

# Current epidemiologic trends in Crohn's disease: data from a tertiary referral centre in Bucharest

(Fundeni Institute, Center of Gastroenterology and Hepatology)

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## ABSTRACT

*The purpose of this study was to estimate the incidence and prevalence of Crohn's disease (CD) in South-Muntenia, Bucharest-Ilfov and the Southwest region, using data collected from the main referral center in the area, during 2005-2009.*

*Materials and methods* A retrospective, descriptive study was conducted based on the 593 patients with CD admitted to the Center of Gastroenterology and Hepatology, Fundeni Institute, during this period. The incidence and the prevalence were reported per 100,000 inhabitants aged over 18.

*Results* The incidence and the prevalence between 2005-2009 were estimated at 0.49 /100,000 and 1.88 / 100,000 inhabitants respectively. They both described an oscillating trend between 2005-2009, increasing in 2009 by 32% ( $p = 0.036$ ) and by 69% ( $p = 0.000$ ) respectively, as compared to 2005. The sex specific incidence rates was slightly, but not significantly, higher among women (0.59) than men (0.49). The average age at admission was 44. A bimodal age distribution was noticed with two peaks: between 30-39 and 50-59 years old. The highest incidence rate was found in the urban areas (1.09) and Bucharest (0.7). The temporal trend analysis showed that incidence of CD does not suffer significant changes over the interval 2010-2014, predicting an annual incidence rate of 0.52 / 100,000.

*Conclusion* Data collected in the main referral center for the South-Muntenia, Bucharest-Ilfov and Southwest regions during the last five years confirms the previously described low frequency of CD in Romania, the bimodal age distribution and later onset of disease. The male to female ratio is close to unity, suggesting that men and women are generally at similar risk. There is a significant increase in both incidence and prevalence of CD when comparing 2005 with 2009. In term of predicting trends, the incidence of CD appears to be relatively stable, whereas the prevalence understandably rises over the interval 2010-2014. A further prospective multicenter study is necessary in order to assess the precise incidence, prevalence CD in Romania and to make more accurate predictions regarding future trends.

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## INTRODUCTION

Epidemiologists have made significant contributions to the understanding of numerous chronic diseases, but both Crohn's disease (CD) and ulcerative colitis (UC) raise a number of questions that make our understanding of inflammatory bowel disease (IBD) still problematic.

The descriptive epidemiology studies the incidence, the prevalence, the role of the demographic factors (age, gender, race, and ethnic groups), the geographic variations and the temporal trends of various diseases. Assessing the incidence and prevalence provide valuable information on the epidemiological magnitude of CD, which are important for determining health politics, resource distribution, insurance companies and pharmaceutical projects. Variations in incidence and prevalence related to the demographic, the geographic or the temporal factors allow considerations on the etiology of the IBD, identifying risk factors and defining areas of future studies. The epidemiological studies in IBD are difficult, being burdened by many difficulties and potential errors caused by: insidious onset of CD and ulcerative colitis, multiple diagnostic criteria, wide differential diagnosis with many other conditions, different availability of technology and variable interest for CD in different geographic areas.(1)

Despite genuine uncertainty about the etiology of CD, there are certain epidemiologic factors that are already established. The incidence of CD has precipitously increased since its description in 1932. It is more common in Europe (Scandinavian countries, United Kingdom, the Netherlands and northwest France) and North-America. There also appears to be a north-south gradient in incidence. The rising incidence has plateaued in most areas, however, it is increasing in less developed countries as they become more industrialized and adopt Western dietary and cultural practices. IBD typically affects young people, but may have a bimodal incidence with a second peak in later life. Women are likely to be slightly more affected by CD.(1)

There are relatively few data about the epidemiology of CD in Romania; the only multicenter study published which was conducted between 2002-2003, placed Romania within the low incidence countries for CD.(2) Reassessing these figures has been so far an unmet need. □

## AIM

The purpose of this study is to estimate the incidence and the prevalence of CD in the South, Bucharest-Ilfov and the Southwest regions, based on patient data collected between 2005-2009 in the main referral center for IBD in the area. □

## MATERIALS AND METHODS

A retrospective descriptive study was performed on the 593 CD patients hospitalized in the Center of Gastroenterology and Hepatology, Fundeni Institute during 2005-2009.

