Annals of Epidemiology 80 (2023) 53–61

Contents lists available at ScienceDirect

Annals of Epidemiology

journal homepage: sciencedirect.com/journal/annals-of-epidemiology

Original article

# Residential mobility and childhood inflammatory bowel disease: a nationwide case–control study

Wafa Alimam, DMD, MSc [a,b,*], Atte Nikkilä, MD, PhD [b], Jani Raitanen, MSc [a,c,d], Kaija-Leena Kolho, MD, PhD [e,f], Anssi Auvinen, MD, PhD [a,f]

[a] The Health Sciences Unit, Faculty of Social Sciences, Tampere University, Tampere, Finland
[b] Tampere Center for Child, Adolescent and Maternal Health Research, Faculty of Medicine and Health Technology, Tampere University, Tampere, Finland
[c] UKK Institute for Health Promotion Research, Tampere, Finland
[d] Special Services Unit, Finnish Institute for Health and Welfare, Helsinki, Finland
[e] Children's Hospital, University of Helsinki, Helsinki, Finland
[f] Tampere University Hospital, Department of Pediatrics, Tampere, Finland

ARTICLE INFO

*Article history:*
Received 5 July 2022
Received in revised form 28 January 2023
Accepted 4 February 2023
Available online 9 February 2023

*Keywords:*
Child
Crohn disease
Etiology
Risk factors
Ulcerative colitis

ABSTRACT

*Purpose:* To examine the association of residential mobility, as a proxy for environmental influences, with childhood inflammatory bowel disease (IBD) risk.
*Methods:* Using nationwide register-based dataset, all 2038 IBD cases in Finland diagnosed at ages less than 15 years in 1992–2016 were individually matched by sex and age with five controls employing risk set sampling. Complete residential histories of the subjects were constructed from birth until the index date (diagnosis date of the case). Movement patterns were assessed by age, distance, and demographics of the departure and destination municipalities. Conditional logistic regression was employed to estimate the association between movements and IBD risk.
*Results:* Overall, residential movement was associated with a slightly decreased odds ratio (OR) for childhood IBD (OR 0.97, 95% confidence interval (CI) 0.95–1.00 for each movement). Further examination showed reduced ORs for moving to rural municipalities (OR 0.94, 95% CI 0.90–0.98) and to distances less than 50 km (OR 0.96, 95% CI 0.93–0.99). In disease subtype analyses, the effect mainly persisted in ulcerative colitis.
*Conclusions:* Our findings suggest lower childhood IBD risk associated with residential mobility. The effect was found in ulcerative colitis, but not in Crohn's disease. Movements to nearby and rural areas may reduce IBD risk, though this requires further investigation.


## Introduction

The incidence of childhood inflammatory bowel disease (IBD), mainly consisting of Crohn's disease (CD) and ulcerative colitis (UC), continues to increase [1–4]. In Europe, the highest incidence has been reported in Northern countries [3,4], where Finland showed a 4.1% annual increase in 1987–2014 for ages under 20 years [5]. In Canada, an annual increase of 7.2% among children younger than 5 years was reported between 1999 and 2010 [6].

The interaction between genetic and environmental factors has been established in IBD pathogenesis [7–10]. Environmental exposures to factors that remain yet to be identified are likely to explain the rising incidence, as population genetic characteristics do not change in a few decades. Several environmental risk factors have been suggested to influence IBD risk, yet its etiology remains elusive [1,7,10–14]. Early-life exposures linked to microbial pathogens can affect the balance between immunity and gut microbiota and have been associated, both positively and inversely, with IBD [2,8,10–12,14]. Multiple proxies have been used to examine the effect of microbial exposures, such as animal contact, housing density, family size, and daycare attendance [15–19]. Nevertheless, the findings remain inconclusive.

