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# High and increasing prevalence of inflammatory bowel disease in Finland with a clear North–South difference☆

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**Abstract**

*Background and aim:* Inflammatory bowel disease (IBD) prevalence has increased and a North–South gradient has been reported. We estimated the nationwide prevalence of IBD, ulcerative colitis (UC) and Crohn's disease (CD) in 1993, and prevalence of IBD in 2008, and assessed the geographical distribution of IBD in Finland. In addition, we investigated the vitamin D levels in a study population from a large, nationally representative health examination survey, the Health 2000 Survey.
*Methods:* The register study for prevalences included all patients who had special reimbursement of medications for IBD in the years 1993 (n=10,958) and 2008 (31,703). The study for D-vitamin measurement consisted of 6134 persons who had participated in the Health 2000 Survey.

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*Results:* The nationwide point prevalence of IBD in 1993 was 216 per 100,000 inhabitants, and 595 in 2008. In 1993, the prevalence of UC (177) was fourfold higher than the prevalence of CD (38). The prevalence of IBD and UC in Finland increased from South to North. For CD, no geographical variation could be demonstrated. In the Health 2000 survey, vitamin D levels were lower in Northern than in Southern Finland.
*Conclusions:* Finland belongs to high prevalence area of IBD and this prevalence has increased nearly threefold during the past 15 years. A clear North–South gradient has been shown for IBD and UC, but not for CD. Slightly lower vitamin D levels in Northern Finland may be associated with the observed higher prevalence of IBD there.


## 1. Introduction

Inflammatory bowel diseases (IBD), consisting of ulcerative colitis (UC) and Crohn's disease (CD), have become more common in different regions of the world over the past decades.[1] Both CD and UC are associated with substantial morbidity and excessive use of healthcare resources. In addition to the incidence of IBD, a knowledge of prevalence is important in estimating the overall disease burden due to IBD including special services, and the need for costly medical therapy and surgery to meet the various needs of IBD patients. Moreover, epidemiological studies may also provide clues to disease etiology. High prevalence of IBD has been reported in Northern Europe, the United Kingdom and North America.[1–11] The highest prevalence values for IBD are in Europe (UC, 505 per 100,000 persons; CD, 322 per 100,000 persons) and North America (UC, 249 per 100,000 persons; CD, 319 per 100,000 persons).[1,6]

A North–South gradient has long been known for IBD. In Europe, higher incidence rates have been found in Northern countries.[12] In several countries including the USA, UK, and France, North–South gradients have also been reported.[13–17] High incidence of CD has also been observed in Northern France based on EPIMAD registry.[18]

Etiology of IBD is unknown. Genetic predisposition has been established, especially in CD.[19] There is also evidence that environmental factors may play a role in the pathogenesis of IBD.[20] Dietary constituents, including linoleic acid have been suggested as contributing factors for IBD, especially UC.[21,22] Many autoimmune diseases have been linked to vitamin D deficiency including multiple sclerosis, rheumatoid arthritis, asthma, and type 1 diabetes among others.[23,24] Vitamin D deficiency is also common among adult, pediatric and young patients with inflammatory bowel disease.[25–28]A high prevalence of hypovitaminosis D has been found among pediatric patients with IBD, regardless of their diagnosis.[26] Lower 25(OH)D concentrations were found among young patients with more active disease, severe disease and those with upper gastrointestinal involvement in patients with CD.[26] In adult CD patients, vitamin D levels were lower in those with severe disease activity and less sun exposure.[28] Recently published data from the United States showed that higher predicted plasma levels of 25(OH)D significantly reduce the risk of incident CD, and nonsignificantly the risk for UC in women.[29] Vitamin D3 can be obtained from the diet, but it is mainly synthesized from 7-dehydrocholesterol in skin as a response to ultraviolet light exposure.[24] Vitamin D status may be one of the environmental factors influencing the prevalence of autoimmune diseases including IBD.[23,24] A recent geographic study from France also suggested that low sunlight exposure was associated with an increased incidence of CD.[30]

The aim of this study was to estimate for the first time the nationwide prevalence of IBD, changes from 1993 to 2008 in Finland, and further to test the North–South gradient hypothesis by analyzing the comprehensive drug reimbursement database. In addition, we had an opportunity to study the vitamin D levels in a large (n = 8028), nationally representative (random sample) health examination survey, the Health 2000 Survey conducted in Finland in 2000–2001, to find out whether there is a geographical variation in vitamin D levels within the population of Finland.