The incidence and the prevalence rates were calculated by reporting to the total adult population (>18 years) in the South region representing 13.55% of the country, Bucharest-Ilfov region representing 0.71% of the country and the South-West region representing 12.28% of the country. In total, it amounts to 6,264,408 inhabitants, with an average density of 93 inhabitants per km<sup>2</sup>, of which 48.7% are men and 51.3% women, and, according to the environment origin, 55% are urban and 45% in the rural areas. Patients from other regions were excluded from study.

For each case the necessary epidemiological data were taken from medical documentation (clinical notes) available from the Center of Gastroenterology and Hepatology, Fundeni Institute.

The new patient was a patient with active CD at diagnosis, with no previous treatment for CD.

Statistical analysis The incidence is the frequency of new cases over a certain time interval and is expressed as an incidence rate (for IBD, the convention is cases per 100,000 person/years). The period prevalence of a disease is the proportion of a population that is affected by the disease during a specific period.

Software used: SPSS vs 16.0 for Windows, MINITAB vs 15.0, Excel; used statistical tests: T-test (student) for independent samples, chi-square test, frequency analysis. □

## RESULTS

Centralizing the data from the 593 CD patients hospitalized in the Center of Gastroenterology and Hepatology, Fundeni Institute between 2005-2009, 152 were new cases.

The incidence of CD between 2005-2009 in the above mentioned regions, was 2.43 per 100,000 inhabitants and the average incidence was 0.49 per 100,000 inhabitants.

An oscillating trend is observed with an overall increase by 32% in 2009, compared to 2005 ( $\chi^2$  test,  $p = 0.036$ ).

The analysis of the observed frequencies reported to the expected frequencies ( $\chi^2$  test) has shown an obvious increase in the number of the new cases in 2009, statistically significant ( $p = 0.035$ ) compared to the average range, but a moderate decrease in the number of the new cases in 2007 and 2008, also significant ( $p = 0.04$ ) (FIGURE 1).

The sex specific incidence was relatively balanced with a slight predominance of women (0.59 / 100,000) than men (0.49 / 100,000), the difference being statistically insignificant ( $p = 0.871$ ).

Regarding the environment of the origin, the highest incidence was found in the urban areas (1.09 / 100,000) and Bucharest (0.70 / 100,000); in the rural areas, the incidence (0.64 / 100,000) was significantly lower compared to the average incidence (0.81) and to the incidence in the urban areas ( $p = 0.010$ ). If we assimilate the cases in Bucharest to the urban environment the difference is highly statistically significant ( $\chi^2$  test,  $p = 0.000$ ), new cases being predominantly urban (1.79)

Average age was 44. Regarding the patients aged between 40-49, by application of the statistical significance tests, we recorded a significant difference between men and women, with men predominance ( $\chi^2$  test,  $p = 0.019$ ) and in the 60-69 year old, women predominated significantly ( $\chi^2$  test,  $p = 0.046$ ) (FIGURE 2).

We found two peak age incidence: 30-39 (0.65 / 100,000) and 50-59 (0.49 / 100,000) (FIGURE 3).

The prevalence between 2005-2009 was 9.47 / 100,000 inhabitants, and the average prevalence was 1.89 / 100,000 inhabitants.

The prevalence recorded a slight increase between 2005-2006, followed by a significant decrease in 2007, and a marked increase between 2008-2009. The prevalence increased by 69% in 2009 compared to 2005 ( $\chi^2$  test,  $p = 0.000$ ) (FIGURE 4).

The temporal trend analysis showed that incidence of CD does not suffer significant changes over the interval 2010-2014, predicting an average of 33 new cases per year, corresponding to an annual incidence rate of 0.52 /

