



HAL
open science

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.

► To cite this version:

Vincent Chouraki, Guillaume Savoye, Luc Dauchet, Gwenola Vernier-Massouille, Jean-Louis Dupas, et al.. 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).. *Alimentary Pharmacology and Therapeutics*, 2011, 33 (10), pp.1133. 10.1111/j.1365-2036.2011.04628.x . hal-00624176

HAL Id: hal-00624176

<https://hal.science/hal-00624176>

Submitted on 16 Sep 2011

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

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).

Journal:	<i>Alimentary Pharmacology & Therapeutics</i>
Manuscript ID:	APT-0704-2010.R2
Wiley - Manuscript type:	Original Scientific Paper
Date Submitted by the Author:	22-Feb-2011
Complete List of Authors:	<p>Chouraki, Vincent; Hospital University of Lille, Epidemiology Savoye, Guillaume; Hospital and University of Rouen, Hepato Gastroenterology</p> <p>Dauchet, Luc; Hospital University of Lille, Epidemiology Vernier-Massouille, Gwenola; Hospital and University of Lille, Hepato Gastroenterology</p> <p>DUPAS, jean-Louis; CHU Amiens, Hepato-Gastroenterologie Merle, Veronique; Hospital and University of Rouen, Epidemiology Laberenne, Eric; General Hospital of Seclin, Hepato Gastroenterology</p> <p>Salomez, Jean-Louis; Hospital University of Lille, Epidemiology Lerebours, Eric; Hospital and University of Rouen, Hepato Gastroenterology</p> <p>Turck, Dominique; Hospital and University of Lille, Pediatrics Cortot, Antoine; CHU de Lille, Hepatogastroenterology Gower, Corinne; University and Hospital of Lille, Epidemiology Unit-EPIMAD Registry</p> <p>Colombel, Jean-Frédéric; Centre Hospitalier Universitaire de Lille, Service d'Hépto-gastroentérologie</p>
Keywords:	Crohn's disease < Disease-based, Inflammatory bowel disease < Disease-based, Ulcerative colitis < Disease-based, Epidemiology < Topics, Paediatric gastroenterology < Topics

1
2
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).**
6
7
8
9

10
11
12
13 **Short title:** Epidemiology of inflammatory bowel disease.
14

15
16 **Authors:**

17
18 Vincent Chouraki¹, Guillaume Savoye², Luc Dauchet¹, Gwénola Vernier-Massouille³, Jean-Louis
19 Dupas⁴, Véronique Merle², Jean-Eric Laberrenne⁵, Jean-Louis Salomez¹, Eric Lerebours²,
20 Dominique Turck⁶, Antoine Cortot³, Corinne Gower-Rousseau¹, Jean-Frédéric Colombel³.
21
22
23
24
25
26

27
28 ¹ Registre des Maladies Inflammatoires Chroniques de l'Intestin du Nord Ouest de la France
29 (EPIMAD), Epidemiology Unit, Lille University Hospital, France.
30

31 ² EPIMAD, Centre of Rouen, Rouen University Hospital, France.
32

33 ³ EPIMAD, Gastroenterology Unit, Lille University Hospital, France.
34

35 ⁴ EPIMAD, Centre of Amiens, Amiens University Hospital, France.
36

37 ⁵ EPIMAD, Gastroenterology Unit, General Hospital, Seclin, France.
38

39 ⁶ EPIMAD, Paediatric Unit, Lille University Hospital, France.
40
41
42
43
44

45 **Abbreviations**

46
47 IBD, Inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis
48
49
50

51
52 **Keywords**

53
54 Inflammatory Bowel Disease, Incidence, Pediatric, Epidemiology,
55
56
57
58
59
60

Correspondence to:

Docteur Corinne Gower-Rousseau, Epidemiology Unit and Registre EPIMAD, Parc Eurasanté, 154 rue du Dr Yersin, CH et U de Lille, 59037 Lille Cedex, France; Tel: (33) 3 20 44 55 18; Fax: (33) 3 20 44 69 45; corinne.gower@chru-lille.fr

Acknowledgements

The authors wish to thank the interviewing practitioners who collected data: B. Lemaire, N. Guillon, I. Rousseau, A Pétillon, B. Turck, P. Fosse, M. Leconte, C. Le Gallo, C. Dias and S. Richon. The authors thank all gastroenterologists and other specialists who participated in this study.

Conflict of interest: None

Guarantor of the article: Jean-Frédéric Colombel.

Financial support: EPIMAD is organized under an agreement between the Institut National de la Santé et de la Recherche Médicale (INSERM) and the Institut National de Veille Sanitaire (InVS) and also received financial support from the François Aupetit Association, Lion's Club of Northern France, Ferring Laboratories, Astra-Zeneca Company (IRMAD), the Société Nationale Française de Gastroentérologie, Lille University Hospital.

