



Original Article

# Long-term Clinical Outcomes of Urban Versus Rural Environment in Korean Patients with Crohn's Disease: Results from the CONNECT Study

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## Abstract

**Background aims:** Environmental factors and genetic predisposition are thought to play important roles in the pathogenesis of Crohn's disease [CD]. Although numerous studies have reported the positive association between urban environment and CD development, few studies have compared the clinical outcomes between urban and rural environments. Therefore, this study aimed to compare the clinical characteristics and long-term prognosis between urban and rural populations of patients with CD.

**Methods:** This retrospective multicenter cohort study included 1002 Korean patients diagnosed with CD [743 urban residents and 259 rural residents] between 1982 and 2008 from 32 medical centers. The clinical outcomes of urban versus rural populations were compared using the KaplanMeier method and log-rank test.

**Results:** Disease distribution and behavior of the urban population did not differ from those of the rural population. There were no significant differences in the cumulative probabilities of perianal fistula [ $P = 0.086$ ] and intestinal complications such as stricture [ $P = 0.109$ ], fistula [ $P = 0.952$ ], abscess [ $P = 0.227$ ], and perforation [ $P = 0.382$ ] between the two groups. In addition, no significant differences were observed between the two groups with regard to the cumulative probabilities of immunosuppressant use [ $P = 0.527$ ] and biologic agent use [ $P = 0.731$ ]. Although the cumulative probability of surgery in the urban population was significantly higher than that in the rural population [ $P = 0.040$ ], this difference was mainly established within the first year from diagnosis [19.1% vs 13.5%,  $P = 0.042$ ] and observed only among patients diagnosed in 2005–2008 [ $P = 0.033$ ].

**Conclusions:** There were no differences in terms of disease presentation and natural history between urban and rural populations, except for a higher rate of surgery in the urban population who were recently diagnosed with CD.

**Keywords:** Crohn's disease; urban environment; rural environment; clinical outcome

## 1. Introduction

The incidence of inflammatory bowel diseases [IBD] varies within different geographical areas. The highest incidence and prevalence rates for IBD have been reported from developed countries in northern Europe, especially the UK and Scandinavia,<sup>1-4</sup> and North America,<sup>5</sup> whereas much lower indices were observed in Asia.<sup>5</sup> However, in recent decades, the incidence and prevalence rates of IBD, especially Crohn's disease [CD], continued to rise in Asia where IBD previously was less common.<sup>6,7</sup> The differences in incidence across geographical regions and time suggest that environmental factors, in addition to genetic predisposition, play an important role in the development of IBD. Many studies in recent decades have sought to identify environmental factors that affect the development of IBD. Environmental factors have been investigated as both protective and inciting factors for IBD onset. One such environmental factor is urban versus rural lifestyle. Several observational studies have shown that living in an urban setting has been associated with an increased risk for IBD.<sup>8-11</sup> A recent systematic review with meta-analysis in which 40 studies were analyzed also reported a positive association between urban environment and IBD (pooled incidence rate ratio [IRR] 1.17 for ulcerative colitis and pooled IRR 1.42 for CD).<sup>12</sup> These results suggest that environmental factors such as population density, socioeconomic status, education, eating habits, lifestyle changes, and air pollution may affect the development of IBD. We speculate that these environmental factors can influence the clinical course as well as the development of IBD. However, few studies have compared the clinical characteristics and clinical outcomes between urban and rural environments, although numerous studies have investigated the association between urban environment and IBD development. Furthermore, most studies on the relationship between urban environment and IBD were conducted exclusively in Western countries. Therefore, the objective of this study was to compare the long-term clinical outcomes as well as clinical characteristics between urban and rural populations of Korean patients with CD.

