East west gradient in the incidence of inflammatory bowel disease in Europe: the ECCO-EpiCom inception cohort

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Statistik II. Course
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Introduction

• Inflammatory bowel disease (IBD): Chronic and relapsing inflammatory state of gastrointestinal tract. Major types are Crohn’s Disease and Ulcerative Colitis (UC).

• UC is an inflammatory disease of the colon affecting the mucosa and submucosa. If severe and longstanding may lead to the development of colon carcinoma.

• Incidence of UC varies between 0 to 24.3 cases/100,000 persons/year, and of CD varies 0 to 20.2 cases/100,000 person/year! IBD is more common in industrialised countries!

• Cause of the disease: unknown! Obviously, it is a disorder of modern society (western life style)!

• Therapy: drug therapy to reduce inflammation and/or surgery.

Problem is far away from being solved!
Potential triggering factors


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<table>
<thead>
<tr>
<th>Acceptance rate</th>
<th>8% for original research submitted in 2013</th>
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</table>
| Time from submission to first decision | 22 days for reviewed original articles  
9 days for all articles |
| Time from acceptance to publication | 19 days (online) |
| Frequency | Monthly |
| Impact factor | 10.732 |
| Indexed by | Index Medicus (Medline), Science Citation Index, ISI  
Current Contents (Clinical Medicine/Life Sciences), Excerpta Medica (Embase), BIOSIS Previews |
| Launch date | 1960 |
| ISSN of Gut | 0017-5749 |
| ISSN of Gut Online | 1468-3288 |
The incidence of IBD is rising world wide, recent studies have reported sharp increases in IBD incidence in Eastern Europe, which are comparable with Western European tendencies.

The question/aim:

Is there any evidence for the existence of an East-West gradient in the incidence of IBD in Europe?
The problem:

The reported increase in Eastern Europe could be due to...

- Methodological bias in previous studies,
- rising awareness of the disease,
- differences in diagnostic practices,
- true changes in IBD incidence.

Design:

- Prospective, uniformly diagnosed, population based inception cohort of IBD patients in 31 centres from 14 Western and eight Eastern European countries.
Methods:

**Study centres:**

- European Crohn’s and Colitis Organisation’s (ECCO) Epidemiology Committee (EpiCom) study. Following an initial meeting, 31 centres from 14 western and 8 Eastern European countries agreed to participate.

- Study covers total background population of approximately 10.1 million people.

- Classification of centres was based on the socioeconomic status of the country before 1990.

- **Pre-requisite for participations:** well defined primary catchment area with population data, including age and gender distribution; established network of gastroenterologists, colorectal surgeons, general practitioners.

- Yearly twice **EpiCom meeting.** Consistency of methods, way of entering data in the EpiCom database.
Methods:

Case definitions:

- Incident cases diagnosed with IBD between 1 Jan. and 31 Dec. 2010 and living in the predefined catchment areas at the time of diagnosis were prospectively included.

- Cases were required to meet the Copenhagen Diagnostic Criteria for CD and UC others classified as IBD unclassified (IBDU)

- Patients younger than 15 years were included as paediatric patients in the paediatric centres (except Czech Republic).

- Disease phenotype classification by disease extent for UC, as well as disease location and behaviour for CD, were defined according to the Montreal classification.

- Medical treatment categories: 5-ASA, steroids, immunomodulators, biological therapy, surgical treatment.
Methods:

**Data collection and validity:**

- Data regarding demographics, disease course, therapy and blood samples were collected at diagnosis and every third month and data were prospectively entered by physicians and/or IBD specialist trained nurses into the EpiCom database (web based inception cohort database).

- Participants took part in the construction and validation tests. All data were standardised by JB, centres were asked to correct inconsistent information.

- Audits of case ascertainment and data quality were performed randomly at 24 of 31 centres. Finland was unable to supply full data on medical treatment due to local restrictions.

**Ethical considerations:**

- The study was approved by the local ethics committees according to local regulations.
Methods:

**Statistical methods:**

- Analysis were performed using SAS V.9.2 software.