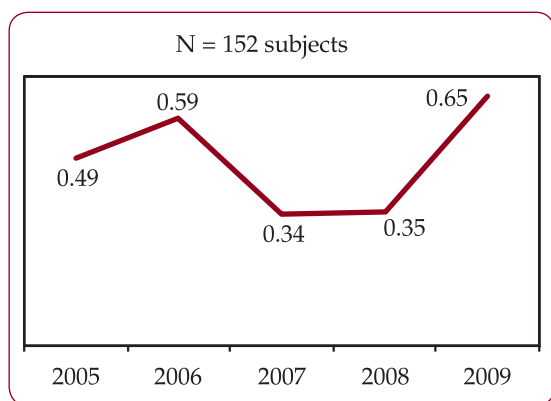


FIGURE 1. Crohn's disease incidence rate between 2005-2009

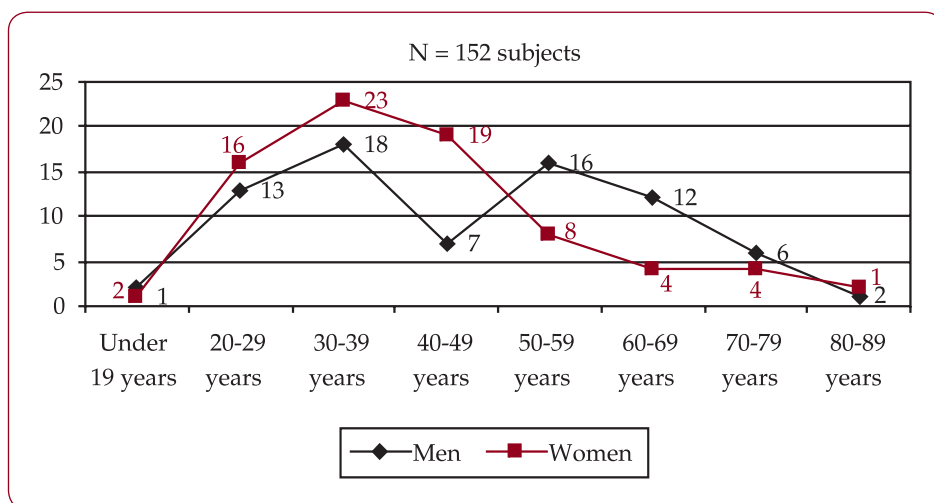


FIGURE 2. Patient distribution by age groups and sex during 2005-2009

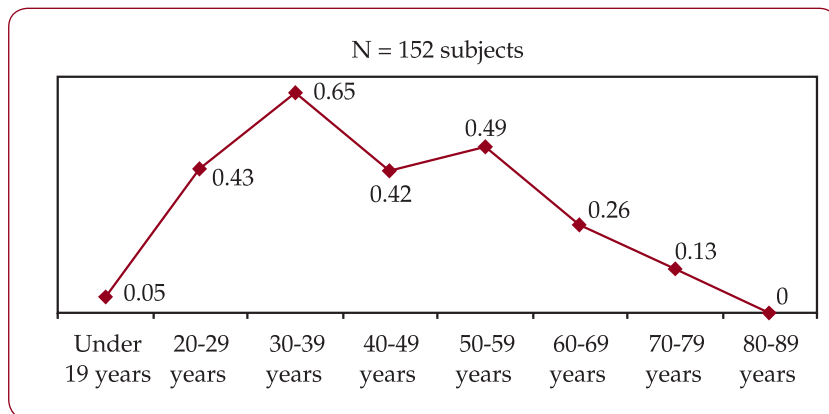


FIGURE 3. The age specific incidence during 2005-2009

100,000 (FIGURE 5); conversely, the prevalence calculated for 2010-2014, comprises a significant difference over the studied period (t-test  $p < 0.001$ ), with an average prevalence around 3.18 / 100,000 (FIGURE 6). □

### DISCUSSION

In Europe, the incidence rate for CD varies between 0.7 (Zagreb, Croatia) and 9.8 cases (Scotland, UK) per 100,000 inhabitants a year. The European Multicentre Study for Inflammatory Bowel Disease (EC-IBD) reported overall incidence rates for CD between 3.9 and 7 cases per 100,000 inhabitants per year, estimating

