	1 223 305	256 020	1 479 325	1 505 979	284 320	1 790 299	1 654 800	317 660	1 972 460	1 697 025	366 960	2 063 985
Santarém	195 820	92 970	288 790	203 690	107 400	311 090	244 599	127 820	372 419	308 580	129 410	437 990	353 087	146 760	499 847
Setúbal	350 935	125 220	476 155	387 630	138 900	526 530	678 842	162 520	841 362	617 521	192 910	810 431	592 584	211 440	804 024
Viana do Castelo	140 470	25 680	166 150	156 980	29 730	186 710	180 857	30 930	211 787	191 770	31 260	223 030	210 366	39 270	249 636
Vila Real	106 240	18 660	124 900	117 845	20 970	138 815	146 736	21 830	168 566	167 122	22 510	189 632	165 440	30 990	196 430
Viseu	142 285	72 210	214 495	157 590	78 630	236 220	197 022	78 480	275 502	228 874	74 220	303 094	256 902	91 560	348 462
National total	4 885 160	1 700 460	6 585 620	5 648 315	1 874 280	7 522 595	7 073 792	2 056 770	9 130 562	7 935 237	2 266 720	10 201 957	8 522 331	2 561 010	11 083 341

UC and CD patients (2.872 g/day and 2.946 g/day, respectively; $p = 0.011$).

IBD prevalence estimates

The data available allowed the estimation of $\hat{n}_e$ and the prevalence of the disease from 2003 to 2007. The prevalence estimation model took into account the proportion of UC and CD patients actually taking IAI drugs and the estimated mean yearly drug intake for mesalazine and sulphasalazine previously described. Additionally, the model took into account two parameters that were subject to sensitivity analysis—(1) the proportion of sulphasalazine used for IBD indication and (2) the magnitude of IAI drugs non-compliance. In the base case scenario of the prevalence estimation model 52% of the total amount of sulphasalazine was assumed to be for IBD indication and an 80% IAI drugs compliance was assumed.

Figure 1 shows the results of the national IBD prevalence estimation model and the sensitivity analysis performed. In the base case scenario, national IBD prevalence varies from 86 per 100 000 persons (95%CI [63–110]) in 2003 to 146 per 100 000 persons (95%CI [116–175]) in 2007. Results of sensitivity analysis are depicted in Figure 1, varying from the best case (lowest prevalence) scenario (estimates based on an assumed proportion of sulphasalazine used by IBD patients of 40% and drug compliance of 85%) to the worst case (highest prevalence) scenario (assumed proportion of sulphasalazine used by IBD patients of 80% and assumed drug compliance of 70%). Sensitivity analysis estimates vary from 79 (95%CI [57–100]) to 107 (95%CI [79–134]) in 2003; and from 133 (95%CI [106–160]) to 178 (95%CI [144–213]) in 2007.

Disease prevalence and estimated number of IBD patients ($\hat{n}_e$) are presented in Table 2 for the 20 Portuguese Districts, from 2003 to 2007, considering the base case scenario. The increase in IBD prevalence, from 2003 to 2007, was consistent in all Districts. The Districts with higher IBD prevalence, consistently throughout the analysed period, are Porto and Lisboa (regions more developed, richer and with younger population, on the littoral part of the country). Figure 2 shows the geographical distribution pattern of IBD prevalence for the year 2007, based on the base case scenario. A north–south geographical distribution pattern is not evident at the national level.

Disease, sex and age specific prevalence estimates

In Table 3 the observed frequencies and percentages for each disease, sex and age strata found in the large

