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## **The changing pattern of Crohn's disease incidence according to age in northern France: a continuing increase in the 10-19-year-old age bracket (1988-2007).**

Vincent Chouraki, Guillaume Savoye, Luc Dauchet, Gwenola Vernier-Massouille, Jean-Louis Dupas, Veronique Merle, Eric Laberrenne, Jean-Louis Salomez, Eric Lerebours, Dominique Turck, et al.

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**The changing pattern of Crohn's disease incidence according to age in northern France: a continuing increase in the 10-19-year-old age bracket (1988-2007).**

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3 **The changing pattern of Crohn's disease incidence according to age in**  
4 **northern France: a continuing increase in the 10-19-year-old age**  
5 **bracket (1988-2007).**  
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13 **Short title:** Epidemiology of inflammatory bowel disease.  
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45 **Abbreviations**

46  
47 IBD, Inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis  
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52 **Keywords**

53  
54 Inflammatory Bowel Disease, Incidence, Pediatric, Epidemiology,  
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**Abstract**

**Background:** Crohn's disease (CD) incidence rates have stabilized in industrialized countries since the 1980's. Conversely, a continuing increase in childhood-onset CD incidence has been reported.

**Aim:** To confirm trends in inflammatory bowel disease (IBD) incidence in northern France over an extended time period (1988-2007) with a focus on childhood-onset CD.

**Methods:** IBD patients recorded in the EPIMAD registry between 1988 and 2007 were included. Standardized incidence rates were calculated for CD and ulcerative colitis (UC) in the entire population, and separately according to age. Evolution of phenotypes at diagnosis was also studied.

**Results:** 12,084 incident IBD cases (7,428 CD and 4,656 UC) were recorded. CD incidence rates increased from 5.2 cases/100,000 persons in 1988-1990 to 6.7 in 2006-2007 (+29%), stabilizing after a peak at 7.1 in 1997-1999. CD incidence rates in the 10-19-year age category increased by 71%, from 6.5 (1988-1990) to 11.1 (2006-2007). The frequency of initial ileo-colonic localization increased from 52.9% in 1988-1990 to 68.6% in 2006-2007 ( $p < 0.0001$ ). UC incidence rates decreased during the same period. **Conclusion:** From 1988 to 2007, CD incidence increased by 29% in northern France and by 71% in the 10-19-year-old age group. Consequently, studies on CD risk factors should focus on the population under 20 years of age.

**Number of words: 205**

## INTRODUCTION

Inflammatory bowel diseases (IBD) represent a major burden for developed countries. It has been estimated that as many as 1.4 million persons may be afflicted with IBD in the US and Canada, and 2.2 million in Europe<sup>1</sup> Crohn's disease (CD) and ulcerative colitis (UC) are the major IBD that challenge gastroenterologists. Although significant advances have been made toward a better understanding of the pathophysiology of IBD<sup>2,3</sup>, their etiology remains unclear<sup>1</sup>. Epidemiological studies of geographic and temporal variations in IBD provide important information on the natural history, health care burden and causal mechanisms of the disease. In particular, population-based epidemiological studies are more likely to reflect the true spectrum of illness than studies performed on patients seen at referral centers. Indeed, epidemiological studies have shown a continuing increase in<sup>4-6</sup> or stabilization<sup>7-9</sup> of CD incidence rates in developed countries over the past 5 decades. In contrast, several studies have described a continuing increase in incidence rates of CD in children and adolescents<sup>10-16</sup>, suggesting that ongoing risk factors may exist in these populations. Nevertheless, these changes in the incidence of juvenile-onset CD remain subject to debate and need to be confirmed in larger population-based registries. The EPIMAD study records all incident cases of IBD since 1988 in northern France. Previously published studies covering the 1988-1999 period reported a significant increase in incidences rates of CD in the overall population<sup>17</sup>, as well as a non-significant increase in the pediatric population<sup>18</sup>. The aim of the present study was therefore to conduct an updated analysis of the evolution of incidence rates and digestive sites of CD and UC for the 1988-2007 periods in a large population registry which included infants and young adults.

## PATIENTS AND METHODS

### Patient population

Cases included all patients from the EPIMAD registry who had a diagnosis of definite or probable IBD, including cases of CD and UC, between January 1988 and December 2007. The

1  
2 study area was the northern part of France, which has 5,790,526 inhabitants (1999 national  
3 population census) residing in four regions: Nord, Pas-de-Calais, Somme and Seine-Maritime. This  
4 part of France represents 9.3% of the total French population and is composed of four sectors: (a)  
5 Nord, with 2,554,449 inhabitants and a population density of 445/km<sup>2</sup>; (b) Pas-de-Calais, with  
6 1,441,422 inhabitants and a population density of 216/km<sup>2</sup>; (c) Somme, with 555,479 inhabitants  
7 and a population density of 90/km<sup>2</sup>; and (d) Seine-Maritime, with 1,239,176 inhabitants and a  
8 population density of 197/km<sup>2</sup>. Both rural and urban populations can be found in these areas (ratio  
9 urban/rural=8.9 in the Nord, 4.5 in the Pas-de-Calais, 1.4 in the Somme, and 3.0 in the Seine-  
10 Maritime). This region is a well-defined geographic entity bordering Belgium and the North Sea  
11 (Figure 1). The population is stable—that is, the percentages of the population moving per year for  
12 each area were 0.8 for Nord and Pas-de-Calais, 1.1 for Somme and 0.9 for Seine-Maritime (French  
13 National Statistical Institute).