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 Europe¹ 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^{2,3}, their etiology remains unclear¹. 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 in⁴⁻⁶ or stabilization⁷⁻⁹ 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 adolescents¹⁰⁻¹⁶, 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 population¹⁷, as well as a non-significant increase in the pediatric population¹⁸. 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 study area was the northern part of France, which has 5,790,526 inhabitants (1999 national
2 population census) residing in four regions: Nord, Pas-de-Calais, Somme and Seine-Maritime. This
3 part of France represents 9.3% of the total French population and is composed of four sectors: (a)
4 Nord, with 2,554,449 inhabitants and a population density of 445/km²; (b) Pas-de-Calais, with
5 1,441,422 inhabitants and a population density of 216/km²; (c) Somme, with 555,479 inhabitants
6 and a population density of 90/km²; and (d) Seine-Maritime, with 1,239,176 inhabitants and a
7 population density of 197/km². Both rural and urban populations can be found in these areas (ratio
8 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-
9 Maritime). This region is a well-defined geographic entity bordering Belgium and the North Sea
10 (Figure 1). The population is stable—that is, the percentages of the population moving per year for
11 each area were 0.8 for Nord and Pas-de-Calais, 1.1 for Somme and 0.9 for Seine-Maritime (French
12 National Statistical Institute).

31 Data collection

32 The methodology of the EPIMAD registry has been previously described in detail¹⁷⁻¹⁹.
33 Interviewing practitioners collected data on all patients diagnosed between 1988 and 2007 from all
34 adult and pediatric gastroenterologists (GE) (total: 248) practicing in the private or public sector.
35 Only patients who had been residents of the study areas at the time of diagnosis of IBD were
36 included. Each GE reported any patient consulting for the first time with clinical symptoms
37 compatible with IBD, and was contacted by phone at least three times a year by an interviewing
38 practitioner. This interviewer went to the GE's consulting room and collected data from charts in a
39 standardized questionnaire for each new case. Main data collected included age, gender, year of
40 diagnosis, interval between onset of symptoms and diagnosis, and clinical, radiological, endoscopic
41 and histological findings at the time of diagnosis. A final diagnosis of CD or UC was made by two
42 expert gastroenterologists and was recorded as definite, probable or possible according to
43 previously published criteria¹⁹. For the purpose of this study, only patients with definite or probable
44 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 classification²⁰ 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.
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28

29 **Statistical Analyses**

30
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 distribution²¹. 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)²².
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
60
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.
2
3
4 Comparisons of distribution of these variables across time were performed using the Wilcoxon,
5
6
7 Kruskal-Wallis or Chi-squared tests for trend. Analyses were performed with R 2.12.1²³.
8
9

10 11 12 **RESULTS**

13 14 15 **IBD cases**

16
17 During the 1988-2007 period, 12,052 patients satisfying the criteria defined above were
18
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
22
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.
30
31
32

33 34 35 **Incidence of CD**

36
37 During the 1988-2007 period, 7,409 patients were diagnosed with either definite (35%
38
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,
46
47 from 28% in 1988-1990 to 22% in 2006-2007 ($p<0.0001$) (Table 1).
48
49

50
51 During the 1988-2007 period, incidence rate of CD was 6.4 (95% confidence interval (CI) 6.2-6.5).
52
53 CD incidence rate increased significantly, from 5.2 cases per 100,000 person-years in 1988-1990 to
54
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) ($p<0.0001$),
60
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
3
4 between women and men remained stable during the study period (p for interaction=0.21).
5
6 Evolutions in incidence rates did not differ according to region (interaction, p=0.08).
7
8 Evolution of incidence differed according to age group (Figure 4a). Incidence rates in the 0-19 age
9
10 group increased steadily over the entire study period, from 3.4 cases per 100,000 person-years in
11
12 1988-1990 to 5.9 in 2006-2007 (p for trend <0.0001). Evolution of incidence rates in the 0-19 age
13
14 group did not differ according to sex or region (interaction, p=0.10 and p=0.22 respectively).
15
16 Further analyses showed that the 10-19-year-old age group was mainly responsible for this increase,
17
18 since the incidence rates increased continuously, from 6.5 cases per 100,000 person-years in 1988-
19
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
25
26 stabilization beginning from the 1997-1999 period, whereas incidence rates in patients aged 30 and
27
28 over remained stable or only slightly increased.
29
30
31
32
33
34
35