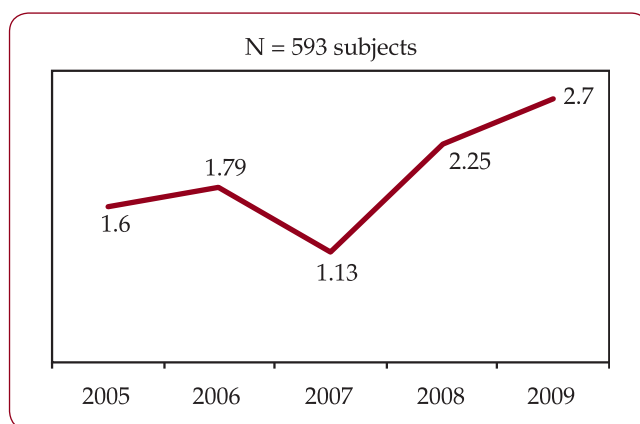


FIGURE 4. The prevalence during 2005-2009

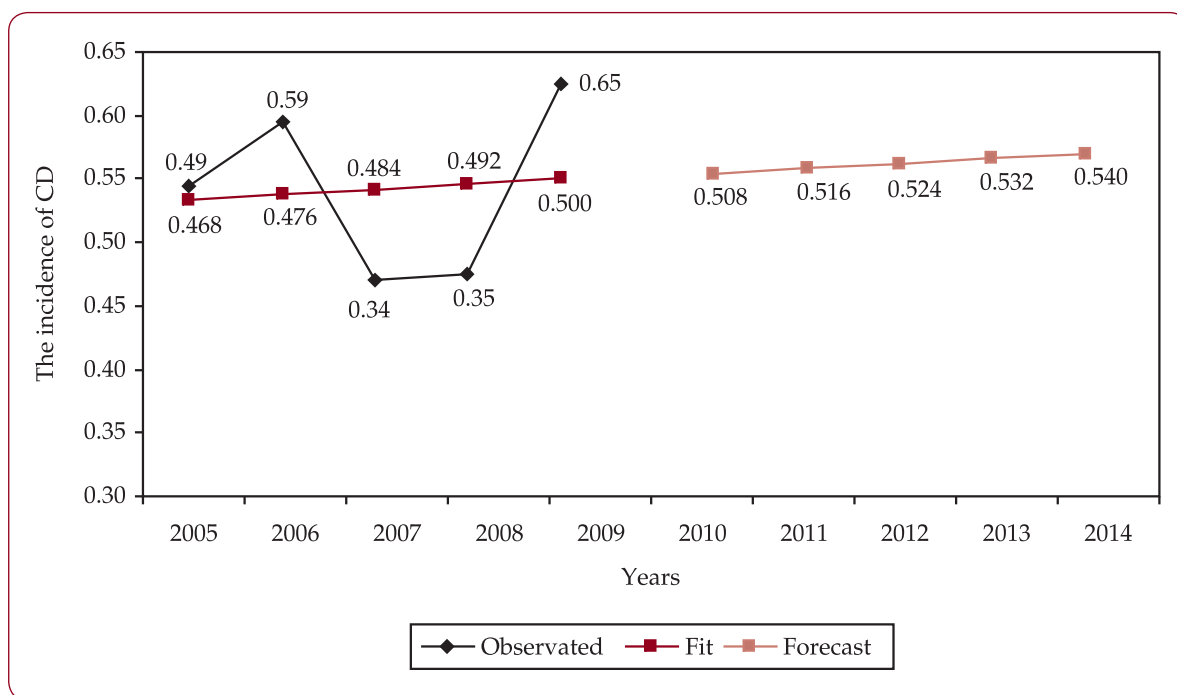


FIGURE 5. Trends in the incidence of CD during 2010-2014

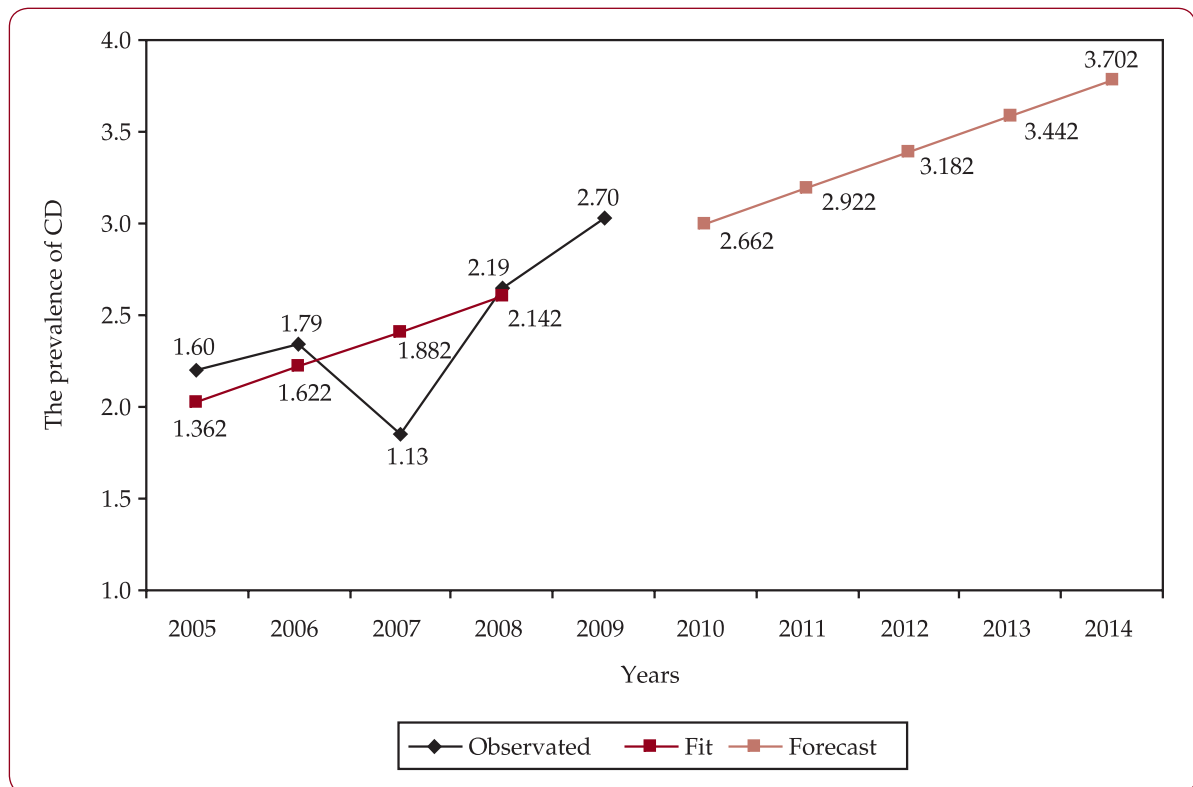


FIGURE 6 Trends in the prevalence of CD

that between 23,000 and 43,000 new cases are detected every year.(3)

Several studies showed that in Europe, the incidence of CD decreased from North to South and from West to East. The EC-IBD study also confirmed the presence of a south-north gradient in incidence, but the differences were smaller than expected. This trend can be explained by the relative stability of the incidence in the areas with high incidence while in the previous areas with low incidence, the incidence continued to rise.

Until recently, very few data have been available about the epidemiology of IBD in Central and Eastern European countries.

In Hungary, a retrospective study during 1977-1985 and prospectively in the period 1985-2001, found the mean incidence rate 2.23 / 100,000 inhabitants. There was a sudden increase of CD incidence from 0.41 / 100,000 to 2.35 during the above mentioned periods. The prevalence was high: 52.9 / 100,000 in late 2001 and the average age at diagnosis was 38.9 years; there was a single peak of incidence, between 21 and 30 years.(4)

In Croatia, Mijandrusic Sincic et al have recently conducted a retrospective study on a

total of 305,000 inhabitants, at the Adriatic Sea coastal area from 1995 to 2001 and reported a mean incidence of 3.92 / 100,000 (5.71 / 100,000 in 2001), with a prevalence of 46.4 / 100,000.(5) In a prospective study on the same geographical area, using the same method found an age specific incidence of 7 (100,000 patients) during 2000-2004, suggesting an increased incidence of CD in Croatia, a similar trend to that in Hungary.(6)

In the Czech Republic, Kolek et al published the results of a prospective population study conducted since 1990 in Moravia, in children and adolescents. They described a dramatic increase in CD incidence from 0.3 to 1.5; CD incidence increased from 0.11 to 0.91 for children under 15 years old and increased from 0 to 3.83 for adolescents (16-18 years) when compared to the periods between 1990-1994 and between 1995-1999.(7)