### 31 Data collection

32  
33 The methodology of the EPIMAD registry has been previously described in detail<sup>17-19</sup>.  
34 Interviewing practitioners collected data on all patients diagnosed between 1988 and 2007 from all  
35 adult and pediatric gastroenterologists (GE) (total: 248) practicing in the private or public sector.  
36 Only patients who had been residents of the study areas at the time of diagnosis of IBD were  
37 included. Each GE reported any patient consulting for the first time with clinical symptoms  
38 compatible with IBD, and was contacted by phone at least three times a year by an interviewing  
39 practitioner. This interviewer went to the GE's consulting room and collected data from charts in a  
40 standardized questionnaire for each new case. Main data collected included age, gender, year of  
41 diagnosis, interval between onset of symptoms and diagnosis, and clinical, radiological, endoscopic  
42 and histological findings at the time of diagnosis. A final diagnosis of CD or UC was made by two  
43 expert gastroenterologists and was recorded as definite, probable or possible according to  
44 previously published criteria<sup>19</sup>. For the purpose of this study, only patients with definite or probable  
45 IBD were considered.

1  
2 For the study of phenotypes of CD, the site of disease was reported only for patients who underwent  
3 a complete bowel investigation (images of small and large bowel). The localizations of the lesions  
4 were coded according to the Montreal classification<sup>20</sup> with modification for CD: L1 referred to ileal  
5 localization of lesions, L2 to colonic localization and L3 to ileocolonic localization, with the  
6 addition that an ileal localization with cecal involvement was considered as a L3 localization. For  
7 UC localization, ulcerative proctitis (E1) was defined as involvement limited to the rectum (i.e, the  
8 proximal extent of inflammation was distal to the rectosigmoid junction), left-sided UC (E2) was  
9 defined as involvement limited to the portion of the colorectum distal to the splenic flexure, and  
10 extensive UC (E3) was defined as involvement extending proximal to the splenic flexure.  
11 Extraintestinal manifestations (EIMs) included joints, skin, ocular and hepato-biliary  
12 manifestations.  
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### 29 **Statistical Analyses**

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31 Incidence rates were computed as the ratio of the number of incident cases with respect to  
32 the number of person-years for both sexes. Yearly estimations of population based on a procedure  
33 mixing exhaustive census before 2004 and random sampling after 2004 were obtained from the  
34 French Statistics Institute (INSEE). Three-year periods were used to ensure better statistical  
35 precision and robustness. Age standardization was performed using European standard population  
36 weights for 5-year age groups. Incidence rates were studied in the overall population and according  
37 to 20-year age brackets. Finally, 10-year category incidence rates were analyzed for patients  
38 diagnosed prior to the age of 20 years. Exact confidence intervals for standardized incidence rates  
39 were approximated using a gamma distribution<sup>21</sup>. Contributions of age, sex, time period and region  
40 were tested for CD in a generalized linear model using Poisson distribution. Second-order  
41 interactions between these variables were selected using Akahike Information Criteria (AIC)<sup>22</sup>.  
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Linearity of the evolution of incidence rates of CD was assessed with a likelihood ratio test using  
nested models. Changes in CD localization and time were assessed with appropriate Chi-squared  
tests. For descriptions of age at diagnosis (years) and time intervals between symptoms and



1 diagnosis (months), median and interquartile ranges (25th and 75th percentiles) are given.  
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4 Comparisons of distribution of these variables across time were performed using the Wilcoxon,  
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6 Kruskal-Wallis or Chi-squared tests for trend. Analyses were performed with R 2.12.1<sup>23</sup>.  
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## 10 11 12 **RESULTS**

### 13 14 15 **IBD cases**

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17 During the 1988-2007 period, 12,052 patients satisfying the criteria defined above were  
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19 recorded in the EPIMAD registry, including 61% (n=7,409) of CD cases and 39% (n=4,643) of UC  
20  
21 cases. Median age at diagnosis was 30 years (interquartile range IQR: 22-42) and was significantly  
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23 higher in patients with UC than in patients with CD (35 vs. 26 years, respectively;  $p < 0.0001$ ).  
24  
25 Median delay between first symptoms and diagnosis was 3 months (IQR: 1-6) and was significantly  
26  
27 higher in CD cases than in UC cases (3 vs. 2 months, respectively;  $p < 0.0001$ ). Five hundred and  
28  
29 sixty cases of indeterminate colitis (IC) were recorded.  
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### 33 34 35 **Incidence of CD**