- Age and gender standardised annual incidence rates for the adult population were obtained using European Standard population. ¹

- For analysis of a possible GDP effect on IBD incidence, for each centre the GDP (PPP version) of the corresponding country versus the centre wise standardised IBD incidence rate (per 100,000 population per year) was predicted.

- \( p < 0.05 \) was considered statistically significant.
  - * statistically significant
  - ** non significant

- Incidence gradient was analysed using log linear (multiplicative) Poisson regression.

Results:

A total of 1515 patients aged 15 years or older were diagnosed with IBD in 2010. Of these, 535 (35%) patients were diagnosed with CD, 813 (54%) with UC and 167 (11%) with IBDU. In total, 1259 (83%) patients were diagnosed in Western European and 256 (17%) in Eastern European centres. Paediatric IBD was diagnosed in 45 patients (see web appendix available online only). Patient demographics (table 1) were similar in the two geographic regions, except for educational status. Nearly all cases of IBDU (96%) were diagnosed in Western European centres.
Results:

**Disease location at diagnosis**

- Western European centers
- Eastern European centers

**Disease behaviour at diagnosis**

- Western European centers
- Eastern European centers

*Figure 2: Disease location and behaviour at diagnosis for adult patients with Crohn’s disease (NS).*
Results:

Figure 1  Extent of disease at diagnosis for adult patients with ulcerative colitis (UC) (NS).
Results:

Table 1: Demographic characteristics of incident adult and paediatric patients with inflammatory bowel disease

<table>
<thead>
<tr>
<th>Adult patients (≥15 years)</th>
<th>Western European centres</th>
<th>Eastern European centres**</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of patients (n %)</td>
<td>CD UC IBDU</td>
<td>CD UC IBDU</td>
</tr>
<tr>
<td>Males (n %)</td>
<td>220 (51) 375 (56) 78 (48)</td>
<td>63 (60) 82 (57) 4 (67)</td>
</tr>
<tr>
<td>Age (year) (median; range)</td>
<td>34 (16–89; 26) 39 (15–89; 27) 38 (16–64; 28)</td>
<td>32 (15–78; 21) 36 (18–81; 26) 30 (20–34; 5)</td>
</tr>
<tr>
<td>Time from symptoms to diagnosis (months) (median; range; IQR)</td>
<td>4.8 (0–31 years; 10 months) 2 (0–21 years; 4 months) 2.4 (0–30 years; 5.5 months)</td>
<td>3.4 (0–20 years; 6.5 months) 2.2 (0–5 years; 4.6 months) 2.7 (0–8 years; 8 months)</td>
</tr>
</tbody>
</table>

For current and former smokers:

<table>
<thead>
<tr>
<th></th>
<th>Western European centres</th>
<th>Eastern European centres</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current smoker (n %)</td>
<td>142 (36) 52 (9) 20 (15)</td>
<td>39 (38) 16 (11) 2 (33)</td>
</tr>
<tr>
<td>Former smoker (n %)</td>
<td>88 (21) 196 (35) 46 (34)</td>
<td>51 (35) 25 (24) 0 (0)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adult patients (≥15 years)</th>
<th>Western European centres</th>
<th>Eastern European centres</th>
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<tbody>
<tr>
<td>Educational status (n %)*</td>
<td></td>
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</tr>
<tr>
<td>Completed academic education</td>
<td>191 (18)</td>
<td>53 (21)</td>
</tr>
<tr>
<td>Completed non-academic education</td>
<td>564 (55)</td>
<td>131 (52)</td>
</tr>
<tr>
<td>Currently in education</td>
<td>151 (15)</td>
<td>57 (23)</td>
</tr>
<tr>
<td>No education</td>
<td>128 (12)</td>
<td>12 (5)</td>
</tr>
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</table>
Results: 1515 patients aged 15 years or older were included, of whom 535 (35%) were diagnosed with Crohn’s disease (CD), 813 (54%) with ulcerative colitis (UC) and 167 (11%) with IBD unclassified (IBDU). The overall incidence rate ratios in all Western European centres were 1.9 (95% CI 1.5 to 2.4) for CD and 2.1 (95% CI 1.8 to 2.6) for UC compared with Eastern European centres. The median crude annual incidence rates per 100 000 in 2010 for CD were 6.5 (range 0–10.7) in Western European centres and 3.1 (range 0.4–11.5) in Eastern European centres, for UC 10.8 (range 2.9–31.5) and 4.1 (range 2.4–10.3), respectively, and for IBDU 1.9 (range 0–39.4) and 0 (range 0–1.2), respectively. In Western Europe, 92% of CD, 78% of UC and 74% of IBDU patients had a colonoscopy performed as the diagnostic procedure compared with 90%, 100% and 96%, respectively, in Eastern Europe. 8% of CD and 1% of UC patients in both regions underwent surgery within the first 3 months of the onset of disease. 7% of CD patients and 3% of UC patients from Western Europe received biological treatment as rescue therapy. Of all European CD patients, 20% received only 5-aminosalicylates as induction therapy.