36 **CD phenotypes**

37
38 During the 1988-2007 periods, 5,790 patients underwent complete bowel investigation. The
39
40 proportion of complete bowel investigations significantly increased, from 76.9% in 1988-1990 to
41
42 86.5% in 2006-2007 (p for trend <0.0001). An ileo-colonic localization (L3 and L3+L4) was
43
44 predominant in the overall population and increased during the study period, from 52.0% in 1988-
45
46 1990 to 68.3% in 2006-2007 (p for trend=0.0004). Extended phenotypes (L3+L4) significantly
47
48 increased, from 8.1% in 1988-1990 to 23.2% in 2006-2007 (p for trend <0.0001), whereas an ileo-
49
50 colonic localization without upper GI lesions (L3) remained stable. Colonic site forms (L2)
51
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).
55
56
57
58

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

1
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-
3
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
6
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-
10
11 year-old age groups, as it decreased from 22.5% to 5.8% (test for trend, $p < 0.0001$) and from 40.3%
12
13 to 4.8% (test for trend, $p=0.004$) respectively, but not in the other age groups.
14
15
16
17
18

19 **Incidence of UC**

20
21 From 1988 to 2007, 4,643 incident cases of UC were recorded in the EPIMAD study, with a
22
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
36
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
40
41 (interaction, $p < 0.0001$) with a more important decrease in the patients aged 60 and over than the
42
43 other age groups.
44
45
46
47
48
49

50 **UC phenotype**

51
52 During the 1988-2007 period, 3,411 patients underwent complete colonic investigation. The
53
54 proportion of complete colonic investigations carried out significantly increased, from 66.1% in
55
56 1988-1990 to 82.6% in 2006-2007 (p for trend < 0.0001). E2 localizations constituted most UC
57
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 Minnesota⁸, the United Kingdom⁹ and Sweden⁷. Conversely, other studies in Denmark^{4,5} and Greece⁶ 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 data¹⁷ 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 Norway¹⁴ and Scotland¹¹, and in other studies in Finland¹⁵, Sweden^{10,12}, Australia¹³ and Canada¹⁶. 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
3
4 lapse between symptoms and diagnosis, thereby increasing the incidence rates of CD in younger
5
6 patients. In the EPIMAD study, the median time between symptoms and diagnosis was 3 months,
7
8 which is low. Even if a decreasing proportion of intervals longer than 9 months had been observed
9
10 over time, it would not easily confirm a decrease of several years of age at diagnosis. We therefore
11
12 feel that a true increase in the incidence rates of CD is occurring in adolescents in Northern France.
13
14 Moreover, if our observations had relied only on advances in diagnosis, then this would have
15
16 impacted the incidence rate of the older age groups, which was not the case here. The increase in
17
18 CD incidence in the 10-19 years group could also reflect an earlier presentation of CD in
19
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
23
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 CD²⁴, 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
29
30 national level, two population-based studies concerning teenagers showed a 30% decrease in the
31
32 proportion of 17-year-old subjects reporting daily tobacco consumption, from 41.1% in 2000 to
33
34 28.9% in 2008²⁵, and a 45% decrease among 15- and 16-year-old subjects, from 31% in 1999 to
35
36 17% in 2007²⁶. Moreover, other national data on smoking habits indicate a decrease in the
37
38 prevalence of smoking in every age group^{27, 28} 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
41
42 that protein intake was associated with a higher risk of IBD, CD in particular²⁹.

43
44
45
46
47
48
49
50
51
52 Analysis of the localizations of CD lesions at diagnosis showed a predominance of ileo-colonic (L3)
53
54 forms, with increasing proportions of extended forms, including ileo-colonic and upper
55
56 gastrointestinal lesions (L3+L4), from 1988 to 2007. These results are unusual compared to the
57
58 literature. Some^{4,7, 9}, but not all³⁰, population-based studies reported a higher proportion of pure
59
60 colonic localizations (L2) in CD patients. A possible explanation for these results might lie in the

1
2 fact that we reported CD sites only in patients who had undergone a complete bowel investigation
3
4 (with imaging of both large and small bowel). In other studies, the proportion of pure colonic
5
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.
15
16
17

18
19 Among patients aged 0 to 19, an ileo-colonic (L3) localization constituted most CD lesions at
20
21 diagnosis and this was stable over time. This is coherent with recent studies reporting extensive
22
23 lesions of CD in childhood at diagnosis, either an ileo-colonic localization^{14, 31, 32} or an association
24
25 of ileo-colonic and upper gastrointestinal lesions³³. These differences in phenotypes between adults,
26
27 children and adolescents may reflect the influence of distinct causal factors or a more systematic
28
29 investigation of the gastrointestinal tract in younger patients. One strength of this study lies in the
30
31 number of registered cases, which enabled precise estimates of incidence rates of CD and
32
33 adjustment for covariates in statistical models. Systematic follow-up of newly diagnosed patients at
34
35 18 months allowed for potential reclassification and well-documented final diagnoses of CD. In
36
37 contrast, questions concerning the completeness of case registration may be raised. The EPIMAD
38
39 registry relied only on gastroenterologists' declarations of incident cases, thereafter confirmed by
40
41 experts. In France, gastroenterologists have a monopoly in their profession, especially in terms of
42
43 administrative authorization to perform endoscopy. As a consequence, there is a strong probability
44
45 that each new IBD patient will consult a gastroenterologist and therefore be included in the study.
46
47
48
49
50