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37 During the 1988-2007 period, 7,409 patients were diagnosed with either definite (35%  
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39 n=2,570) or probable (65% n=4,839) CD, with a predominance of women (56% n=4,180). Median  
40  
41 age at diagnosis was 26 years (IQR: 20-38) and was not statistically different between men and  
42  
43 women ( $p=0.8$ ). Median interval between first symptoms and diagnosis was 3 months (IQR: 1-8)  
44  
45 for the entire period, with a significant decrease in the proportion of intervals longer than 9 months,  
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47 from 28% in 1988-1990 to 22% in 2006-2007 ( $p<0.0001$ ) (Table 1).  
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51 During the 1988-2007 period, incidence rate of CD was 6.4 (95% confidence interval (CI) 6.2-6.5).  
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53 CD incidence rate increased significantly, from 5.2 cases per 100,000 person-years in 1988-1990 to  
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55 6.7 in 2006-2007 (test for trend,  $p<0.0001$ ) (Figure 2). Rates reached a maximum of 7.1 in 1997-  
56  
57 1999 and then remained stable (test for non-linearity,  $p=0.0003$ ). CD incidence rate was  
58  
59 significantly higher in women (7.1; 95% CI 6.9-7.3) than in men (5.7; 95% CI 5.5-5.9) ( $p<0.0001$ ),  
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but analyses performed in each age group showed that this difference was present only in patients

1  
2 aged 20 to 24 years (p for interaction between age and sex <0.0001) (Figure 3). This difference  
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4 between women and men remained stable during the study period (p for interaction=0.21).  
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6 Evolutions in incidence rates did not differ according to region (interaction, p=0.08).  
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8 Evolution of incidence differed according to age group (Figure 4a). Incidence rates in the 0-19 age  
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10 group increased steadily over the entire study period, from 3.4 cases per 100,000 person-years in  
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12 1988-1990 to 5.9 in 2006-2007 (p for trend <0.0001). Evolution of incidence rates in the 0-19 age  
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14 group did not differ according to sex or region (interaction, p=0.10 and p=0.22 respectively).  
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16 Further analyses showed that the 10-19-year-old age group was mainly responsible for this increase,  
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18 since the incidence rates increased continuously, from 6.5 cases per 100,000 person-years in 1988-  
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20 1990 to 11.1 in 2006-2007 (p for trend <0.0001), whereas the incidence rates in the 0-9-year-old age  
21  
22 group only slightly increased during the same period (p for trend=0.02, Figure 4b). Furthermore, the  
23  
24 incidence rate in the age group 20-29 was similar to incidence rates in the overall population, with  
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26 stabilization beginning from the 1997-1999 period, whereas incidence rates in patients aged 30 and  
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28 over remained stable or only slightly increased.  
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### 36 **CD phenotypes**

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38 During the 1988-2007 periods, 5,790 patients underwent complete bowel investigation. The  
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40 proportion of complete bowel investigations significantly increased, from 76.9% in 1988-1990 to  
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42 86.5% in 2006-2007 (p for trend <0.0001). An ileo-colonic localization (L3 and L3+L4) was  
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44 predominant in the overall population and increased during the study period, from 52.0% in 1988-  
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46 1990 to 68.3% in 2006-2007 (p for trend=0.0004). Extended phenotypes (L3+L4) significantly  
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48 increased, from 8.1% in 1988-1990 to 23.2% in 2006-2007 (p for trend <0.0001), whereas an ileo-  
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50 colonic localization without upper GI lesions (L3) remained stable. Colonic site forms (L2)  
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52 significantly decreased, from 22.6% in 1988-1990 to 5.4% in 2006-2007 (p for trend < 0.0001),  
53  
54 whereas other sites remained stable (Table 1).  
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59 The proportion of patients with complete bowel investigation was stable in the 0-19 age group (test  
60  
for trend, p=0.12) and increased from 77.9% to 88.8% (test for trend, p <0.0001), from 68.6% to

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2 83.9% (test for trend,  $p=0.003$ ) and from 52.5% to 74.4% (test for trend,  $p=0.013$ ) in the 20-39, 40-  
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4 59 and 60 and over age groups, respectively. Similarly to the overall population, ileo-colonic (L3  
5 and L3+L4) forms of CD were predominant in children and adolescents, but a higher proportion of  
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7 extended lesions (L3+L4) than in other age groups was observed. The decreasing proportion of pure  
8  
9 L2 localizations observed in the overall population was found in the 20-39-year-old and the 40-59-  
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11 year-old age groups, as it decreased from 22.5% to 5.8% (test for trend,  $p < 0.0001$ ) and from 40.3%  
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13 to 4.8% (test for trend,  $p=0.004$ ) respectively, but not in the other age groups.  
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### 19 **Incidence of UC**

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21 From 1988 to 2007, 4,643 incident cases of UC were recorded in the EPIMAD study, with a  
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23 predominance of men (55%;  $n=2,566$ ). Median age at diagnosis was 35 (IQR: 26-47) years and was  
24  
25 significantly higher in men than in women: 38 versus 32, respectively ( $p < 0.0001$ ). The median  
26  
27 interval between first symptoms and diagnosis was 2 months (IQR: 1-6) for the entire period, with  
28  
29 stable proportions over the time (Table 2). During the total period, UC incidence rate was 4.1  
30  
31 (95%CI 4.0-4.2) and was significantly higher in men (4.7; 95%CI 4.5-4.9) than in women (3.6;  
32  
33 95%CI 3.4-3.7) ( $p < 0.0001$ ) (Figure 2). This difference in UC incidence rates according to gender  
34  
35 was observed for patients over 35 (Figure 5). A significant decrease in UC incidence rate was  
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37 observed from 4.3 (95%CI 4.0-4.7) in 1988-1990 to 3.4 (95%CI 3.1-3.7) in 2006-2007 (test for  
38  
39 trend,  $p=0.001$ ). Time trends of UC incidence rates differed significantly according to age group  
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41 (interaction,  $p < 0.0001$ ) with a more important decrease in the patients aged 60 and over than the  
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43 other age groups.  
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### 50 **UC phenotype**

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52 During the 1988-2007 period, 3,411 patients underwent complete colonic investigation. The  
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54 proportion of complete colonic investigations carried out significantly increased, from 66.1% in  
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56 1988-1990 to 82.6% in 2006-2007 ( $p$  for trend  $< 0.0001$ ). E2 localizations constituted most UC  
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58 cases, followed by E1 and E3 localizations (45%, 29% and 26% respectively). These proportions  
59  
60 remained stable during the study period (Table 2).