A single study by Wierska-Drapalo et al was published in Poland in 2005; they reported 248 patients diagnosed with inflammatory bowel disease between 1990-2003 at a total of 1,000,000 inhabitants, in the north-east Poland. Based on the published data the average incidence of CD was estimated at 0.1 / 100,000 inhabitants.(8)

The only Romanian prospective multicentric epidemiologic study on IBD was published in 2004 and reported low incidence rates. It has been conducted by the Romanian Society of Digestive Endoscopy between 2002-2003 and included 18 secondary and tertiary centers for adult patients. The data based on questionnaires were collected from gastroenterology departments. During the study, 254 cases of CD (85 incident cases) were identified, with a reported incidence of 0.50 / 100,000 and a prevalence of 1.51 / 100,000; the average age at diagnosis was 43.9 years, with a incidence peak between 20 – 39 years. (2)

All these studies, however, present several limitations. First, being based on records provided by secondary and tertiary referral centres, there is no assurance that these data are representative of the entire country. Second, the process of reporting cases by a voluntarily questionnaire is a matter of debate, with the knowledge that the self report frequency of such questionnaires is limited.

Like most previous studies on IBD in Eastern Europe (4, 9) our study has limitations related to the retrospective nature and the collection of the cases from a single tertiary center. Considering that the data collection was based solely on the inpatients' records of a single hospital and on extrapolation of the results to the investigated area, the incidence rate is probably underestimated. Because most investigators do not have access to true population-based registries, surrogates (including hospitalization) have to be used often to estimate incidence. In addition, this is the largest IBD referral center in the country and, hence concentrates the most IBD cases in the area.