51
52 In Northern France, incidence rates of CD continue to rise among younger patients, with a more
53
54 extensive phenotype than in adults. These findings suggest that different causal factors may exist in
55
56 patients aged 10 to 20. It is therefore of great importance to focus etiological research on
57
58 comparisons of trends in incidence rates and phenotypes between adult- and childhood-onset CD.
59
60

Number of words: 3149

1
2 **Figure legends**
3
4

5 **Figure 1:** Geographic situation in Europe of the EPIMAD Registry area.
6

7
8 **Figure 2:** Trends in standardised incidence (95% confidence interval) of Crohn's disease (CD) and
9 ulcerative colitis (UC) in Northern France from 1988–1990 to 2006-2007.
10
11

12
13 **Figure 3:** Incidence rate of Crohn's disease (CD) by sex and age in Northern France from 1988 to
14 2007.
15
16

17
18 **Figure 4a:** Evolution of the incidence of Crohn's Disease in Northern France from 1988-1990 to
19 2006-2007 according to 20-year age groups.
20
21

22
23 **Figure 4b:** Evolution of the incidence of Crohn's Disease in Northern France from 1988-1990 to
24 2006-2007 according to 10-year age groups.
25
26

27
28
29 **Figure 5:** Incidence rate of Ulcerative Colitis (UC) by sex and age in Northern France from 1988 to
30 2007.
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

References

- 1 Loftus E.V. Clinical epidemiology of inflammatory bowel disease: Incidence, prevalence, and environmental influences. *Gastroenterology* 2004; 126: 1504-17.
- 2 Xavier R.J, Podolsky D.K. Unravelling the pathogenesis of inflammatory bowel disease. *Nature* 2007; 448: 427-34.
- 3 Budarf M.L, Labbé C, David G, Rioux J.D. GWA studies: rewriting the story of IBD. *Trends Genet* 2009; 25: 137-46.
- 4 Jacobsen B.A, Fallingborg J, Rasmussen H.H, et al. Increase in incidence and prevalence of inflammatory bowel disease in northern Denmark: a population-based study, 1978-2002. *Eur J Gastroenterol Hepatol* 2006; 18: 601-6.
- 5 Vind I, Riis L, Jess T, et al. Increasing incidences of inflammatory bowel disease and decreasing surgery rates in Copenhagen City and County, 2003-2005: a population-based study from the Danish Crohn colitis database. *Am J Gastroenterol* 2006; 101: 1274-82.
- 6 Economou M, Filis G, Tsianou Z, et al. Crohn's disease incidence evolution in North-western Greece is not associated with alteration of NOD2/CARD15 variants. *World J Gastroenterol* 2007; 13: 5116-20.
- 7 Lapidus A. Crohn's disease in Stockholm County during 1990-2001: an epidemiological update. *World J Gastroenterol* 2006; 12: 75-81.
- 8 Loftus C.G, Loftus E.V, Harmsen W.S, et al. Update on the incidence and prevalence of Crohn's disease and ulcerative colitis in Olmsted County, Minnesota, 1940-2000. *Inflamm Bowel Dis* 2007; 13: 254-61.
- 9 Gunesh S, Thomas G.A.O, Williams G.T, Roberts A, Hawthorne A.B. The incidence of Crohn's disease in Cardiff over the last 75 years: an update for 1996-2005. *Aliment Pharmacol Ther* 2008; 27: 211-19.
- 10 Askling J, Grahnquist L, Ekblom A, Finkel Y. Incidence of paediatric Crohn's disease in Stockholm, Sweden. *Lancet* 1999; 354: 1179.