## DISCUSSION

In Northern France, from 1988 to 2007, incidence rates of CD stabilized following an initial increase, while those of UC decreased during that period. Conversely, CD incidence rates increased in the 0-19-year-old age category, mainly due to the 10-19-year-old category whereas they remained stable or stabilized after initial increase in the other age groups. For CD localization at diagnosis, ileo-colonic forms (L3) of CD were predominant in the overall population, with an increase of extended forms (at least 3 affected segments). In the 0-19-year-old category, a higher proportion of L3+L4 localizations than in the whole population was observed, with similar evolution. Incidence rates of CD have stabilized in northern France since 1999. These results are coherent with previous studies in Minnesota<sup>8</sup>, the United Kingdom<sup>9</sup> and Sweden<sup>7</sup>. Conversely, other studies in Denmark<sup>4,5</sup> and Greece<sup>6</sup> have shown a continuing increase. Since only definite and probable cases of CD were included in the EPIMAD study, underestimation of incidence rates due to incomplete CD case ascertainment cannot be ruled out. Potential IBD cases likely to be reclassified as definite or probable CD, such as possible CD, UC or IC cases, represented 2,436 patients in the entire database. Indeed, only continuous surveillance of these populations will enable us to more precisely determine the stabilization of incidence rates of CD. It might be speculated that accuracy of case recording has improved with time in the EPIMAD registry following a learning curve from the time of registry creation. However, in our opinion, this is unlikely since, in this case, the same variation (i.e. modification in the slope beginning in 1997-1999) in incidence rates of UC would have been observed. Our earlier data<sup>17</sup> as well as the present report did not support this hypothesis; indeed, a significant decrease in UC incidence over time was observed.

Our main result, indicating that incidence rates of CD continue to increase in young persons in Northern France, is of interest. Indeed, there existed stable incidence rates in the 0-9 year age group but increasing incidence rates in the 10-19-year-old age group. Similar results have been observed in Norway<sup>14</sup> and Scotland<sup>11</sup>, and in other studies in Finland<sup>15</sup>, Sweden<sup>10,12</sup>, Australia<sup>13</sup> and Canada<sup>16</sup>. Those studies showed an overall increase in the incidence of childhood-onset CD. Better diagnostic

1  
2 procedures and greater awareness by parents of the risk of CD may have led to reducing the time  
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4 lapse between symptoms and diagnosis, thereby increasing the incidence rates of CD in younger  
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6 patients. In the EPIMAD study, the median time between symptoms and diagnosis was 3 months,  
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8 which is low. Even if a decreasing proportion of intervals longer than 9 months had been observed  
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10 over time, it would not easily confirm a decrease of several years of age at diagnosis. We therefore  
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12 feel that a true increase in the incidence rates of CD is occurring in adolescents in Northern France.  
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14 Moreover, if our observations had relied only on advances in diagnosis, then this would have  
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16 impacted the incidence rate of the older age groups, which was not the case here. The increase in  
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18 CD incidence in the 10-19 years group could also reflect an earlier presentation of CD in  
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20 predisposed patients as proportion of familial history of CD increased and at the same time  
21  
22 proportions of extra intestinal manifestations and anoperineal lesions decreased between 1988 and  
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24 2007. It might be hypothesized that, in Northern France over time, a change in smoking habits, a  
25  
26 well known risk factor for CD<sup>24</sup>, would explain the differential evolution in incidence rates of CD  
27  
28 according to age. However, accurate regional data supporting this hypothesis are scarce. At a  
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30 national level, two population-based studies concerning teenagers showed a 30% decrease in the  
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32 proportion of 17-year-old subjects reporting daily tobacco consumption, from 41.1% in 2000 to  
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34 28.9% in 2008<sup>25</sup>, and a 45% decrease among 15- and 16-year-old subjects, from 31% in 1999 to  
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36 17% in 2007<sup>26</sup>. Moreover, other national data on smoking habits indicate a decrease in the  
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38 prevalence of smoking in every age group<sup>27, 28</sup> during the study period. Change of diet has also been  
39  
40 incriminated as a risk factor for IBD. A recent French cohort study of middle aged women showed  
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42 that protein intake was associated with a higher risk of IBD, CD in particular<sup>29</sup>.