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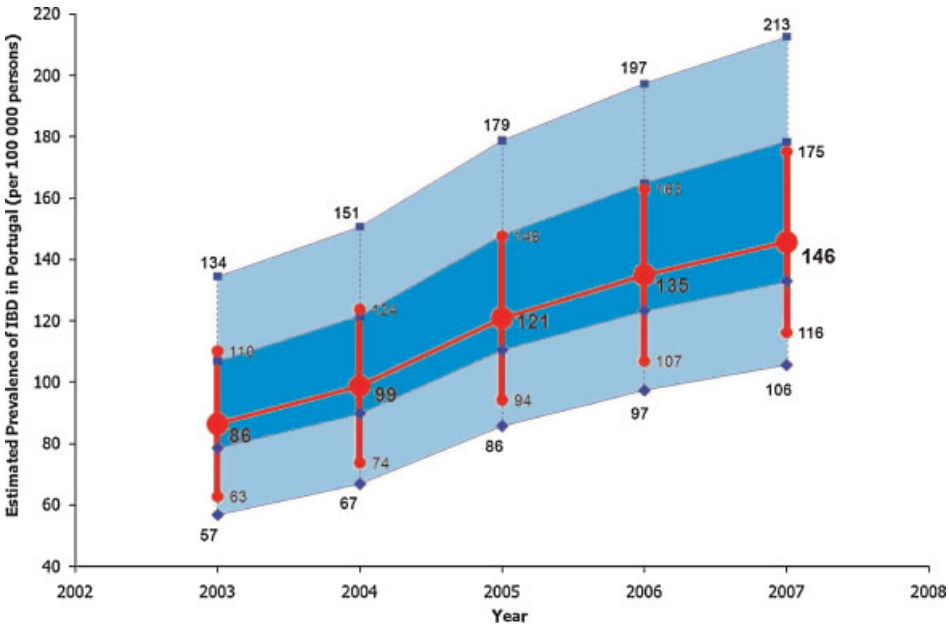

Figure 1. Estimated prevalence of IBD in Portugal (per 100 000 persons) based on national intestinal anti-inflammatory drugs (ATC group A07E) consumption data, from 2003 to 2007. Point estimates and 95% confidence intervals for the base case model and point estimates and 95% CI for estimates derived by sensitivity analysis taking into account five different levels for the proportion of Sulphasalazine prescribed for IBD and four different levels of drug compliance (best case and worst case scenarios).

Note: Prevalence estimates are derived from a model based on total national consumption of IAI drugs (sulphasalazine and mesalazine) and an estimate of the mean individual prescribed daily dose calculated from a sample of IBD patients. In the base case scenario (red circles and red thick line) we assume that 52% of sulphasalazine was taken by IBD patients and the population drug compliance was 80%. 95% confidence intervals for the base case scenario are presented (red thick error bars). Sensitivity analysis was performed having into account two variables in the model: (1) proportion of sulphasalazine taken by IBD patients (five levels assumed: 40%, 52%, 60%, 70% and 80%) and (2) patients population compliance with IAI drugs prescriptions (four levels of compliance assumed: 70%, 75%, 80% and 85%). The central dark blue area represent the intervals were point estimates of the different sensitivity analysis scenarios are located, varying from the best case scenario (blue diamonds and thin blue line; estimates based on an assumed proportion of sulphasalazine used by IBD patients of 40% and assumed drug compliance of 85%) to the worst case scenario (blue squares and thin blue line; assumed proportion of sulphasalazine used by IBD patients of 80% and assumed drug compliance of 70%). The upper and lower light blue areas represent the upper bound of 95% CI for the worst case scenario and the lower bound of 95% CI for the best case scenario. With this representation it is possible to fully evaluate the uncertainty in the prevalence estimation models (stochastic components and deterministic sensitivity analysis components).

national cross-sectional study on IBD patients, performed by the Portuguese IBD Study Group in 2006 ($n = 5893$), are presented in the left columns for each diagnosis category. Estimates of disease prevalence ($\hat{P}_{ijk}$) for each sex and age strata, for 2007, based on the base case scenario, are also presented in Table 3. Prevalence increased from 42 (95%CI [30–54]) and 43 (95%CI [31–55]) per 100 000 in 2003 to 71 (95%CI [56–85]) and 73 (95%CI [58–87]) in 2007, respectively for UC and CD. It is evident from Table 3 that estimated prevalence of UC and CD are similar and follow a similar age and sex distribution pattern. Prevalence is higher in the 40–64 age stratum for UC and in the 17–39 age stratum for CD. Prevalence is moderately but consistently higher in female gender.

DISCUSSION

Despite the limitations of the prevalence estimation methods presented and its proposed extension, it seems reasonable to draw four main conclusions. First, IBD prevalence in Portugal has increased from 86 per 100 000 in 2003 to 146 in 2007. Second, this increase was consistent in all Portuguese districts, no north–south geographical distribution gradient was detected at the national level and the districts more affected by IBD were Lisboa and Porto, with a prevalence that reached 173 and 163 per 100 000 in 2007, respectively. Third, the estimated prevalence of UC increased from 42 per 100 000 in 2003 to 71 in 2007; and the prevalence of CD increased from 43 per 100 000 in 2003 to 73 in 2007. Fourth, prevalence of UC was higher in the 40–64 age stratum, prevalence of CD was higher in the 17–39 age stratum and females had slightly higher prevalence than males.