## 2. Materials and Methods

### 2.1 Study population

The Crohn's disease clinical network and cohort study was conducted nationwide in Korea.<sup>13</sup> This retrospective multicenter cohort study included patients diagnosed with CD between July 1982 and December 2008 from 30 university hospitals and 2 local hospitals with a gastroenterology specialty. IBD specialists who are members of the Korean Association for the Study of Intestinal Diseases diagnosed and treated all patients. CD diagnoses were confirmed by previously established international criteria based on clinical, endoscopic, histopathological, and radiological findings.<sup>14</sup>

We identified patients' residences at the time of CD diagnosis and at the time of last follow-up. Patients were separated into two groups according to their residences [urban versus rural regions]. Any patients who resided within cities with > 500 000 inhabitants were regarded as belonging to an urban population, and patients who

resided within areas with < 500 000 inhabitants as belonging to a rural population, based on the Korean Local Autonomy Law, Article 175. Patients with incomplete medical records or those who changed their residences such as urban to rural area or rural to urban area were excluded. Urban regions included Seoul, Busan, Incheon, Daegu, Daejeon, Gwangju, Ulsan, Suwon-si, Changwon-si, Seongnam-si, Goyang-si, Yongin-si, Bucheon-si, Ansan-si, Cheongju-si, Jeonju-si, Anyang-si, Cheonan-si, Pohang-si, Namyangju-si, Hwaseong-si, and Gimhae-si. This study was approved by the institutional review boards at the participating medical centers.

### 2.2 Data collection and clinical outcome measurement

Patient demographics and clinical information were obtained by reviewing administered questionnaires and electronic medical records at each participating hospital. Demographic data including age at diagnosis, gender, disease duration [from diagnosis to last follow-up], and family history of IBD [first-degree relative with IBD] were collected. Disease location and disease behavior were classified according to the Montreal classification.<sup>15</sup>

The long-term clinical outcomes were assessed based on cumulative probabilities of perianal fistula, intestinal complications, immunosuppressant use, biologic agent use, and operation after diagnosis, and cumulative probabilities of reoperation after surgery. Intestinal complications such as free perforation, fistula, stricture, and abscess were assessed by radiologic or endoscopic modalities. Stricture was defined as luminal narrowing demonstrated by radiologic, endoscopic, or surgical pathologic methods with prestenotic dilatation or obstructive symptoms. Surgery was defined as an intestinal resection related to CD [excluding anal fistula-related surgery such as anal fistulotomy or fistulectomy and strictureplasty]. Hospitalizations included only CD-related admissions. Immunosuppressants referred to thiopurine drugs such as azathioprine and 6-mercaptopurine because other immunosuppressants, including methotrexate, tacrolimus, etc., are rarely used for patients with CD in Korea. Biologic agents referred to infliximab or adalimumab.

### 2.3 Statistical analysis

The software program SPSS [v. 18, Chicago, IL] was used for statistical analysis and a value of  $P < 0.05$  was considered statistically significant. The Student's *t*-test or Mann-Whitney *U*-test was used to compare numerical variables between the groups. The chi-square or Fisher's exact test was used to compare categorical variables. The cumulative probabilities of perianal fistula, intestinal complications, immunosuppressant use, biologic agent use, operation after diagnosis, and reoperation after surgery were calculated using the Kaplan-Meier method, with differences determined using the log-rank test. We constructed multivariate logistic regression models to identify whether urban versus rural environment is an independent factor associated with outcomes of interest. Correlations between potential predictors and outcomes of interest were estimated by hazard ratios [HRs] with 95% confidence intervals [CIs].