## 2. Patients and methods

Finland has a National Health Insurance Policy that covers all residents, and a unique personal social security number which can be used to identify each insured person. This code identifies the owner and reveals his/her date of birth and gender. The costs for drugs prescribed by a physician are reimbursed by the Social Insurance Institution (SII) of Finland. The basic refund rate is 42%. Certain severe and chronic diseases such as IBD are entitled to special refunds (72% or 100% category) of the drug costs.

For IBD, the intestinal anti-inflammatory agents (e.g. mesalazine, sulfasalazine, and budesonide), the glucocorticoids for systemic use (e.g. prednisolone), the immunosuppressants (e.g. azathioprine), the nitroimidazole antibiotics (metronidazole), and also drugs for local therapy (glucocorticoids and mesalazine) are included in this special refund category. TNF-α inhibitor adalimumab has been in the refund category for IBD since December 2007. In Finland, the infliximab therapy is given only in hospital, and the hospital has to cover all costs without refund from the SII.

To be eligible for drug reimbursement under the special refund categories, the patient's condition and diagnosis must meet explicit, predefined criteria, and a written certificate is required from the treating physician. As a rule, the diagnosis of IBD has to be assessed by a specialist in gastroenterology, internal medicine, pediatrics, digestive surgery, or surgery. The drug certificates are checked by a medical examiner,

physician or pharmacist at the SII before entitlement to the special refund can be granted.

For classification of IBD, the criteria include endoscopy, and usually histological verification.

### 2.1. Data sources

Since 1986, the SII has recorded all decisions on the entitlements for the special refunds of IBD patients in a nationwide register. Between 1986 and 1993, CD and UC had separate reimbursement codes in the register. Between the years 1994 and 1999, CD and UC were recorded with the same IBD-code, and diagnosis codes of subtypes were not registered. Therefore the prevalence of CD and UC cannot be calculated separately after 1993.

The prevalence rates were calculated by dividing the number of IBD patients at the end of the year by the population at risk (per 100,000 persons). The group at risk comprised the total population of Finland in 1993 (5.0 million) and 2008 (5.3 million). The prevalence rates for spatial geographical study were based on place of patients' residence at IBD diagnosis. The population is concentrated in cities and in the south and central part of Finland. Population sizes for calculation of rates were obtained from the National Population Information System of Finland.[31]

Serum 25-hydroxy vitamin D [S-25(OH)D] concentrations were measured in a comprehensive health survey, the Health 2000 Survey, conducted in Finland in 2000–2001. A stratified two-stage cluster sample (N = 8028) representative of the Finnish population aged 30 years or over was drawn from the population registry. Those aged 80 years or over were oversampled (2:1) relative to their proportion in the population. The study population of the present study consisted of the 6134 participants for whom serum vitamin D status was available. S-25(OH)D concentrations were measured by radioimmunoassay (Incstar, Stillwater, MN, USA). The intra-assay coefficient of variation (CV) was 3.5%, and the inter assay CV was 6.9% at the concentration of 36 nmol/l. The limit of detection was 3.8 nmol/l. The serum specimens were stored frozen (at −70 °C) until analyzed, and protected from light when processed. For evaluation of the seasonal variation in S-25(OH)D, the period August–October represented autumn, and the period November–March, winter.

Finland is located in Northern Europe (latitude 60–70°N) and the distance between the northernmost to the southernmost parts is about 1100 km.

### 2.2. Statistics

The 95% confidence intervals (95% CI) for the prevalence rates were calculated assuming a Poisson distribution. The areal comparisons were made between the five University Hospital districts in Finland (Fig. 1), and also between three geographical regions: Southern Finland (Helsinki and Turku University Hospital districts), Central Finland (Tampere and Kuopio) and Northern Finland (Oulu) in prevalence rates, and the linear trends over three geographical regions were tested by Poisson regression models (adjusted for gender and age groups). Poisson regression model was also used to quantify the statistical significance between annual (2008 vs. 1998) prevalence of IBD by calculating the prevalence rate ratio (PRR) with a 95% CI (adjusted for gender and age groups). Regional trends in D vitamin levels were tested by general linear models [adjusted for age and seasons of blood sampling (September–October, November–December or January–February)]. Statistical analyses were performed using the SAS system for Windows (version 9.2 SAS Institute Inc., Cary, NC, USA).