- 1
2 11 Armitage E, Drummond H.E, Wilson D.C, Ghosh S. Increasing incidence of both juvenile-onset
3
4 Crohn's disease and ulcerative colitis in Scotland. *Eur J Gastroenterol Hepatol* 2001; 13: 1439-47.
5
6 12 Hildebrand H, Finkel Y, Grahnquist L, Lindholm J, Ekblom A, Askling J. Changing pattern of
7
8 paediatric inflammatory bowel disease in northern Stockholm 1990-2001. *Gut* 2003; 52: 1432-4.
9
10 13 Phavichitr N, Cameron D.J.S, Catto-Smith A.G. Increasing incidence of Crohn's disease in
11
12 Victorian children. *J Gastroenterol Hepatol* 2003; 18: 329-32.
13
14 14 Perminow G, Frigessi A, Rydning A, Nakstad B, Vatn M.H. Incidence and clinical presentation
15
16 of IBD in children: comparison between prospective and retrospective data in a selected Norwegian
17
18 population. *Scand J Gastroenterol* 2006; 41: 1433-9.
19
20 21
22 15 Turunen P, Kolho K.-L, Auvinen A, Iltanen S, Huhtala H, Ashorn M. Incidence of inflammatory
23
24 bowel disease in Finnish children, 1987-2003. *Inflamm Bowel Dis* 2006; 12: 677-83.
25
26 27
28 16 Benchimol E.I, Guttman A, Griffiths A.M, et al. Increasing incidence of paediatric
29
30 inflammatory bowel disease in Ontario, Canada: evidence from health administrative data. *Gut*
31
32 2009; 58: 1490-7.
33
34 17 Molinié F, Gower-Rousseau C, Yzet T, et al. Opposite evolution in incidence of Crohn's disease
35
36 and ulcerative colitis in Northern France (1988-1999). *Gut* 2004; 53: 843-8.
37
38 18 Auvin S, Molinié F, Gower-Rousseau C, et al. Incidence, clinical presentation and localization at
39
40 diagnosis of pediatric inflammatory bowel disease: a prospective population-based study in
41
42 northern France (1988-1999). *J Pediatr Gastroenterol Nutr* 2005; 41: 49-55.
43
44 45
46 19 Gower-Rousseau C, Salomez J.L, Dupas J.L, et al. Incidence of inflammatory bowel disease in
47
48 northern France (1988-1990). *Gut* 1994; 35: 1433-8.
49
50 51
52 20 Satsangi J, Silverberg M.S, Vermeire S, Colombel J.-F. The Montreal classification of
53
54 inflammatory bowel disease: controversies, consensus, and implications. *Gut* 2006; 55: 749-53.
55
56 21 Fay M.P, Feuer E.J. Confidence intervals for directly standardized rates: a method based on the
57
58 gamma distribution. *Stat Med* 1997; 16: 791-801.
59
60 22 Akaike H. A new look at the statistical model identification *IEEE T. Automat. Contr.* 1974; 19:

1
2 716-23.
3

4 23 R Development Core Team. R: A Language and Environment for Statistical Computing 2010.
5

6 24 Lakatos P.L, Szamosi T, Lakatos L. Smoking in inflammatory bowel diseases: good, bad or
7 ugly? World J Gastroenterol 2007; 13: 6134-9.
8

9 25 Legleye S, Spilka S, Nezet O.L, Laffiteau C. Drug use among 17 years old. Results of the 2008
10 ESCAPAD survey. Tendances OFDT 2009; 66: 6.
11

12 26 Legleye S, Spilka S, Nezet O.L, Hassler C, Choquet M. Alcohol, tobacco and cannabis at 16
13 years old - Initial results of the French part of the ESPAD 2007 survey. Tendances OFDT 2009; 64:
14 6.
15

16 27 Grizeau D, Baudier F, Janvrin M.P. [Epidemiology of tobacco smoking in France] Rev Prat
17 1993; 43: 1197-202.
18

19 28 Brucker G, Josseran L. [Smoking behavior in France: recent developments] Rev Prat 2004; 54:
20 1871-6.
21

22 29 Jantchou P, Morois S, Clavel-Chapelon F, Boutron-Ruault M.-C, Carbonnel F. Animal protein
23 intake and risk of inflammatory bowel disease: The E3N prospective study. Am J Gastroenterol
24 2010; 105: 2195-201.
25

26 30 Loftus E.V, Silverstein M.D, Sandborn W.J, Tremaine W.J, Harmsen W.S, Zinsmeister A.R.
27 Crohn's disease in Olmsted County, Minnesota, 1940-1993: incidence, prevalence, and survival.
28 Gastroenterology 1998; 114: 1161-8.
29

30 31 Cucchiara S, Latiano A, Palmieri O, et al. Polymorphisms of tumor necrosis factor-alpha but not
31 MDR1 influence response to medical therapy in pediatric-onset inflammatory bowel disease. J
32 Pediatr Gastroenterol Nutr 2007; 44: 171-9.
33

34 32 Gupta N, Bostrom A.G, Kirschner B.S, et al. Gender differences in presentation and course of
35 disease in pediatric patients with Crohn disease. Pediatrics 2007; 120: e1418-e1425.
36

37 33 VanLimbergen J, Russell R.K, Drummond H.E, et al. Definition of phenotypic characteristics of
38 childhood-onset inflammatory bowel disease. Gastroenterology 2008; 135: 1114-22.
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