IBD prevalence estimates reported for European countries are heterogeneous.[1–3] The highest prevalence has been found in the UK (from 122 to 144 per 100 000 persons for UC and 214 to 243 for CD),[25,26] Denmark[27]

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Table 2. Total population, estimated number of IBD patients and estimated IBD prevalence (per 100 000 persons) for the 20 Portuguese districts from 2003 to 2007

District	2003			2004			2005			2006			2007		
	Total population*	Estimated n° of IBD patients†	Estimated prevalence IBD‡	Total population*	Estimated n° of IBD patients†	Estimated prevalence IBD‡	Total population*	Estimated n° of IBD patients†	Estimated prevalence IBD‡	Total population*	Estimated n° of IBD patients†	Estimated prevalence IBD‡	Total population*	Estimated n° of IBD patients†	Estimated prevalence IBD‡
Açores	240 024	222	92.3	241 206	202	83.6	242 241	196	80.9	243 018	313	128.7	244 006	391	160.4
Aveiro	722 753	647	89.5	727 041	714	98.2	730 372	797	109.1	732 867	865	118.0	734 195	910	123.9
Beja	156 664	89	56.9	156 153	117	74.9	155 254	141	90.7	154 325	189	122.3	153 091	246	160.6
Braga	845 054	675	79.9	851 337	804	94.5	856 171	1010	118.0	859 918	1150	133.7	862 191	1177	136.5
Bragança	146 103	98	67.0	145 486	108	74.5	144 467	136	94.2	143 337	188	131.4	142 049	189	133.1
Castelo Branco	204 013	188	92.3	203 314	214	105.0	201 983	255	126.1	200 705	301	149.9	199 094	320	160.9
Coimbra	437 838	334	76.3	437 642	352	80.5	437 086	394	90.1	436 056	445	102.1	434 311	468	107.9
Évora	170 981	116	67.8	171 130	141	82.5	170 810	157	91.7	170 535	177	103.8	169 788	187	110.2
Faro	405 380	258	63.5	411 468	336	81.8	416 847	391	93.8	421 528	411	97.4	426 386	503	118.0
Guarda	176 731	109	61.7	176 086	123	69.6	175 090	139	79.5	173 831	163	93.6	172 304	184	106.8
Leiria	469 159	480	102.4	472 895	538	113.8	475 662	575	121.0	477 967	634	132.6	479 499	682	142.3
Lisboa	2 190 197	1997	91.2	2 203 503	2396	108.7	2 215 319	3007	135.7	2 224 426	3461	155.6	2 232 700	3854	172.6
Madeira	243 007	179	73.7	244 286	203	82.9	245 197	256	104.2	245 806	267	108.8	246 689	335	135.6
Portalegre	122 386	91	74.2	121 653	102	84.1	120 581	115	95.0	119 543	141	117.6	118 141	154	130.1
Porto	1 796 573	1830	101.8	1 805 015	2130	118.0	1 812 325	2598	143.3	1 817 986	2859	157.2	1 820 752	2965	162.8
Santarém	461 562	383	82.9	463 676	407	87.7	464 740	488	104.9	465 599	590	126.6	466 011	674	144.5
Setúbal	819 248	653	79.7	829 007	722	87.0	837 696	1199	143.1	845 858	1127	133.2	853 445	1102	129.2
Viana do Castelo	251 014	242	96.3	251 937	271	107.5	252 272	309	122.6	252 011	327	129.7	251 676	362	144.0
Vila Real	221 567	182	82.2	221 218	202	91.4	220 172	248	112.8	218 935	281	128.3	217 338	285	131.2
Viseu	394 431	282	71.5	395 202	311	78.7	395 307	373	94.4	394 844	420	106.3	393 909	478	121.3
National total	10 474 685	9053	86.4	10 529 255	10 393	98.7	10 569 592	12 782	120.9	10 599 095	14 306	135.0	10 617 575	15 466	145.7

*Total population for each district based on data from the national statistics authority (Instituto Nacional de Estatística—INE).
†Estimated number of IBD patients for the base case scenario (52% of sulphasalazine used by IBD patients and drug compliance of 80%).
‡Estimated prevalence (per 100 000 persons) of IBD for the base case scenario.