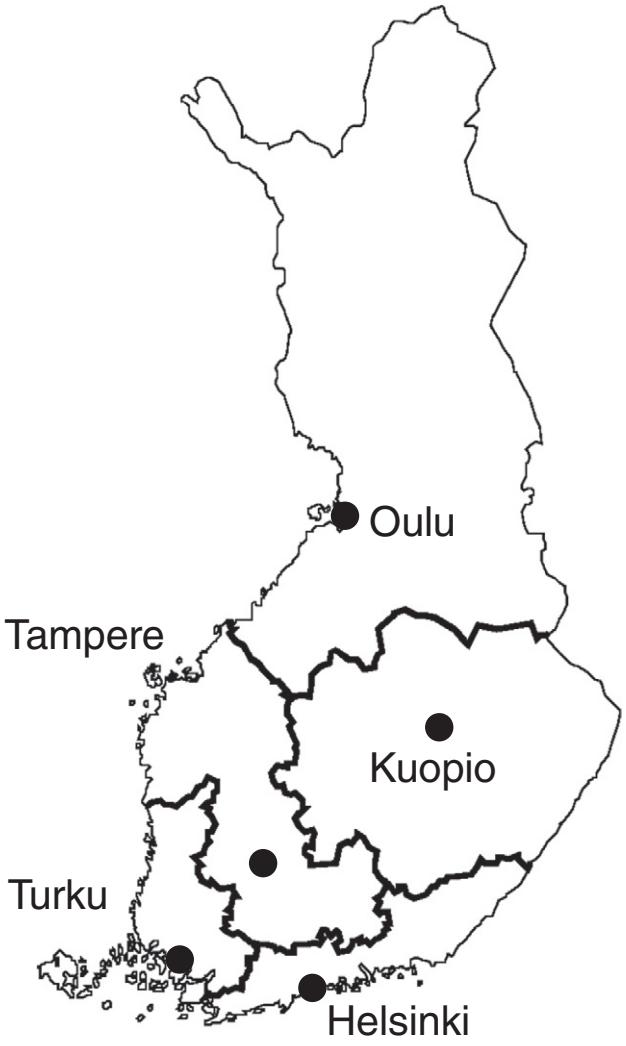


**Figure 1** University Hospital regions in Finland.

### 2.3. Ethical considerations

The IBD prevalence study protocol was approved by the Ethical Committee of The Hospital District of South Ostrobothnia. No informed consent was required in accordance with Finnish regulations for registry-based studies without contact with the study subjects. The Health 2000 Survey study was approved by the Ethics Committee for epidemiology and public health in the hospital district of Helsinki and Uusimaa, Finland. All participants gave their signed informed consent.

## 3. Results

In total, 31,708 IBD patients were identified at December 2008 giving a nationwide point prevalence of IBD 595 per 100,000 inhabitants (Table 1). At December 1993, there were 10,958 IBD patients giving the prevalence rate of IBD 216. The prevalence of IBD in Finland has increased nearly threefold during 15 years; 2008/1993 PRR was 2.73 (95% CI: 2.67–2.79), $p<0.001$, after adjusting for gender and age (see Table 1). In 1993, the prevalence rate for UC (177) was fourfold higher than the prevalence for CD (38).

In 2008, the highest prevalence rate of IBD, 914 in both genders, was seen in patients aged 35–44, after which the prevalence decreased in both genders with age. The IBD prevalence in 1993 and in 2008, and the prevalence of UC in 1993 were notably higher in males than in females (Table 1), especially in the age group over 44 years (Fig. 2). In CD, no significant gender difference was found.

The prevalence rates of IBD in Finland varied in five University Hospital areas and in three geographical regions (Tables 2 and 3). In both years 1993 and 2008, the prevalences of IBD increased from South to North, and in the latter year the highest prevalence was seen in North Finland (702) and the lowest in South Finland (561). In the prevalence of IBD and UC, a statistically highly significant increasing linear trend ($p<0.001$) from South to North was found (Table 3). CD did not show any significant North–South difference.