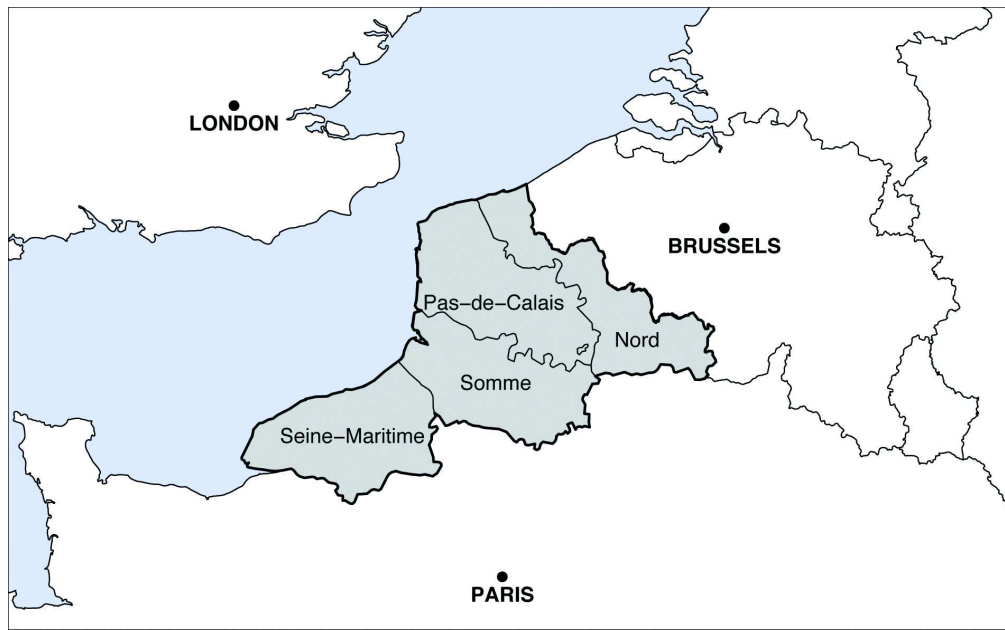
Table 2: Trends in Ulcerative Colitis phenotype modifications at diagnosis from 1988 to 2007

	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)

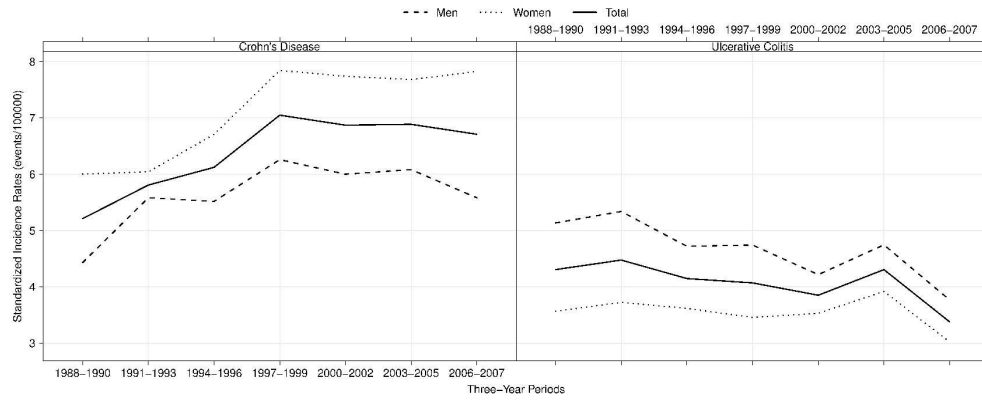
EIMs : Extra intestinal manifestations

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60



Geographic situation in Europe in the area of the EPIMAD registry.
80x49mm (600 x 600 DPI)