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44 Analysis of the localizations of CD lesions at diagnosis showed a predominance of ileo-colonic (L3)  
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46 forms, with increasing proportions of extended forms, including ileo-colonic and upper  
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48 gastrointestinal lesions (L3+L4), from 1988 to 2007. These results are unusual compared to the  
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50 literature. Some<sup>4,7, 9</sup>, but not all<sup>30</sup>, population-based studies reported a higher proportion of pure  
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52 colonic localizations (L2) in CD patients. A possible explanation for these results might lie in the  
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2 fact that we reported CD sites only in patients who had undergone a complete bowel investigation  
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4 (with imaging of both large and small bowel). In other studies, the proportion of pure colonic  
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6 localizations (L2) may have been overestimated; as they were calculated from the entire population  
7  
8 regardless of whether or not small bowel investigation had been performed. Moreover, the recent  
9  
10 use of wireless capsule endoscopy (WCE) may have impacted the proportion of patients diagnosed  
11  
12 with extensive small bowel involvement. In France, however, use of WCE remained scarce before  
13  
14 2007 so it is unlikely to have influenced diagnostic of more extensive forms of CD.  
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19 Among patients aged 0 to 19, an ileo-colonic (L3) localization constituted most CD lesions at  
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21 diagnosis and this was stable over time. This is coherent with recent studies reporting extensive  
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23 lesions of CD in childhood at diagnosis, either an ileo-colonic localization<sup>14, 31, 32</sup> or an association  
24  
25 of ileo-colonic and upper gastrointestinal lesions<sup>33</sup>. These differences in phenotypes between adults,  
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27 children and adolescents may reflect the influence of distinct causal factors or a more systematic  
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29 investigation of the gastrointestinal tract in younger patients. One strength of this study lies in the  
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31 number of registered cases, which enabled precise estimates of incidence rates of CD and  
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33 adjustment for covariates in statistical models. Systematic follow-up of newly diagnosed patients at  
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35 18 months allowed for potential reclassification and well-documented final diagnoses of CD. In  
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37 contrast, questions concerning the completeness of case registration may be raised. The EPIMAD  
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39 registry relied only on gastroenterologists' declarations of incident cases, thereafter confirmed by  
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41 experts. In France, gastroenterologists have a monopoly in their profession, especially in terms of  
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43 administrative authorization to perform endoscopy. As a consequence, there is a strong probability  
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45 that each new IBD patient will consult a gastroenterologist and therefore be included in the study.  
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52 In Northern France, incidence rates of CD continue to rise among younger patients, with a more  
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54 extensive phenotype than in adults. These findings suggest that different causal factors may exist in  
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56 patients aged 10 to 20. It is therefore of great importance to focus etiological research on  
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58 comparisons of trends in incidence rates and phenotypes between adult- and childhood-onset CD.  
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**Number of words: 3149**

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2 **Figure legends**  
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5 **Figure 1:** Geographic situation in Europe of the EPIMAD Registry area.  
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8 **Figure 2:** Trends in standardised incidence (95% confidence interval) of Crohn's disease (CD) and  
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10 ulcerative colitis (UC) in Northern France from 1988–1990 to 2006-2007.  
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13 **Figure 3:** Incidence rate of Crohn's disease (CD) by sex and age in Northern France from 1988 to  
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18 **Figure 4a:** Evolution of the incidence of Crohn's Disease in Northern France from 1988-1990 to  
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20 2006-2007 according to 20-year age groups.  
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23 **Figure 4b:** Evolution of the incidence of Crohn's Disease in Northern France from 1988-1990 to  
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25 2006-2007 according to 10-year age groups.  
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29 **Figure 5:** Incidence rate of Ulcerative Colitis (UC) by sex and age in Northern France from 1988 to  
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31 2007.  
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**Table 1: Trends in Crohn's disease phenotype modifications at diagnosis from 1988 to 2007**

	1988-1990	1991-1993	1994-1996	1997-1999	2000-2002	2003-2005	2006-2007
Age at diagnosis (years)*	27 (20-38)	27 (20-38)	27 (21-38)	27 (20-38)	27 (20-38)	26 (20-39)	25 (19-37)
Interval before diagnosis (months)*	3 (1-12)	3 (1-11)	3 (1-8)	3 (1-7)	3 (1-6)	3 (1-6)	3 (1-8)
Family history of IBD % (n)**	9.4 (70)	11 (95)	11.6 (99)	14.4 (150)	13.9 (136)	15.6 (163)	14.8 (107)
EIMs % (n)**	15.6 (121)	14.5 (146)	11 (113)	13.7 (163)	11.4 (133)	9.9 (118)	11.8 (90)
Complete gut investigation % (n)**	76.9 (618)	72 (752)	73.3 (809)	79.4 (997)	79 (953)	81.2 (987)	86.5 (674)
Disease localization % (n)**							
L1	18.4 (100)	14.8 (102)	15.9 (117)	16 (144)	18 (144)	15 (118)	15.5 (84)
L2	22.6 (123)	16.6 (115)	12.6 (93)	13 (117)	9 (72)	9 (71)	5.4 (29)
L3	43.9 (239)	48.3 (334)	49.3 (363)	46.1 (416)	44.4 (356)	48.3 (380)	45 (244)
L1+L4	3.7 (20)	3.8 (26)	5.3 (39)	4.7 (42)	3.6 (29)	5 (39)	7.6 (41)
L2+L4	3.3 (18)	3 (21)	2.7 (20)	3.2 (29)	2.9 (23)	1.7 (13)	3.3 (18)
L3+L4	8.1 (44)	13.5 (93)	14.1 (104)	17.1 (154)	22.2 (178)	21 (165)	23.2 (126)
Anoperineal lesions % (n)**	17.8 (135)	15.4 (148)	12.1 (122)	11.2 (132)	11.4 (128)	12.2 (141)	12 (91)