A West-East gradient of 2 in IBD incidence exist in Europe!
Results:

The regional annual incidence rates for IBD combined, and for CD, UC and IBDU separately, differed significantly between Eastern and Western Europe (p<0.01)

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### Table 2: Incidence rates per 100,000 for inflammatory bowel disease, Crohn’s disease, ulcerative colitis and inflammatory bowel disease unclassified in Europe for patients aged 15 years or older in 2010

<table>
<thead>
<tr>
<th>Western European centres</th>
<th>No of patients</th>
<th>IBD adjusted (SE)</th>
<th>CD adjusted (SE)</th>
<th>UC adjusted (SE)</th>
<th>IBDU adjusted (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyprus, Nicosia</td>
<td>27</td>
<td>11.2</td>
<td>6.2</td>
<td>6.3 (1.4)</td>
<td>2.9</td>
</tr>
<tr>
<td>Denmark, Aarhus</td>
<td>55</td>
<td>21.2</td>
<td>8.5</td>
<td>8.2 (2.0)</td>
<td>10.8</td>
</tr>
<tr>
<td>Denmark, Aalborg</td>
<td>52</td>
<td>21.2</td>
<td>8.5</td>
<td>8.2 (2.0)</td>
<td>10.8</td>
</tr>
<tr>
<td>Denmark, Amager</td>
<td>23</td>
<td>17.2</td>
<td>5.2</td>
<td>4.8 (1.0)</td>
<td>7.5</td>
</tr>
<tr>
<td>Denmark, Fanø</td>
<td>123</td>
<td>30.7</td>
<td>10.7</td>
<td>11.4 (1.0)</td>
<td>18.7</td>
</tr>
<tr>
<td>Denmark, Herlev</td>
<td>48</td>
<td>22.4</td>
<td>6.6</td>
<td>7.0 (0.9)</td>
<td>7.5</td>
</tr>
<tr>
<td>Denmark, Helsingør</td>
<td>49</td>
<td>21.2</td>
<td>6.5</td>
<td>7.1 (1.0)</td>
<td>12.6</td>
</tr>
<tr>
<td>Denmark, Viborg</td>
<td>37</td>
<td>24.6</td>
<td>8.6</td>
<td>9.6 (2.7)</td>
<td>14.6</td>
</tr>
</tbody>
</table>

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Färö Islands: 31, 81.5, 83.1 (15.0), 10.5, 11.1 (1.6), 31.5, 31.8 (9.3), 39.4, 40.2 (10.5)

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Europe: 107, 20.2, 27.7 (1.7), 14.0, 14.0 (2.7), 20.8, 20.8 (2.7), 40.8, 40.8 (2.7)

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France, Alsace: 15, 9.2, 10.2 (2.6), 3.1, 3.5 (1.6), 5.5, 6.0 (2.0), 0.6, 0.7 (0.7)

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Greece, Ioannina: 4, 2.0, 4.4 (1.6), 0.0, 0.0 (0.0)

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Iceland: 72, 28.7, 28.5 (3.4), 5.6, 5.6 (1.5), 17.6, 17.8 (2.7), 5.2, 5.1 (1.4)