Review

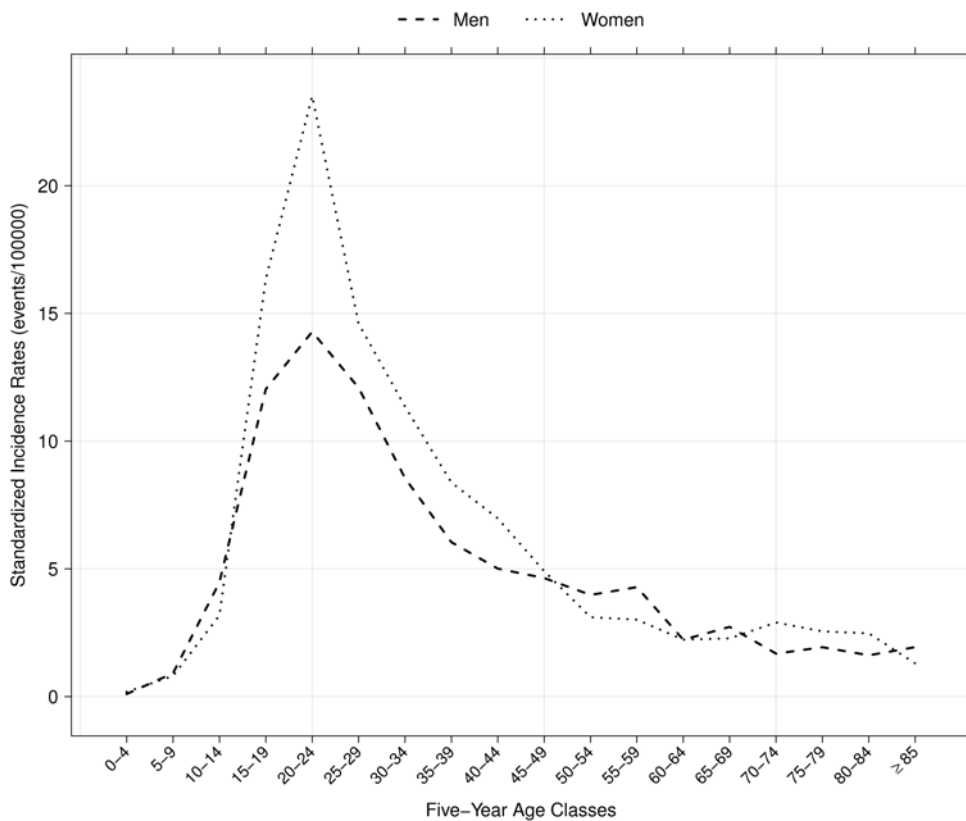


508x203mm (600 x 600 DPI)

Peer Review

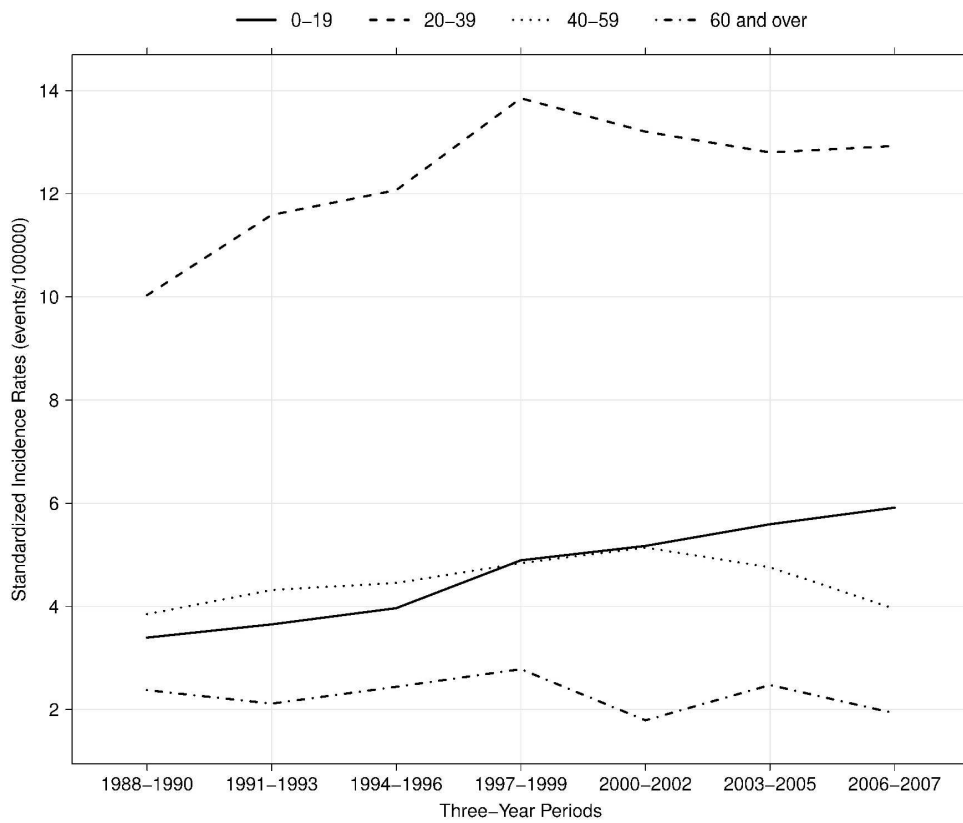
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60