In accordance to the North–South gradient of IBD, serum vitamin D levels in both genders were also found to be higher in southern (46) than Northern Finland (44) in the Health 2000 survey (Table 4). A statistically significant linear trend ($p<0.05$) in vitamin D levels over three regions was observed.

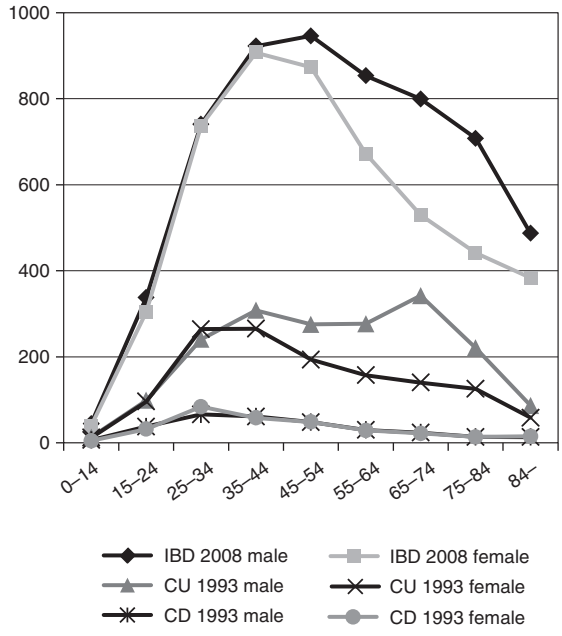


**Figure 2** Age specific prevalences of IBD in 2008 and age specific prevalences of CD and UC in 1993 calculated per 100,000 persons in Finland.

## 4. Discussion

The present study showed a high prevalence of IBD in Finland; in fact, 0.6% of the Finnish population has IBD, and in the age group 35–54 almost 1% suffers from it. Equally high prevalences have so far been reported only from Canada and Norway.[6,8,32] Moreover, the prevalence of IBD has increased nearly threefold during 15 years in Finland (Table 1). The increase of prevalence is mainly a consequence of rising incidence.[33] The disease is also most often diagnosed at a young age, and mortality is low.[1,34] The incidence and prevalence of IBD have increased worldwide in the past 50 years; also in developing countries over the last 15 years.[35] There are only a few studies concerning the prevalence of IBD at different times in the same area. In contrast to our study, in Olmsted County, Minnesota, the prevalence of IBD increased little from 1991 to 2000.[9] The prevalence of CD in 2001 was 30% higher than that measured in 1991, while the prevalence of UC changed very little from that of 1991.

We found a significant North–South difference in the prevalence of IBD and UC, but not for CD, in 1993. The prevalence rates of IBD and UC were higher in the northern than the southern part of Finland. A hospital-based study of Medicare beneficiaries (over 65 years of age) found that both CD and UC appeared to be more frequent in northern parts of the United States than in southern parts.[13] In a large, multi-State sample from the United States, the prevalence of both UC and CD was lower in the South compared with all other regions.[14] Recently Sonnenberg also reported a North–South gradient in UC and CD based on colonic biopsies.[17] In contrast to our paper, both a Scottish study of juvenile IBD[15] and a French study of IBD,[16] using their respective national health insurance data, found a clear North–South gradient for CD, but not for UC. The North–South gradient in the prevalence of IBD in Finland was seen in 1993 and also in 2008, indicating a constant difference. Unfortunately the prevalence of CD and UC cannot be calculated separately after 1993 since between

**Table 1** The crude prevalence of IBD (as absolute numbers and as rates per 100,000 persons) in Finland in 1993 and 2008.

| | All | | Male | | Female | |
|---|---|---|---|---|---|---|
| | N | Prevalence rate (95% CI) | N | Prevalence rate (95% CI) | N | Prevalence rate (95% CI) |
| CD 1993 | 1,945 | 38 (37–40) | 956 | 39 (36–41) | 989 | 38 (36–40) |
| UC 1993 | 9,013 | 177 (174–181) | 4,982 | 202 (196–207) | 4,031 | 155 (150–159) |
| IBD 1993 | 10,958 | 216 (212–220) | 5,938 | 240 (234–247) | 5,020 | 192 (187–198) |
| IBD 2008 | 31,703 | 595 (589–602) | 16,680 | 639 (629–648) | 15,023 | 553 (545–562) |