*Abbreviations:* BIC, Bayesian information criteria; CD, Crohn's disease; CI, confidence interval; IBD, inflammatory bowel disease; IBDU, IBD-unclassified; OR, odds ratio; SII, Social insurance institution; UC, ulcerative colitis

Conflict of Interests: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

* Corresponding author: The Health Sciences Unit, Faculty of Social Sciences, Tampere University, Tampere, Finland.
*E-mail addresses:* wafa.alimam@tuni.fi (W. Alimam), atte.nikkila@tuni.fi (A. Nikkilä), jani.raitanen@tuni.fi (J. Raitanen), kaija-leena.kolho@helsinki.fi (K.-L. Kolho), anssi.auvinen@tuni.fi (A. Auvinen).

https://doi.org/10.1016/j.annepidem.2023.02.003
1047-2797/

**Table 1**
Characteristics of children with inflammatory bowel disease (IBD), Crohn's disease (CD), and ulcerative colitis (UC) and their individually matched controls (1:5), Finland, 1992–2016

| | Cases | | | Controls |
|---|---|---|---|---|
| | IBD, n = 2038 | CD, n = 828 | UC, n = 1210 | n = 10,190 |
| Sex, % (n) | | | | |
| Male | 56.0% (1141) | 63.2% (523) | 51.1% (618) | 56.0% (5705) |
| Female | 44.0% (897) | 36.8% (305) | 48.9% (592) | 44.0% (4485) |
| Year of birth, % (n) | | | | |
| 1977–1989 | 25.2% (514) | 23.9% (198) | 26.1% (316) | 25.2% (2570) |
| 1990–1999 | 49.5% (1009) | 50.1% (415) | 49.1% (594) | 49.5% (5045) |
| 2000–2009 | 24.4% (497) | 25.4% (210) | 23.7% (287) | 24.4% (2485) |
| 2010–2016 | 0.9% (18) | 0.6% (5) | 1.1% (13) | 0.9% (90) |
| Age at diagnosis, % (n) | | | | |
| Mean (SD) | 10.9 (3.4) | 11.2 (3.1) | 10.7 (3.6) | |
| Median (IQR) | 12 (9–14) | 12 (10–14) | 12 (9–14) | |
| 0–5 | 9.1% (186) | 6.9% (57) | 10.7% (129) | |
| 6–10 | 22.4% (456) | 21.5% (178) | 23.0% (278) | |
| 11–15 | 68.5% (1396) | 71.6% (593) | 66.3% (803) | |
| Year of diagnosis, % (n) | | | | |
| 1992–1999 | 21.3% (434) | 18.7% (155) | 23.1% (279) | |
| 2000–2009 | 44.9% (915) | 45.4% (376) | 44.5% (539) | |
| 2010–2016 | 33.8% (689) | 35.9% (297) | 32.4% (392) | |
| Number of movements, % (n) | | | | |
| Mean (SD) | 1.7 (2.0) | 1.8 (1.9) | 1.6 (2.0) | 1.8 (2.0) |
| Median (IQR) | 1 (0–2) | 1 (0–3) | 1 (0–2) | 1 (0–3) |
| 0 | 31.4% (639) | 28.4% (235) | 33.4% (404) | 29.0% (2960) |
| 1–2 | 44.3% (903) | 43.7% (362) | 44.7% (541) | 44.9% (4573) |
| ≥3 | 24.3% (496) | 27.9% (231) | 21.9% (265) | 26.1% (2657) |
| Movements within or between municipalities in Finland, or abroad, % (n) | | | | |
| No movements | 31.4% (639) | 28.4% (235) | 33.4% (404) | 29.0% (2960) |
| Movements only within a single municipality in Finland | 37.1% (756) | 39.3% (325) | 35.6% (431) | 37.1% (3784) |
| At least one movement between different municipalities in Finland | 30.9% (629) | 31.6% (262) | 30.3% (367) | 32.0% (3264) |
| At least one movement from or to abroad | 0.7% (14) | 0.7% (6) | 0.7% (8) | 1.8% (182) |

SD = standard deviation; IQR = interquartile range.