### 3. Results

#### 3.1 Clinical characteristics of urban versus rural populations

In total, 1382 patients with a diagnosis of CD were identified. Of these patients, 380 were excluded for the following reasons: incomplete data on residence [ $n = 327$ ], incomplete clinical data [ $n = 33$ ], and change of residence such as urban to rural area or rural to urban area [ $n = 20$ ]. Finally, 1002 patients [743 urban residents and 259 rural residents] were included in the study. The clinical characteristics of the urban and rural populations with CD are summarized in Table 1. Both groups showed male predominance [72.4% vs 75.7%,  $P = 0.306$ ]. The mean disease duration for the urban population was longer than that for the rural population [8.4 years vs 7.7 years,  $P = 0.031$ ]. The median duration from symptom onset to diagnosis did not differ significantly between the urban and rural populations [3.7 vs 3.9 months,  $P = 0.634$ ]. In addition, there were no significant differences in the mean age at diagnosis, disease distribution, disease behavior, or frequency of CD-related hospitalization between

the two groups. However, the urban population showed a significantly higher frequency of CD-related operation compared with that for the rural population [32.0% vs 23.9%,  $P = 0.014$ ]. During the follow-up period, colorectal or small bowel cancer occurred in five patients, four of whom were urban residents and one of whom was a rural resident [0.5% vs 0.4%,  $P = 1.000$ ].

#### 3.2 Long-term clinical outcomes of urban versus rural populations

There were no significant differences in the cumulative probabilities of perianal fistula [ $P = 0.086$ ] and intestinal complications such as stricture [ $P = 0.109$ ], fistula [ $P = 0.952$ ], abscess [ $P = 0.227$ ], and perforation [ $P = 0.382$ ] between urban and rural populations. At 5 years after diagnosis, the cumulative probabilities of perianal fistula, intestinal stricture, intestinal fistula, intra-abdominal abscess, and intestinal perforation were 31.0%, 18.8%, 9.5%, 9.4%, and 7.6%, respectively, for the urban population; and 39.2%, 25.3%, 11.0%, 13.1%, and 6.5%, respectively, for the rural population.

**Table 1.** Clinical characteristics of patients with Crohn's disease from urban versus rural regions.

Characteristics	Urban population [ $n = 743$ ]	Rural population [ $n = 259$ ]	P-value
Sex, male [%]	538 [72.4]	196 [75.7]	0.306
Age at diagnosis [years]	27.8 ± 11.9	27.2 ± 12.7	0.518
Disease duration [years]	8.4 ± 4.6	7.7 ± 4.2	0.031
Duration from symptom onset to diagnosis [months]	3.7 [0.7–16.2]	3.9 [0.8–12.4]	0.634
Family history of IBD	18 [2.4]	3 [1.2]	0.221
Disease distribution <sup>a</sup>			
L1 [isolated ileal disease] <sup>b</sup>	162 [23.0]	63 [25.8]	0.374
L2 [isolated colonic disease] <sup>b</sup>	101 [14.3]	37 [15.2]	0.755
L3 [ileocolonic disease] <sup>b</sup>	441 [62.6]	144 [59.0]	0.315
L4 [concomitant UGI disease]	163 [21.9]	52 [20.1]	0.530
EGD disease	46 [6.2]	20 [7.7]	0.392
Jejunal disease	132 [17.8]	37 [14.3]	0.198
Disease behavior <sup>a</sup>			
B1 [nonstricturing, nonpenetrating]	438 [59.0]	142 [54.8]	0.247
B2 [stricturing]	113 [15.2]	47 [18.1]	0.266
B3 [penetrating]	192 [25.8]	70 [27.0]	0.708
History of perianal fistula	256 [34.5]	103 [39.8]	0.125
CD-related hospitalization	552 [74.3]	196 [75.7]	0.660
Number of CD-related hospitalizations	1 [0–4]	2 [1–3]	0.570
CD-related surgery <sup>c</sup>	238 [32.0]	62 [23.9]	0.014
Surgery <sup>c</sup> within the first year from diagnosis	142 [19.1]	35 [13.5]	0.042
Surgery <sup>c</sup> after 1 year from diagnosis	96 [12.9]	27 [10.4]	0.292
History of intestinal complications			
Stricture	182 [24.5]	74 [28.6]	0.195
Fistula <sup>d</sup>	101 [13.6]	33 [12.7]	0.729
Abscess	97 [13.1]	39 [15.1]	0.418
Perforation	74 [10.0]	20 [7.7]	0.288
Medication			
5-Aminosalicylate	715 [96.2]	252 [97.3]	0.421
Antibiotics	413 [55.6]	154 [59.5]	0.279
Corticosteroids	462 [62.2]	166 [64.1]	0.584
Methotrexate	8 [1.1]	3 [1.2]	1.000
Azathioprine/6-mercaptopurine	518 [69.7]	175 [67.6]	0.519
Biologic agent [infliximab/adalimumab]	212 [28.5]	69 [26.6]	0.559
Colorectal or small bowel cancer	4 [0.5]	1 [0.4]	1.000