**Table 2** The crude prevalence rates of IBD by the University Hospital areas of Finland in 1993 and 2008.

| | Helsinki | Turku | Kuopio | Tampere | Oulu |
|---|---|---|---|---|---|
| | Prevalence rate (95% CI) | Prevalence rate (95% CI) | Prevalence rate (95% CI) | Prevalence rate (95% CI) | Prevalence rate (95% CI) |
| CD 1993 | 42 (38–45) | 33 (29–37) | 24 (21–27) | 47 (44–52) | 38 (34–43) |
| UC 1993 | 153 (147–159) | 156 (147–159) | 178 (170–187) | 194 (186–202) | 219 (208–230) |
| IBD 1993 | 195 (188–202) | 189 (179–199) | 202 (193–212) | 242 (223–251) | 257 (246–269) |
| IBD 2008 | 554 (543–565) | 578 (562–597) | 572 (556–588) | 610 (596–624) | 702 (683–721) |

the years 1994 and 1999, CD and UC were recorded with the same IBD-code, and diagnoses of subtypes were not registered in the SII registry.

There are several possible explanations for regional variations in IBD risk. A recent geographic study from France suggested that low sunlight exposure was associated with an increased incidence of CD.[30] Several studies have reported a regional association between IBD occurrence and urbanization, some describing a positive association with urban location[8,13,36–39], some describing a positive association with rural location,[40] and others finding no significant associations.[41] The relationship between the incidence rate and education, and incidence rate and more affluent area is also to be found in several studies.[15,37,39] In Northern France, there was a noteworthy predominance of CD in agricultural areas in contrast to most studies, and no clear link with affluence.[40] Genetic and other environmental factors may account for the North–South gradient in IBD and UC prevalence in Finland. The northern part of Finland is more rural, and income levels and education are lower than in southern Finland. Diet may also be different in the North and South. Finally, we cannot exclude the possibility that genetic factors may contribute to the North–South difference, although a geographical variation in the genetics of Finnish IBD patients has not been shown.[42]

We found that vitamin D levels in both genders were higher in southern Finland than in Northern Finland in the Health 2000 survey of the general population. There is growing evidence of the immunological role of vitamin D and its association with autoimmune diseases including IBD.[23,24] Vitamin D deficiency is common in patients with IBD, and it is yet unclear whether such a deficiency is a cause or consequence of underlying IBD.[25–28] A recent study from the United States demonstrated that higher predicted plasma levels of 25(OH)D significantly reduced the risk of incident CD, and nonsignificantly the risk of UC in women.[29] The median interval between assessment of predicted plasma 25(OH)D level and time of IBD diagnosis was however very long; 12 years for UC and 10 years for CD. A French study suggested that low sunlight exposure is associated with an increased CD risk.[30] Vitamin D3 is mainly biosynthesized from 7-dehydrocholesterol in skin exposed to ultraviolet light.[24] In Finland, the level of sun exposure changes considerably with the seasons, and is also conspicuously different in the North and South. The annual amount of sunshine is highest (1900 h) in the southwestern maritime and coastal regions, and lowest (1300 h) in eastern Lapland.[43] Low sunlight exposure in Northern Finland may lead to low vitamin D values there. Lower D vitamin levels in Northern Finland can have some influence on the observed North–South gradient in the prevalence of IBD, and also UC. Although according to the French study low sunlight exposure was associated with higher CD risk,[30] it has been observed that the prevalence of IBD, and also UC, is higher in areas that receive less sunlight, such as the northernmost parts of Europe and America.[1,3–8]