Residential movement involves encountering a new environment, which may entail exposure to novel pathogens [9,13,14,20–23]. A recent study has suggested that childhood IBD, specifically UC, exhibits a clustering pattern in relation to location and time for some cases, indicating shared environmental exposures [24] Moreover, immigration studies have shown that IBD risk among immigrants starts to approach that of the host population, which denotes an effect from the environment [20,25–27]. However, few immigration studies have considered the pediatric population [25,28,29], and none has evaluated mobility within a country.

We investigated residential movement patterns between birth and diagnosis of pediatric IBD in a nationwide register-based case–control study. We hypothesized that mobility is a proxy for encountering new pathogens in the environment, including microbial profiles, which may change IBD risk. Our aim was to examine the frequency of early-life residential movements in relation to IBD onset in childhood.

## Materials and methods

### *Study population and data sources*

We used a matched case–control study design. All pediatric patients diagnosed with IBD in Finland before the age of 15 years between 1992 and 2016 were identified from the Social Insurance Institution (SII) special reimbursement database. As a part of the Finnish national health insurance, all IBD patients (ICD codes K50 for CD and K51 for UC including unclassified colitis IBDU) receive a special reimbursement for medication costs administered by the SII. The eligibility for this reimbursement requires a medical certificate issued by a specialist describing the diagnostic findings, including endoscopy and histological verification. An application for reimbursement is filed for practically all patients diagnosed with the disease. The completeness and consistency of the database have been shown to be high [30]. Date of reimbursement approval was considered to represent the diagnosis date, that is, index date.

Five controls individually matched by sex and age (year of birth) were randomly chosen from the Digital and Population Data Services Agency for each case. The controls had to be alive and free of IBD at the index date. Matching was employed using risk set sampling, accounting for temporal changes over the study period. A comprehensive residential history from birth until the index date was constructed for all study participants. Residential information was obtained from the Digital and Population Data Services Agency and linked through the unique personal identification number assigned to all residents in Finland and used extensively in registries and databases. Residential data included the address, municipality, postal code, and map coordinates of each dwelling inside Finland, in addition to place of birth, and start and end dates of all residential periods between 1977 and 2016 (indicating movement).

Finland is divided into municipalities, the number of which has been reduced from roughly 450 to 350 during the past four decades. For each municipality, demographic information on population size, population density, relocation intensity (sum of the intermunicipal

**Table 2**
Odds ratios (OR) (with 95% CI) of the association for early and recent number of movements before the index date and childhood inflammatory bowel disease (IBD), Crohn's disease (CD), and ulcerative colitis (UC) and frequencies among cases/controls, Finland, 1992–2016

| | IBD | CD | UC |
|---|---|---|---|
| | OR (95% CI) number of movements, cases/controls | OR (95% CI) number of movements, cases/controls | OR (95% CI) number of movements, cases/controls |
| Movements until 15th birthday or the index date if earlier | 0.97 (0.95–1.00) 3453/18,308 | 0.99 (0.96–1.03)1502/7619 | **0.96 (0.92–0.99)** 1951/10,689 |
| Movements until 6th birthday or the index date if earlier | 0.96 (0.93–1.00) 2298/12,219 | 0.99 (0.94–1.05) 994/5036 | **0.94 (0.89–0.98)** 1304/7183 |
| Movements until 2nd birthday or the index date if earlier | 0.98 (0.91–1.04) 986/5051 | 0.98 (0.89–1.09) 411/2092 | 0.97 (0.89–1.06) 575/2959 |
| Movements during 6 years before the index date | 0.97 (0.93–1.02)1484/7773 | 1.00 (0.94–1.06) 621/3119 | 0.96 (0.91–1.01) 863/4654 |
| Movements during 2 years before the index date | 0.96 (0.88–1.05) 453/2382 | 1.05 (0.92–1.20) 199/935 | 0.90 (0.80–1.01) 254/1447 |

OR = odds ratio; CI = confidence interval. Bold indicates significant findings on the 95% confidence limit.

movements to a municipality divided by the average population size of the municipality), and rurality (proportion of people living in rural areas greater than 30% or population size less than 10,000) was obtained from Statistics Finland for the whole study period. Municipalities were classified for each year as rural or urban, and to three categories for each of the other characteristics (population size: less than 20,000, 20,000–149,999, at least 150,000 inhabitants; population density: less than 50, 50–399, at least 400 person/km$^2$; relocation intensity: based on tertiles).