IBD, inflammatory bowel disease; UGI, upper gastrointestinal; EGD, esophagogastroduodenal; CD, Crohn's disease.

Data are presented as mean ± SD, median [interquartile range] or number [%].

<sup>a</sup>Montreal classification.

<sup>b</sup>The disease distribution of 54 patients was not documented.

<sup>c</sup>Excluded anal fistula-related surgery and strictureplasty.

<sup>d</sup>Excluded anal fistula formation.

At 10 years after diagnosis, the cumulative probabilities of perianal fistula, intestinal stricture, intestinal fistula, intra-abdominal abscess, and intestinal perforation were 36.6%, 28.5%, 17.1%, 14.6%, and 11.8%, respectively, for the urban population; and 42.4%, 35.9%, 13.7%, 17.2%, and 8.5%, respectively, for the rural population.

In addition, no significant differences were observed between the two groups with regard to the cumulative probabilities of immunosuppressant use [ $P = 0.527$ ] and biologic agent use [ $P = 0.731$ ]. At 1 year, 5 years, and 10 years after diagnosis, the cumulative rates of immunosuppressant use were 26.3%, 54.3%, and 75.0%, respectively, for the urban population; and 26.8%, 56.1%, and 72.7%, respectively, for the rural population. For biologic agent use, the rates were 2.2%, 15.5%, and 33.0%, respectively, for the urban population; and 4.4%, 17.9%, and 31.7%, respectively, for the rural population.

Among 743 urban residents and 259 rural residents, 238 [32.0%] and 62 [23.9%] patients underwent at least one surgical intestinal resection, respectively [ $P = 0.014$ ]. The urban population showed a significantly higher cumulative operation rate compared with that for the rural population [ $P = 0.040$ , Figure 1]. At 1 year, 5 years, and 10 years after diagnosis, the cumulative rates of surgery were 19.2%, 25.8%, and 35.8%, respectively, for the urban population; and 13.6%, 20.4%, and 29.8%, respectively, for the rural population. The urban population showed a significantly higher frequency of CD-related surgery within the first year from diagnosis compared with that for the rural population [19.1% vs 13.5%,  $P = 0.042$ ],

whereas there was no difference in frequency of surgery after 1 year from diagnosis between the two groups [12.9% vs 10.4%,  $P = 0.292$ ] [Table 1]. Also, we analyzed differences in outcomes according to diagnosis time [138, 331, and 533 patients diagnosed in 1986–1999, 2000–2004, and 2005–2008, respectively] between the two groups using the log-rank test. Interestingly, the urban population showed a significantly higher cumulative operation rate compared with that for the rural population only among patients diagnosed in 2005–2008 [ $P = 0.033$ ], whereas there were no significant differences in cumulative operation rates between the two groups among patients diagnosed in 1986–1999 and 2000–2004 [ $P = 0.150$  and  $P = 0.524$ , respectively]. Regarding indications for surgery, intestinal obstruction or stricture was more common in rural population [23.9% vs 38.7%,  $P = 0.020$ ] [Table 2]. In a multivariate analysis that adjusted for sex, age, disease duration, disease distribution, disease behavior, and medication use, the urban environment was identified as an independent predictive factor for operation [Table 3].