We believe that the true prevalence of IBD in Finland does not significantly differ from our estimation. The patients were identified from a nationwide, comprehensive register, including data of the reimbursements for therapeutic agents of chronic diseases, and therefore it is likely that the coverage of patients with maintenance medication for IBD is high; e.g. for pediatric IBD the coverage was 94%, and 98% of the cases met modern diagnostic criteria.[44] The key issue is the validity of the written SII certificates. Administrative databases concerning IBD have not so far been validated against medical chart reviews in adult patients. However, in a recent Finnish study of pediatric IBD-patients between the years 1987–2003, 50 reimbursement reports were randomly selected from the two hospital districts with the highest incidence to assess consistency in the diagnostic criteria.[44] Only 1 of the 50 diagnoses was considered questionable. According to a Finnish survey, IBD patients have been diagnosed by specialist (in Finland usually a gastroenterologist or a specialist in internal medicine) in over 96% of cases.[45] It is also noteworthy that in Finland the eligibility for the special reimbursements for drug therapy is independent of

**Table 3** The prevalence rates of IBD in three geographical regions in Finland in 1993 and 2008.

| | Southern Finland | Central Finland | Northern Finland | |
|---|---|---|---|---|
| | Prevalence rate (95% CI) | Prevalence rate (95% CI) | Prevalence rate (95% CI) | *P* value for linear trend [a] |
| CD 1993 | 39 (36–41) | 37 (35–40) | 38 (34–43) | 0.631 |
| UC 1993 | 154 (149–159) | 187 (182–193) | 219 (208–230) | <0.001 |
| IBD 1993 | 193 (187–199) | 225 (218–231) | 257 (246–269) | <0.001 |
| IBD 2008 | 561 (552–571) | 594 (584–605) | 702 (683–721) | <0.001 |

[a] Adjusted for gender and age groups.

**Table 4** Means of vitamin 25(OH)D concentration (nmol/l) in the Health 2000 survey by sex in three geographical regions of Finland.

| | Southern Finland | | Central Finland | | Northern Finland | | |
|---|---|---|---|---|---|---|---|
| | Mean [a] | SE [b] | Mean [a] | SE [b] | Mean [a] | SE [b] | *P* value for linear trend |
| Men (n = 2796) | 46.071 | 0.633 | 44.082 | 0.791 | 44.109 | 1.366 | 0.036 |
| Women (n = 3338) | 46.631 | 0.552 | 43.716 | 0.765 | 44.631 | 1.033 | 0.024 |

[a] Adjusted for age and time of blood drawing.
[b] Standard error.

an IBD patient's socioeconomic situation or place of residence, and reimbursements are included in the routine care of patients. Despite the high prevalence rates reported in our study, an underestimation of the true prevalence of IBD is still possible. To some extent, better diagnostic tools and the availability of endoscopy, and an increased awareness of IBD can explain a slight increase in the prevalence of IBD. While new diagnostic tools could have increased the detection rate of CD, this is not the case for UC since it is diagnosed by blood in stools and sigmoideoscopy, a diagnostic tool available for several decades. However, we have found a continuous and significant increase in the incidence of UC compared to CD in our earlier study between years 2000–2007.[33] Some mild IBD cases as well as UC patients who are operated soon after becoming ill may not require any medication, and these may not have been included in the register. Our register- based figures concerning the prevalence of IBD are also in line with the results from a Finnish population-based prospective study from the Tampere area (446,000 inhabitants). The prevalence of adult IBD patients was 442 per 100,000 inhabitants in 1999.[7] The observed North–South gradient in Finland is unlikely to be due to disparate patient access to healthcare. In fact, there are far more doctors and gastroenterologists in the South than in the North of Finland. The prevalence rates for spatial geographical study were based on place of patients' residence at IBD diagnosis. Patients' migration does not have significant influence to our results concerning North–South gradient in the prevalence of IBD. Migration in Finland takes place mainly from north to south and inside the areas North, Central and South Finland. Although we do not have direct vitamin D measurements from IBD patients, especially before they have contracted the disease, the unselected population-based vitamin D data gives a good estimation of differences in vitamin levels between South and North in the Finnish population.

In summary, the prevalence of IBD in Finland is high and at age 35–54 nearly 1% of population has IBD. The prevalence has increased nearly threefold during the past 15 years. Moreover, a clear North–South gradient is seen in IBD, especially in UC. Lower vitamin D levels in Northern Finland may be associated with the observed higher prevalence of IBD there.

## Conflict of interest

None.

## Acknowledgments

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