*Statistical analysis*

Conditional logistic regression was used to estimate odds ratios (OR) and their 95% confidence intervals (CI) for the matched case–control sets as indicators of the association between residential mobility (number of movements) before the index date and IBD risk. The effects of frequency of movements, age at the time of movement, and distance of movement were analyzed. Mobility between urban and rural municipalities, and by other demographic characteristics of the municipalities was also analyzed. Analyses were repeated excluding the 60 days preceding the index date to eliminate for potential reverse causality, that is, movement due to incipient IBD. In addition, the influence of duration of living in urban and rural municipalities was explored. The main explanatory variable (movement overall) was defined as a change in residence within or between Finnish municipalities, or moving between Finland and another country. Movements based on demographic categories were limited to those inside Finland, as we did not have access to such information in other countries. Analyses were stratified by the matching factors and performed for IBD overall, and separately for CD and UC. Different versions of the main explanatory variable measured in counts were evaluated based on Bayesian information criteria (BIC). The number of movements was analyzed in continuous (with and without a quadratic term), categorical (0, 1, ≥2; 0, 1, 2, ≥3; 0, 1, 2, 3, ≥4; 0, 1, 2–3, ≥4; 0, 1–2, 3–4, ≥5; 0, 1–2, 3–5, ≥6 movements), and spline forms (both linear and restricted cubic splines where knots were either equally spaced or placed at percentiles). The model with the continuous variable had the lowest BIC value, and therefore it was preferred. No correction for multiple testing was employed. Moreover, multicollinearity between the explanatory variables was evaluated based on the variance inflation factor (e.g., moving to municipalities of low population size and low relocation intensity). Effect modification was evaluated using interaction terms for movement and subgroup indicators for sex, age group (≤5, 6–10, ≥11 years), and diagnosis period (1992–1999, 2000–2009, and 2010–2016), by assessing improvement in model fit (based on the likelihood ratio test) in nested models with the main effects only versus one including the main effects and an interaction term. Analyses were performed using SPSS (version 26.0; IBM Corp.; Armonk, NY) and Stata (version 16.1; StataCorp LLC; College Station, TX).

*Ethical approval*

In Finland, research based purely on documentation or registered materials does not require review by the regional ethics committees. This has been defined in the laws on medical research, health care, and patient's rights (Laws 621/1999, 984/2021, 488/1999). Permission to use registry data was obtained from each database controller (SII and Digital and Population Data Services Agency). The data linkage of registries was based on unique personal identifiers and once linked the data were pseudo-anonymous.

## Results

The final analysis included 2038 cases and 10,190 individually matched controls. Of the cases, there were more UC patients than CD and more males than females (Table 1). Nevertheless, the proportion of males relative to females was higher among CD patients (63.2% vs. 36.8%) compared with UC (51.1% vs. 48.9%). Cases in older age groups comprised the majority, with 90.9% diagnosed greater than 5 years. Of the disease subtypes, UC was more diagnosed at a younger age than CD. Only 1.8% (n = 182) of children had residential periods abroad, 14 of which were IBD cases.

Overall, residential relocation was associated with a slightly reduced risk of childhood IBD. When the number of movements was examined as a continuous variable, each movement was associated with a 3% decrease in the OR (0.97, 95% CI 0.95–1.00) (Table 2). The OR was also reduced when the number of movements defined as categories (e.g., 0, 1, 2, ≥3 movements: OR 0.93, 0.89, 0.86; results not shown). The disease subtype analysis showed a protective effect in UC, but not CD (OR: 0.96, 95% CI 0.92–0.99 vs. 0.99, 0.96–1.03).