Among the 238 urban residents and 62 rural residents who underwent operation, 56 [23.5%] and 11 [17.7%] patients underwent reoperation, respectively. There were no significant differences in the cumulative reoperation rate between urban and rural populations [ $P = 0.336$ ].

4. Discussion

This large, multicenter, cohort study is the first and largest to compare the long-term clinical outcomes of urban versus rural populations systematically and in detail among patients with CD. To date, no studies have investigated the clinical characteristics or long-term prognosis between urban and rural environments, especially among patients with IBD from Asia, although several epidemiologic studies<sup>8–11</sup> and a recent meta-analysis study<sup>12</sup> from Western countries have reported that living in urban environments has increased the risk of developing IBD. Contrary to Western studies that demonstrated a positive association between urban environment and the IBD development, our study showed that there were no differences in terms of disease presentation or clinical outcomes between urban and rural populations, except for a higher rate of surgery in the urban population.

Several factors may affect the clinical outcomes of CD, including population density, air pollution, exposure to industrial agents, dietary factors, and lifestyle changes. In an ecologic study, total air emissions of criteria pollutants were associated with hospitalizations for IBD in adults.<sup>16</sup> The urban diet may also influence the clinical course of CD. Compared with its rural counterpart, the urban diet contains significantly higher quantities of inert inorganic non-nutrient microparticles such as natural contaminants [soil and dust] and food

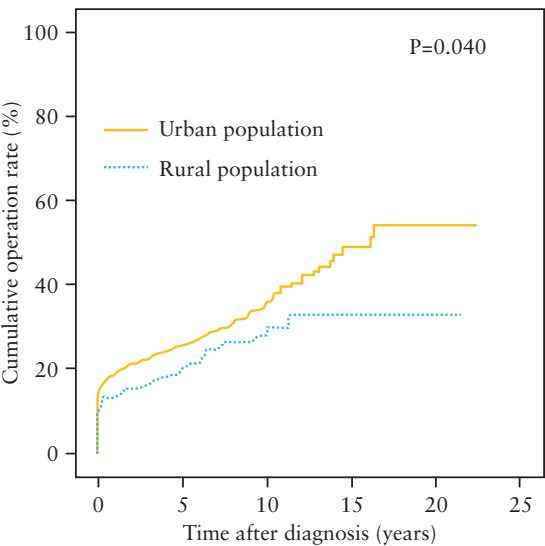


Figure 1. The cumulative probability of operation.

Table 2. Indications for surgery in patients with Crohn's disease from urban versus rural regions.

Indication	Urban population [n = 238]	Rural population [n = 62]	P-value
Intractability with medical treatment	29 [12.2]	8 [12.9]	0.878
Intestinal obstruction or stricture	57 [23.9]	24 [38.7]	0.020
Intestinal fistula	25 [10.5]	7 [11.3]	0.858
Intra-abdominal abscess	34 [14.3]	10 [16.1]	0.715
Intestinal perforation	65 [27.3]	12 [19.4]	0.201
Intestinal bleeding	8 [3.4]	0	0.213
Abdominal mass or to rule out cancer	10 [4.2]	3 [4.8]	0.736
Unknown	27 [11.3]	2 [3.2]	0.054

Data are presented as number [%].

**Table 3.** Predictive factors for operation<sup>a</sup> using multivariate Cox hazard regression analysis.

Variable	HR	95% CI	P-value
Urban regions	1.34	1.01–1.78	0.046
Sex, male	1.01	0.78–1.30	0.947
Age at diagnosis	1.02	1.01–1.03	0.001
Disease duration	1.02	0.99–1.05	0.083
Ileocolonic disease	1.05	0.82–1.33	0.721
UGI involvement	1.55	0.20–1.98	0.001
Stricture or penetrating disease	7.90	5.82–10.74	<0.001
Perianal fistula	0.70	0.54–0.90	0.006
Corticosteroids use	0.96	0.75–1.24	0.774
Immunosuppressants use	0.85	0.64–1.12	0.249
Biologic agent [infliximab, adalimumab] use	1.14	0.88–1.48	0.318

HR, hazard ratio; CI, confidence interval; UGI, upper gastrointestinal.