\* Continuous variables: median (interquartile range); \*\*Categorical variables: % (n)  
EIMs : Extra intestinal manifestations

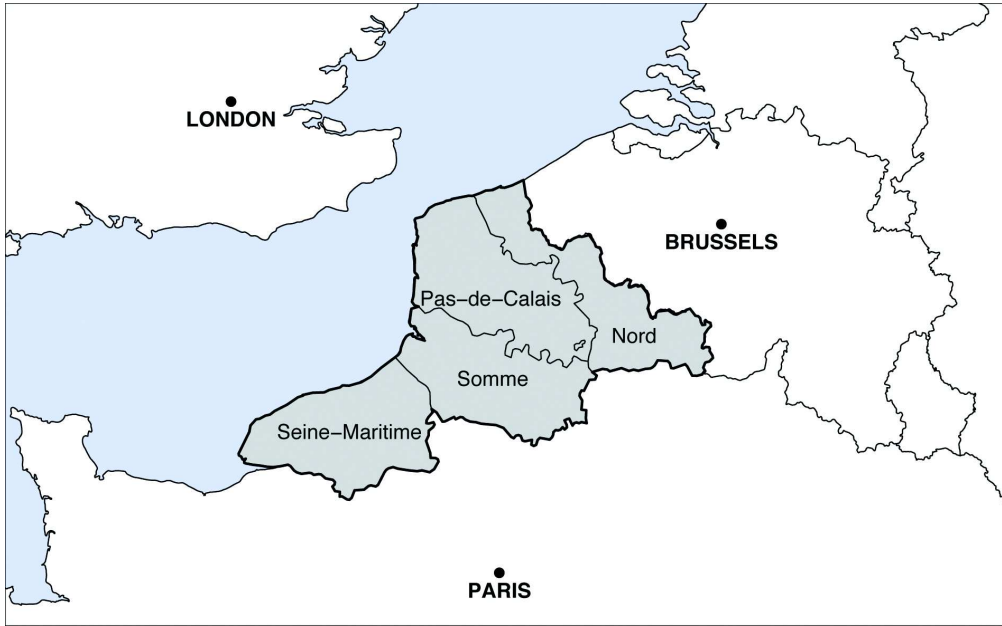
**Table 2: Trends in Ulcerative Colitis phenotype modifications at diagnosis from 1988 to 2007**

	1988-1990	1991-1993	1994-1996	1997-1999	2000-2002	2003-2005	2006-2007
Age at diagnosis (years)*	34 (26-48)	36 (27-49)	34 (26-47)	35 (26-47)	36 (27-48)	36 (27-48)	34 (23-47)
Interval before diagnosis (months)*	2 (1-6)	2 (1-6)	2 (1-6)	2 (1-4)	2 (1-4)	2 (1-5)	3 (2-6)
Family history of IBD % (n)**	3.9 (23)	3.9 (24)	6.1 (35)	7.1 (42)	7.3 (42)	7.8 (52)	7 (26)
EIMs % (n)**	4.9 (30)	3.3 (24)	2.8 (19)	2.9 (20)	2.3 (15)	2.8 (21)	3.1 (12)
Disease localization % (n)**							
E1	28.8 (120)	32.4 (164)	28.3 (141)	27.2 (150)	28 (144)	27.1 (163)	31.3 (101)
E2	45.7 (190)	42.9 (217)	43.6 (217)	45.1 (249)	46.6 (240)	47.4 (285)	39.3 (127)
E3	25.5 (106)	24.7 (125)	28.1 (140)	27.7 (153)	25.4 (131)	25.5 (153)	29.4 (95)

\*Continuous variables: median (interquartile range); \*\*Categorical variables: % (n)