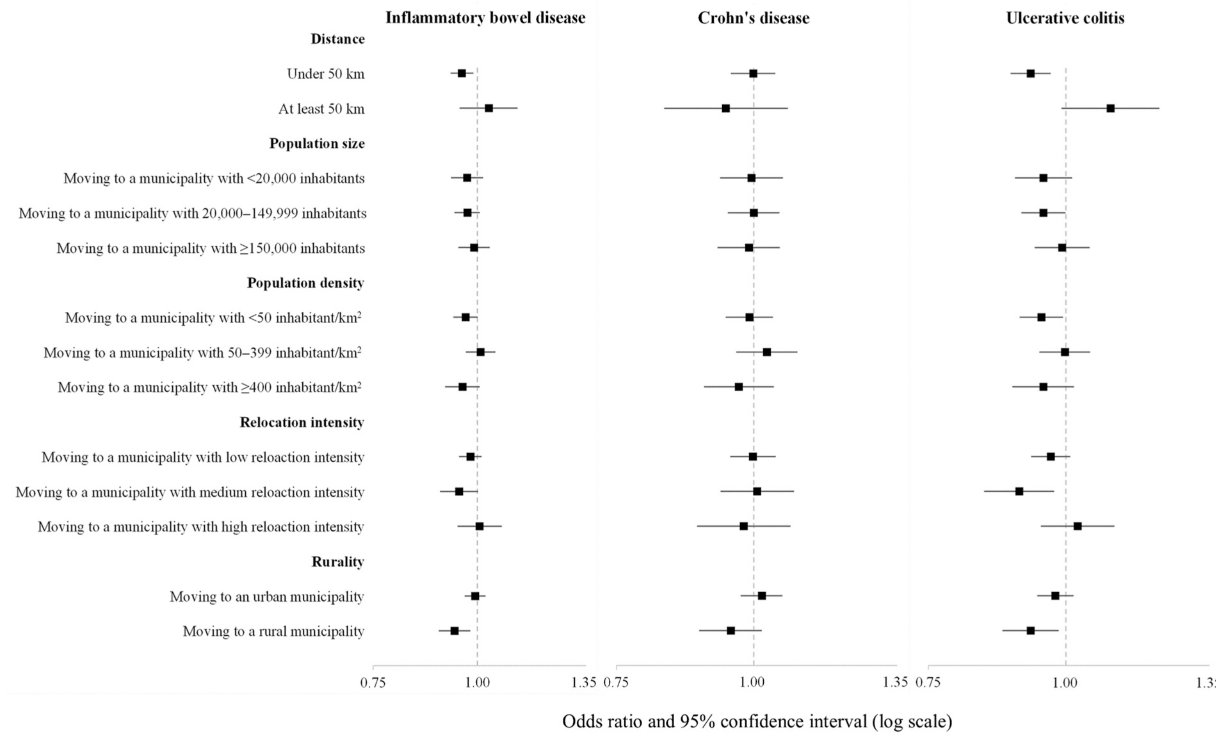


**Fig. 1.** Odds ratios of the association between the number of movements (based on distance and characteristics of the destination municipality) and childhood inflammatory bowel disease, Crohn's disease, and ulcerative colitis, Finland, 1992–2016. Bars, 95% confidence interval.

Comparable results were obtained in an analysis restricted to ages less than 6 years. Furthermore, mobility in the recent 2 and 6 years before the index date showed lower ORs for IBD overall. This was shown, in a further analysis, to be related mainly to UC (OR: 0.90, 95% CI 0.80–1.01 and 0.96, 0.91–1.01) and not CD (OR: 1.05, 95% CI 0.92–1.20 and 1.00, 0.94–1.06).