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Ireland, Ballymena: 36, 13.2, 12.9 (2.2), 4.8, 4.3 (1.2), 4.4, 4.2 (1.2), 4.0, 4.4 (1.4)

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The paper

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Results:

Figure 3  Incidence rates (100 000) of cases aged 15 years or older for inflammatory bowel disease (IBD) in selected areas in Europe in 2010.
Results:

The observed incidences correlated with the GDP!!!
The observed regional differences in treatment for UC and CD patients were significant (p<0.01)!!!
Conclusion:

- An **East-West gradient in IBD incidence exists in Europe!**
**Design:**

Europe

Western Europe

Eastern Europe

Population based cohort

2010. 1. jan.  
2010. 31. dec.

Prospective cohort
Critical appraisal

- Population based inception cohort. Total background of 10,1 million people (population), unselected IBD patients treated in centers (cohort), inclusion at the time of registration (inception) in 2010.

- Study design is relevant to clinical population. The study addresses an appropriate and clearly focused question! The outcomes are clearly defined.

- Inclusion criteria are well defined. Inclusion criteria patients with IBD living in the predefined areas older than 15 years. That means, everybody, who had to be included was integrated in the study!

- No selection bias!

- Inclusion of the centers is well defined! Amount of Western- (14) and Eastern- (8) European centers and number of patients differ!

- Diagnostic methods and criteria, international guidelines, disease severity, demographic details etc. were clearly specified. Participants have been educated in order to achieve consistency of methods. No information, detection bias!
Critical appraisal

• Groups: IBD, CD, IBDU. well defined! The same objective measurements in the groups! Systematic errors if exist should be equal in the groups! Results should be valid!

• Patient populations in Eastern and Western Europe are identical (patient characteristics, disease extent and phenotype, smoking habits, diagnostic delay). The cohorts are comparable!

• But we don’t know if the patients are representative samples of the population? (Alteration of the education level!)

• Open study. Patients and participants were not blinded, study design doesn’t need it! Maybe at the level of statistical analysis?
Incidence of inflammatory bowel disease in the province of Styria, Austria, from 1997 to 2007: a population-based study.

**BACKGROUND:**
The incidence of inflammatory bowel disease (IBD) varies widely between different countries. This large variation is also observed for the incidence of its main two forms, ulcerative colitis (UC) and Crohn's disease (CD). Controversy exists whether IBD incidence is increasing, especially in western countries. Currently no data are available for Austria. This study therefore aimed to evaluate for the first time the incidence of IBD over an eleven-year period in Styria, a province of Austria with a population of 1.2 million.

**METHODS:**
All patients with an initial diagnosis of IBD between 1997 and 2007, who were Styrian residents, were eligible for this retrospective study. Data were acquired from electronically stored hospital discharge reports and individual reports by patients and physicians. According to population density Styria was divided into two rural and one urban area.

**RESULTS:**
Throughout the study period 1527 patients with an initial diagnosis of IBD were identified. The average annual incidence was 6.7 (95% CI 6.2-7.1) per 100,000 persons per year for CD and 4.8 (95% CI 4.5-5.2) for UC. The average annual incidence increased significantly (p<0.01) for both diseases during the 11 year study period. Median age at initial diagnosis was 29 years (range 3-87) for CD and 39 years (range 3-94) for UC. At diagnosis, 8.5% of all IBD patients were <18 years of age. The incidence of both CD and UC was significantly higher in the urban area than in rural areas (CD: 8.8, 95% CI 7.8-9.8 versus 5.5, 95% CI 4.7-6.4 and 5.9, 95% CI 5.3-6.7; [p<0.001]; UC: 5.8, 95% CI 5.1-6.6 versus 4.0, 95% CI 3.4-4.7 and 4.7, 95% CI 4.1-5.4; [p=0.04]).

**CONCLUSION:**
We observed an overall increase in the incidence of ulcerative colitis and Crohn's disease in a part of Austria during an eleven year period. IBD was more predominant in the largest urban area than in rural areas.