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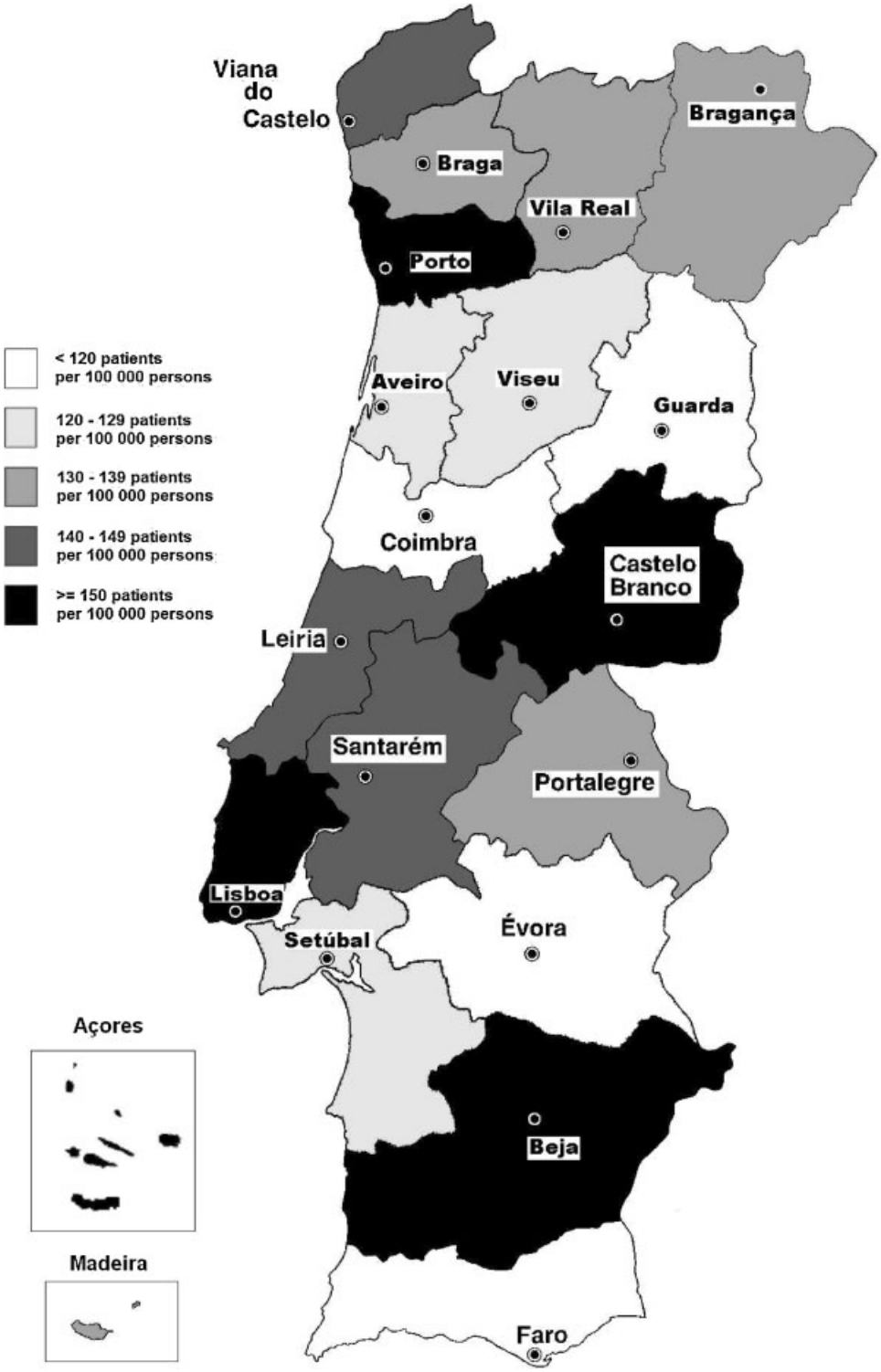

Figure 2. Prevalence of inflammatory bowel disease in the 20 districts of Portugal (patients per 100 000 persons) for the year of 2007, estimated by a pharmacoepidemiological model based on regional intestinal anti-inflammatory drugs consumption data

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Table 3. Total national population, estimated number of IBD patients and estimated national prevalence for each of the diagnosis (Ulcerative Colitis—UC and Crohn's Disease—CD), sex and age stratum, for the year 2007