Between 2005-2009, we audited the notes of 593 CD patients and identified 152 incident cases of CD. The average age was 43.9 years. It presented a typical bimodal age distribution, with two peaks of incidence at 30-39 years and 50-59 years, thus confirming a clear tendency of slightly delayed onset of disease in our population. Interestingly, not all studies show a bimodal age distribution and it is not clear whether these variations in age distribution are real differences in the age of onset or are due to differences in classification of various entities that might be confused with CD (infectious/ ischemic colitis/ diverticular colitis).

The average incidence during the study period in the regions studied (Bucharest-Ilfov,

South, South-west) was estimated as 0.49 / 100,000 inhabitants, revealing a low incidence comparing to the literature.

Consistent with the existing data, the incidence of CD was slightly higher in women (0.59 / 100,000) than men (0.49 / 100,000), but the difference was not significant ( $p = 0.871$ ). Differences in risk by sex, if significant, could indicate hormonal, occupational or lifestyle factors as responsible.

Some studies describe a gender divergence later in life UC, but not CD. After a peak in the third-fourth decade, the incidence of UC significantly decreases in women. Interestingly, we found a significant female predominance in the 60-69 year old CD group ( $p = 0.046$ ).

There is a definitely higher incidence in the urban areas and Bucharest in comparison to rural areas ( $p = 0.010$ ). Also, a highly statistically significant difference between rural and urban areas was noticed after assimilating the patients from Bucharest in the urban environment ( $p = 0.000$ ). This is a historically known fact and the causes for these differences could be related to the westernization of lifestyle and diet but also to the threshold of addressability and accessibility of patient to the medical system.(1)

Regarding the CD trend in the studied regions, an oscillating trend was observed with an increased incidence between 2005-2006, followed by a decrease and a plateau between 2007-2008, then a significant increase in 2009. The incidence and the prevalence increased in 2009 by 32% ( $p = 0.036$ ) and by 69% ( $p = 0.000$ ) respectively, as compared to 2005. The incidence rate for 2009 is higher both in the Bucharest-Ilfov region (0.82 / 100,000) and in the South (0.63 / 100,000) as compared to 2005, showing on the whole a light up trend in the incidence.

All the international registries demonstrate a rise in incidence followed by a plateau. Some increase in incidence can be related to shortening of interval between symptom onset and disease diagnosis, diagnostic transfer from UC to CD, better appreciation of the disease, but these cannot account entirely for the trends noticed over time. Furthermore in westernized countries where CD is common, the most reliable data have shown incidence stable since 1980. Conversely in areas of Europe where historically CD was uncommon, the incidence is

raising also some of the rising may reflect higher standards of healthcare. (10)

Surprisingly, the analysis of the temporal trends predicts no significant changes in the incidence rate, but it outlines a statistically significant increase in the prevalence between 2010-2014, totally explainable given the chronic nature of CD (a life-long disease has a low annual incidence but high prevalence). However, since the prevalence figures represent the healthcare burden in a population, it is relevant to the policy makers in order to allocate proper funding for treatment and investigation.

It should be noted that the incidence and the prevalence indicators were weighted subtraction due to the decline in 2007. Unlike the incidence recorded in 2008 comparable value to 2007, the prevalence in 2008 involves a significant upward trend over the 2007 index, which suggests an increase of readmission cases diagnosed in the previous years.

Despite years of investigation, the root causes of CD are yet to be identified. There were described many factors which can significantly modify the expression of CD but are needed more efforts for understanding how these factors influence the incidence and the prevalence.(1) □

## CONCLUSION

- Data collected in the main referral center for the South-Muntenia, Bucharest-Ilfov and Southwest regions during the last five years confirm the previously described low frequency of CD in Romania.
- The male to female ratio is close to unity, suggesting that men and women are generally at similar risk.
- The study shows a bimodal age distribution, with the first peak of incidence occurring slightly later in life, at 30-39 years old.
- There is a significant increase in both incidence and prevalence of CD when comparing 2009 with 2005.
- The study of the temporal trends shows that the incidence of CD appears to be relatively stable, whereas the prevalence understandably rises over the interval 2010-2014.
- Since our study is limited by the retrospective, monocentric design, a further prospective multicenter study is necessary in order to accurately assess the incidence and prevalence of CD in Romania and to make more accurate predictions regarding future trends. □



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