304x254mm (600 x 600 DPI)

view

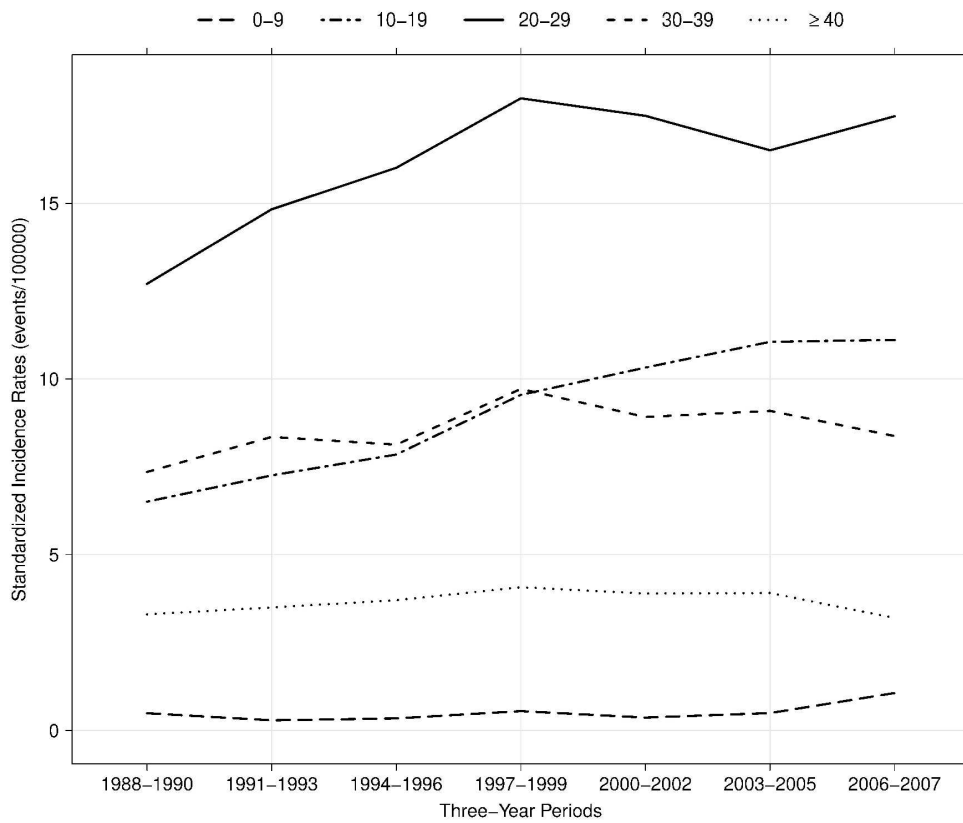


304x254mm (600 x 600 DPI)

view

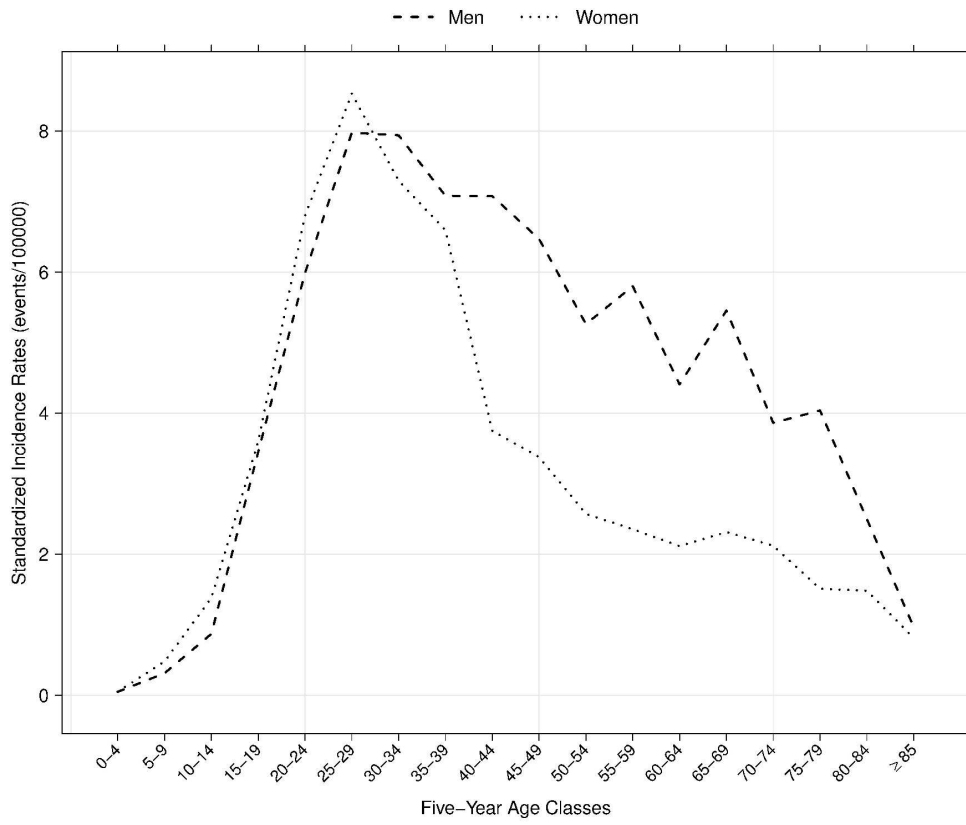
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60



304x254mm (600 x 600 DPI)

view



304x254mm (600 x 600 DPI)

view

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60