Sex	Age group (year)	Diagnosis											
		UC				CD				Total IBD			
		Estimates national cross-sectional study		Total national population[†]	Estimated prevalence[‡]	Estimates national cross-sectional study		Total national population[†]	Estimated prevalence[‡]	Estimates national cross-sectional study		Total national population[†]	Estimated prevalence[‡]
		Observed n^*	Observe %[*]			Observed n^*	Observe %[*]			Observed n^*	Observe %[*]		
Male	0–16	15	0.3	952 017	4.1	25	0.4	952 017	6.9	42	0.7	952 017	11.6
	17–39	395	6.7	1 735 878	59.9	716	12.2	1 735 878	108.6	1127	19.2	1 735 878	171.0
	40–64	597	10.2	1 678 507	93.7	445	7.6	1 678 507	69.8	1060	18.0	1 678 507	166.3
	65–79	192	3.3	613 874	82.4	77	1.3	613 874	33.0	272	4.6	613 874	116.7
	≥80	44	0.7	158 531	73.1	8	0.1	158 531	13.3	53	0.9	158 531	88.0
	Total	1243	21.2	5 138 807	63.7	1271	21.6	5 138 807	65.1	2554	43.5	5 138 807	130.9
Female	0–16	27	0.5	905 598	7.9	22	0.4	905 598	6.4	50	0.9	905 598	14.5
	17–39	619	10.5	1 700 673	95.9	856	14.6	1 700 673	132.5	1493	25.4	1 700 673	231.2
	40–64	706	12.0	1 795 071	103.6	659	11.2	1 795 071	96.7	1388	23.6	1 795 071	203.6
	65–79	212	3.6	789 533	70.7	105	1.8	789 533	35.0	322	5.5	789 533	107.4
	≥80	49	0.8	287 893	44.8	15	0.3	287 893	13.7	66	1.1	287 893	60.4
	Total	1613	27.5	5 478 768	77.5	1657	28.2	5 478 768	79.6	3319	56.5	5 478 768	159.5
Total	0–16	42	0.7	1 857 615	6.0	47	0.8	1 857 615	6.7	92	1.6	1 857 615	13.0
	17–39	1014	17.3	3 436 551	77.7	1572	26.8	3 436 551	120.5	2620	44.6	3 436 551	200.8
	40–64	1303	22.2	3 473 578	98.8	1104	18.8	3 473 578	83.7	2448	41.7	3 473 578	185.6
	65–79	404	6.9	1 403 407	75.8	182	3.1	1 403 407	34.2	594	10.1	1 403 407	111.5
	≥80	93	1.6	446 424	54.9	23	0.4	446 424	13.6	119	2.0	446 424	70.2
	Total	2856	48.6	10 617 575	70.8	2928	49.9	10 617 575	72.6	5873	100.0	10 617 575	145.7

[*]Observed frequency and proportion for each diagnosis, sex and age category from the nation-wide cross-sectional study on IBD patients ($n = 5893$) described in the methods section. Differences in totals are due to a small subset of patients with unclassified colitis (not yet defined as UC or CD).

[†]Estimates of the national population for each sex and age category and totals based on data from the national statistics authority (Instituto Nacional de Estatística—INE).

[‡]Estimated prevalence (per 100 000 persons) for each disease, sex and age category for the base case scenario (52% of sulphasalazine used by IBD patients and drug compliance of 80%).

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and Italy.[28] Lower estimates have been found in Germany (25 and 55 per 100 000 for UC and CD respectively[29]), Spain[30] and Croatia.[31,32] The estimates available for North American countries are similar to the highest level group in Europe[2,3] and the estimates for Asian countries are smaller than the lowest level group in Europe.[2,3]

Based on presented estimates, Portugal is half way between countries with the highest prevalence estimates and those with the lowest, but seems to be making the road to the highest level group. The comparison is nonetheless difficult given the wide temporal gap between reported estimates.

There is an interesting discussion in the literature about the hypothesized 'north–south gradient'[1–3,33–36] in IBD epidemiology. The present study contradicts this hypothesis because in Portugal, a southern European country, a lower prevalence would eventually be expected and because a geographical north–south gradient at a national level was not evident.

Some methodological aspects of this work have limitations and deserve further comment. First, we relied on the assumption that 75% of IBD patients are taking IAI drugs. Although this assumption seems reasonable in Portugal, and it is an estimate derived from a large national cross-sectional study on IBD patients, it is possible that the proportion could eventually be lower in the general population, where some less severe or long-term remission patients may be found.