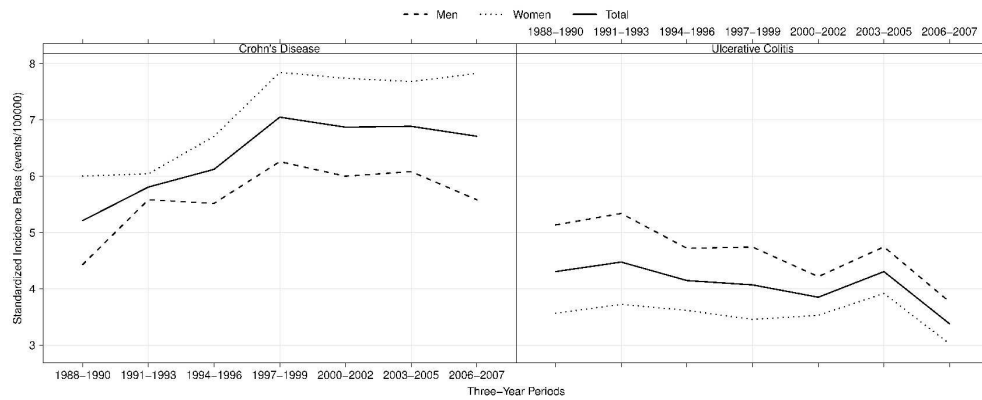
EIMs : Extra intestinal manifestations

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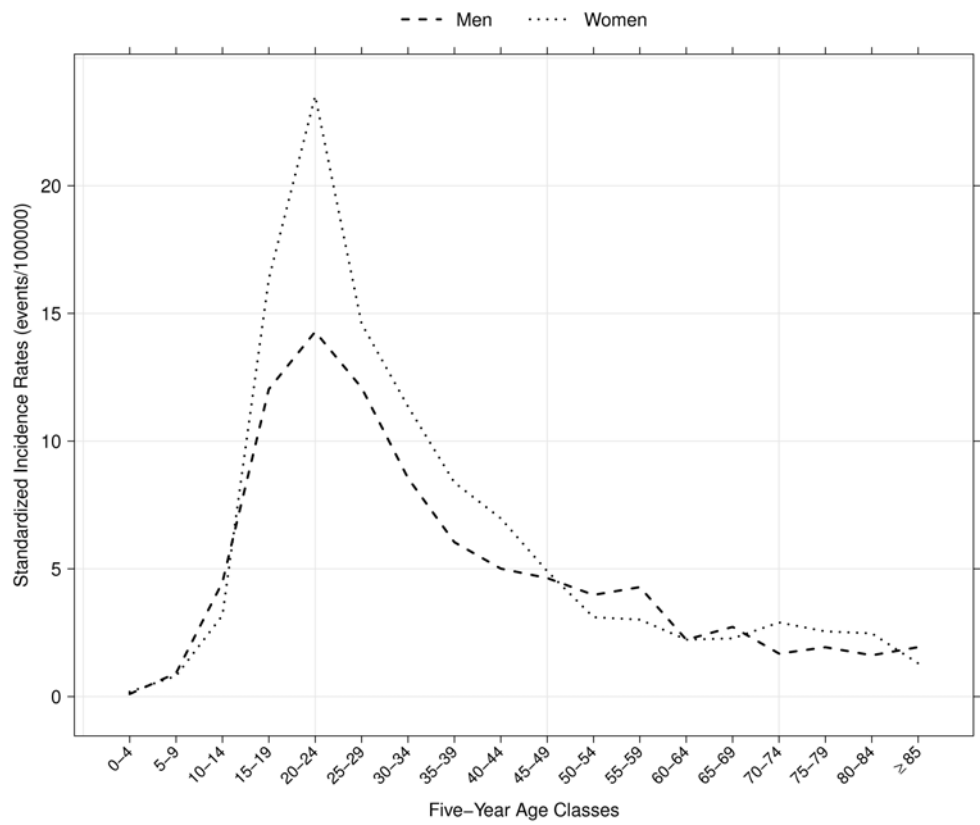