<sup>a</sup>Excluded anal fistula-related surgery and strictureplasty.

additives, which may combine with intestinal luminal components such as bacterial cell wall lipopolysaccharides to form antigenic particles.<sup>17</sup> A preliminary trial showed that patients with CD allocated to a low microparticle diet experienced a significant reduction in disease activity and the requirement for corticosteroids when compared with the control group on a normal diet.<sup>18</sup>

It is possible that sociodemographic factors such as occupation and education level affect the clinical outcomes of CD. Previous studies have shown that IBD tends to affect the more educated and affluent socioeconomic strata of the population.<sup>11,19,20</sup> In a study of German employees, occupations involving work in the open air and physical exercise are protective, whereas being exposed to air-conditioned artificial working conditions or extended and irregular shift working confer a risk of contracting IBD.<sup>21</sup> A study using a large national database in the USA reported that IBD mortality was relatively more common in white-collar workers than in blue-collar workers.<sup>22</sup> Another study demonstrated that urban occupations such as driving and manufacturing carry a significantly increased risk of hospitalization for IBD.<sup>23</sup>

Numerous studies have proved that the intestinal microbiota play an important role in the pathogenesis of IBD.<sup>24</sup> Differences in intestinal microbiota between urban and rural populations may influence the clinical course of CD. Reduced exposure to immunoregulation-inducing macro- and microorganisms and microbiota predisposes to poor regulation of inflammation [the hygiene hypothesis].<sup>25</sup> The lack of exposure to enteric pathogens with improved sanitation in urban cities may lead to a greater susceptibility to develop an inappropriate immunologic response upon exposure to new antigens [e.g. gastrointestinal infection].<sup>26</sup>

On the basis of the above-mentioned studies, we expected that urban environments may play a role in poor clinical outcomes of CD. Contrary to expectations, our study demonstrated that there were no differences in terms of disease presentation or natural history between the two groups. Although the cumulative probability of surgery in the urban population was significantly higher than that in the rural population, it cannot be considered that urban environments were associated with poor prognosis. The reasons are as follows. First, surgery is mainly needed in CD to treat intestinal complications such as stricture, fistula, abscess, and perforation. If there were no significant differences in the cumulative probabilities of intestinal complications between urban and rural populations, a higher rate of surgery in the urban population is likely to be related

to non-clinical factors. Second, the difference in the cumulative surgery rate between two groups was mainly established within the first year from diagnosis and, thereafter, both survival curves ran in parallel, suggesting that this difference was only at disease onset and the first following months. Third, the urban population showed a significantly higher cumulative surgery rate compared with that for the rural population only among patients diagnosed in 2005–2008, whereas there were no significant differences in cumulative surgery rates between the two groups among patients diagnosed in 1986–1999 or 2000–2004. Considering the follow-up duration, outcomes for patients diagnosed in 1986–1999 and 2000–2004 [patients with longer follow-up duration] are more reliable than outcomes for patients diagnosed in 2005–2008 [patients with shorter follow-up duration]. The mean disease duration of patients diagnosed in 2005–2008 was approximately 5 years, which was not long enough to compare the long-term outcomes. Further follow-up data are needed to compare the prognosis of these patients.