Second, a mean yearly intake of IAI drugs (c_i) had to be estimated from a sub-sample ($n = 513$) of a national cross-sectional study. This was not a random sample from the IBD population, but instead a sample of patients willing to participate in a follow-up study and for whom data were available on IAI drugs use. Although it does not seem probable that factors involved in patient recruitment could have biased the estimates, existence of selection bias is impossible to exclude.

Third, another important parameter in the prevalence estimation model was the proportion of sulphasalazine used for IBD indication. The choice of a proportion of 52% for the base case scenario was based on the best available evidence, although it was limited in this case.[10–12,37–39] Sensitivity analysis was performed, but a small effect on the estimates was found for this parameter.

Fourth, IAI drugs compliance could importantly affect the prevalence estimates presented. The best available evidence regarding this parameter was used[13,14] and sensitivity analysis was performed. In the absence of a better estimate, sensitivity analysis as performed is the best method to incorporate the uncertainty related to this parameter in the model.

Fourth, the disease, age and sex specific prevalence estimates presented depend on the proportions of patients pertaining to each stratum in our country, and these were estimated based on the results of a large national cross-sectional study.[19,20] If some selection bias is present in this study, it would affect the quality of the estimates. However, in the cross-sectional study almost half of the predicted IBD patients in our country were included and there is an adequate representation of all the spectrum of disease severity.[19,20] We believe that no major selection bias is present, but age and sex specific estimates must be interpreted with caution and are most valuable for comparative purposes.

Fifth, the methods proposed for estimation of the variance of prevalence estimates are new in this context and were based on the delta method.[16–18] Although this is an adequate method, there are other approaches that could have been implemented. A Bayesian approach, for example in the context of the multiparameter evidence synthesis methodology, could have been very interesting to implement.[40–43]

Sixth, although the prevalence estimates presented along the study period might be interpreted as representing an extreme increase in the number of IBD patients in our country, the fact is that, in the base case analysis, the mean annual incidence resulting from these prevalence estimates would be around 15 per 100 000 person-years; and such an incidence is in accordance with the estimates presented for southern European countries in the European Collaborative Study on IBD, the biggest study undertaken on IBD epidemiology in Europe.[1,35]

Seventh, regional prevalence estimates for each Portuguese district are based on local IAI drugs consumption, thus it is possible that some over-estimation of drug consumption, and consequently disease prevalence, could exist around large reference treatment centres (for example, Lisboa and Porto). However, this fact does not affect national estimates and it does not explain the high prevalence observed in some inland districts. Although some bias may exist, it seems reasonable to believe that most patients, most of the time, buy their regular prescription drugs in pharmacies close to their residencies.

Finally, no changes in diagnostic tools and disease awareness existed in Portugal in the last decade; the diagnosis and treatment strategies of IBD have been constant over the studied period; no differences exist between maintenance and active disease IAI drugs doses in Portugal (in accordance with international guidelines[44,45]); and no changes in prescription habits

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KEY POINTS

- IBD prevalence in Portugal increased from 86 patients per 100 000 persons in 2003 to 146 in 2007, using estimates derived from a pharmaco-epidemiological approach based on intestinal anti-inflammatory drugs consumption.
- Prevalence increased from 42 and 43 per 100 000 in 2003 to 71 and 73 in 2007, respectively for Ulcerative Colitis and Crohn's Disease.
- The districts more affected by IBD were Lisboa and Porto, with prevalence reaching 173 and 163 per 100 000 in 2007, respectively, and a north–south gradient was not evident at the national level.
- Portugal is half way between the group of European countries with the highest and the group with the lowest IBD prevalence estimates, but is steeply making the road to the highest level group.
- The feasibility and comparability of the proposed pharmaco-epidemiological approach makes it an interesting tool for future studies on IBD epidemiology.

of 5-ASA existed in Portugal in the last 10 years. The Portuguese IBD study group has analysed this question and concluded that, although there was an important change in 5-ASA prescription dose habits in the 1990's decade, in the last 10 years these have remained constant. Thus, these factors do not seem to account for the increase in IBD prevalence reported in the present study.

Despite the limitations discussed, the assumptions and parameters used in the base case analysis seem to be the most reasonable and we believe the prevalence estimates are acceptable. If some bias exists, it should certainly be the assumed risk of some degree of underestimation. The feasibility and low financial and organizational demand of this methodology, and the seemingly valid and reasonably precise estimates that it allows to obtain, makes it a very interesting tool to study IBD epidemiology.

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