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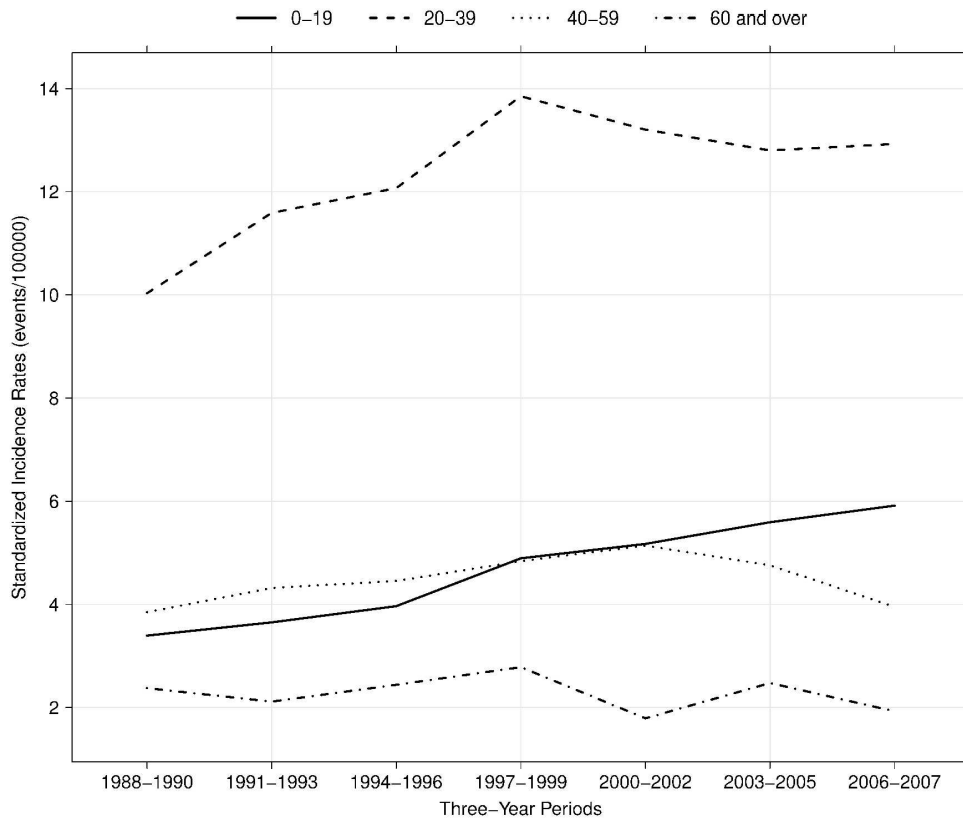
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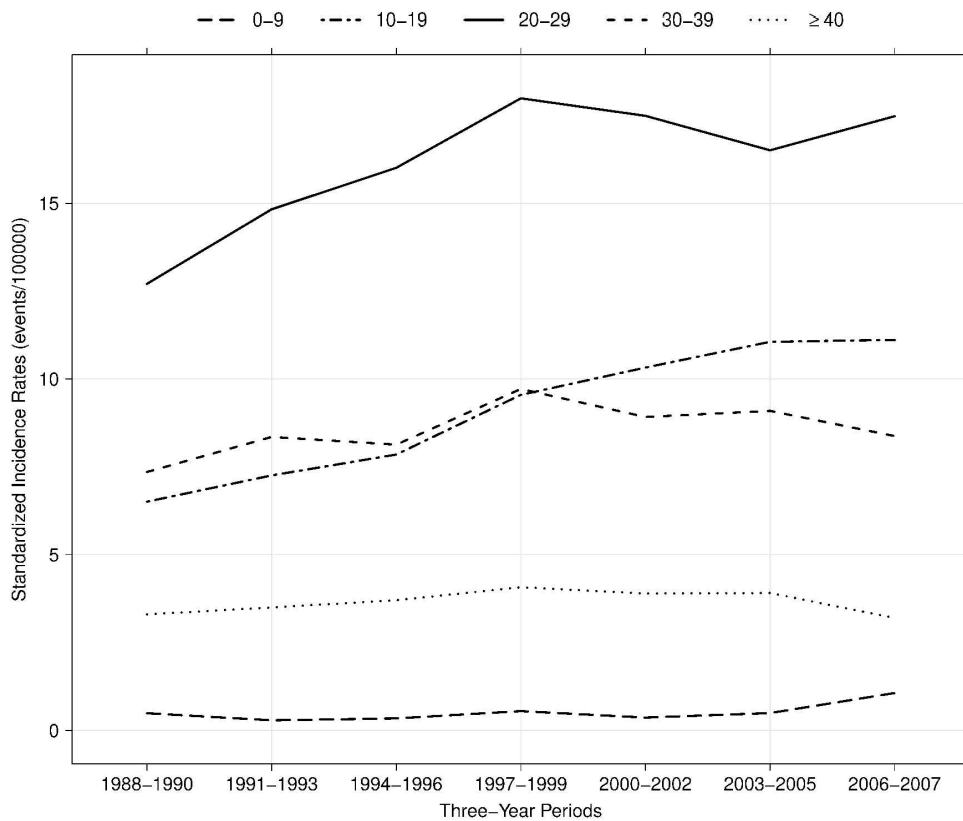
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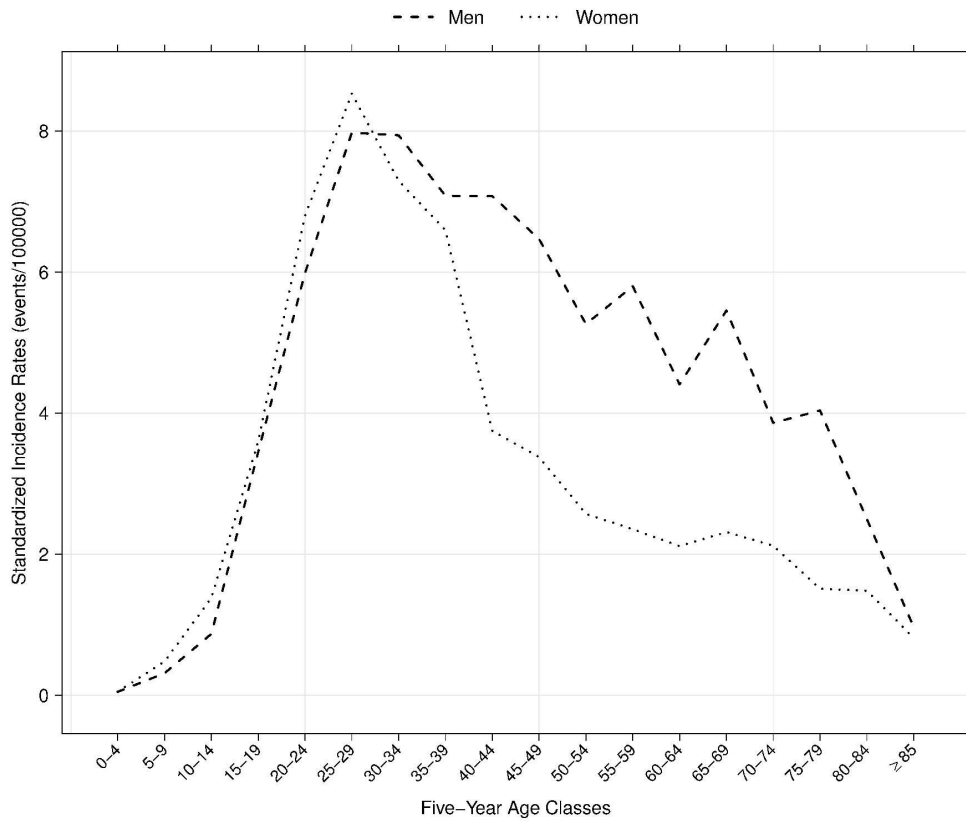


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