The reasons for a higher rate of surgery within the first year from diagnosis in the urban population who were recently diagnosed with CD [2005–2008] are not clear. It may be due to differences in how the disease is managed. As the incidence and prevalence of Korean IBD are increasing rapidly,<sup>27</sup> awareness among Korean clinicians of the natural course of CD has improved and the treatment method for CD has also been improved. For example, in the past, patients with intestinal stricture initially underwent medical treatment with such as corticosteroids and immunosuppressants, and thereafter patients refractory to medical treatment underwent surgery. On the other hand, recently clinicians have tried to differentiate between strictures that are inflammatory or fibrotic in the early diagnosis stage, through advanced imaging studies and, if strictures are severe and fibrotic, early surgery rather than medical treatment can be considered.

Patients with CD from rural regions may have less access to health care, leading to a lower cumulative operation rate. However, we confirmed that the duration from symptom onset to diagnosis and cumulative probabilities of medication use including immunosuppressant and biologic agents were not different between urban and rural populations.

In the current study, we found that the demographic data, disease distribution, and disease behavior in the urban population were similar to those of the rural population. A recent study from Poland also showed that the demographic data, clinical presentation, and disease location in patients with IBD from rural regions were similar to those of patients from urban communities.<sup>28</sup>

In our study, the classification of urban and rural populations was based on the number of inhabitants of the region. Similar to our study, several cohort studies for IBD in Western countries classified urban and rural populations based on the number of inhabitants and defined urban as a population greater than 10 000.<sup>12</sup> Because the population density differs from country to country, the criteria for classification of urban and rural populations should differ from country to country. The population density of South Korea is very high. In South Korea, metropolitan cities were defined as cities with > 500 000 inhabitants based on the Korean Local Autonomy Law, Article 175. Risk associated with urban society may well be driven by greater population size [e.g. living in a metropolis]. Moreover, most South Koreans live in urban areas and intensive industrial development is focused on urban areas rather than rural areas, because of rapid migration from the countryside during the country's quick economic expansion in the 1970s, 1980s, and 1990s. Because of these demographic characteristics of South Korea, it is reasonable that the



classification of urban and rural populations should be based on the number of inhabitants, and urban areas were defined as cities with > 500 000 inhabitants.

Our study had several limitations. First, this study was conducted in a retrospective manner; thus, we could not control all confounding factors in the analysis. Particularly, confounding factors such as different indications or timing for surgery and immunosuppressant and biologic agent use according to physicians might influence the clinical outcomes. Second, data on dietary and socio-demographic factors such as economic status, education level, and occupation, which could be possible confounders, were not evaluated. Third, because our study was not population-based but rather hospital-based, referral center bias with inclusion of more severe cases in our cohort cannot be excluded. However, because CD is a rare disease in Korea, more than 70% of patients with CD are diagnosed at university hospitals.<sup>7</sup> Most patients with IBD in Korea were referred by primary care physicians and were subsequently diagnosed and treated by IBD specialists at a university hospital. Finally, the main limitation of our study is that data on where patients were living prior to diagnosis and for how long, as well as how many moved from a rural setting to a urban setting shortly before diagnosis, were not available. This might bias the results. However, the outcome of interest in our study was not the development of CD but clinical course after diagnosis. We think that patients' residences after CD diagnosis have a stronger influence on clinical course of the disease than patients' residences before CD diagnosis.

In conclusion, there were no significant differences in the disease distribution or behavior between urban and rural populations. In addition, there were no significant differences in the cumulative probabilities of intestinal complications and immunosuppressant or biologic agent use between the two groups. Although the cumulative probability of surgery in the urban population was significantly higher than that in the rural population, this difference was mainly established within the first year from diagnosis and observed only among patients diagnosed in 2005–2008. Our study showed that there are no differences in terms of disease presentation or long-term clinical outcomes between urban and rural populations of Korean patients with CD.

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## Conflict of interest statement

COI forms are available as supplementary files [xlink:href="http://ecco-jcc.oxfordjournals.org/lookup/suppl/doi:10.1093/ecco-jcc/jjv003/-/DC1"](http://ecco-jcc.oxfordjournals.org/lookup/suppl/doi:10.1093/ecco-jcc/jjv003/-/DC1)

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