In an analysis of movements by distance, moving to nearby locations (< 50 km away) was associated with a decreased OR for IBD (OR 0.96, 95% CI 0.93–0.99) (Fig. 1). Further investigation showed a comparable effect in UC, but not CD (OR: 0.93, 95% CI 0.89–0.97 vs. 1.00, 0.95–1.05). In a complementary analysis, ORs were estimated based on movements within Finnish municipalities, between Finnish municipalities, and abroad compared with no movements at all. Moving abroad at least once was associated with a decreased IBD risk (OR: 0.36, 95% CI 0.21–0.62) (Supplementary Table 1), while moving only within municipalities and moving at least once between municipalities in Finland did not show a clear effect (OR 0.92, 95% CI 0.82–1.04 and 0.89, 0.79–1.01). Similar results were also found in both CD and UC. Moving to municipalities in all population-size categories was associated with low ORs in IBD overall. The effect was more noticeable for destination municipalities with low and medium population size in UC (Fig. 1). Moreover, relocation to municipalities of low or high population density and low or medium relocation intensity showed low ORs for IBD overall, with the effect also persisting in UC. Lower ORs of IBD were found for moving to rural areas (OR 0.94, 95% CI 0.90–0.98). Similar results were observed for the two disease subtypes (UC: OR 0.93, 95% CI 0.88–0.99 vs. CD: 0.95, 0.89–1.02). After exclusion of 60 days preceding the index date for potential reverse causality, almost identical results were found (Supplementary Table 2). Moreover, the effect of residential duration in rural areas per se showed null findings in relation to IBD risk (Supplementary Table 3). Only 13.2% of study participants had lived in both urban and rural areas in the period before the index date. No evidence of multicollinearity was detected for the number of movements between explanatory variables (all variance inflation factor values were less than 10, results not reported).

We further examined the association between the disease risk and the characteristics of municipalities of departure. Mixed results were found, with no consistent patterns for moving from areas of a certain feature in relation to the risk of IBD or the subtypes CD and UC (Table 3). Last, we tested the interaction between the number of movements and sex, age, or diagnosis year. No effect modification between the subgroups was detected (all p-values were > 0.1, results not shown).

## Discussion

In our population-based study, residential movement was associated with a slightly reduced risk of childhood IBD. The effect was mainly observed in UC, but not CD. Further investigation indicated a slightly decreased risk for moving to rural locations in both disease subtypes. Moreover, movements within two and six years preceding the index date and to nearby areas were associated with lower ORs

**Table 3**
Odds ratios (OR) (and 95% CI) of the association for the number of movements (based on characteristics of the departure and destination municipality) and childhood inflammatory bowel disease (IBD), Crohn's disease (CD), and ulcerative colitis (UC) with frequencies among cases/controls, Finland, 1992–2016

| | IBD | CD | UC |
|---|---|---|---|
| | OR (95% CI) number of movements, cases/controls | OR (95% CI) number of movements, cases/controls | OR (95% CI) number of movements, cases/controls |
| Population size | | | |
| Moving to a municipality with < 20,000 inhabitants | 0.97 (0.93–1.02) 944/5067 | 1.00 (0.93–1.06) 426/2154 | 0.95 (0.90–1.01) 518/2913 |
| From a municipality with < 20,000 inhabitants | 0.98 (0.93–1.03) 733/3874 | 1.01 (0.94–1.09) 338/1641 | 0.95 (0.89–1.02) 395/2233 |
| From a municipality with 20,000–149,999 inhabitants | 0.87 (0.73–1.04)133/775 | 0.87 (0.67–1.13) 59/345 | 0.87 (0.69–1.10) 74/430 |
| From a municipality with ≥150,000 inhabitants | 0.99 (0.78–1.27) 71/357 | 0.90 (0.60–1.34) 26/146 | 1.06 (0.78–1.46) 45/211 |
| Moving to a municipality with 20,000–149,999 inhabitants | 0.97 (0.94–1.01)1558/8326 | 1.00 (0.95–1.06) 672/3360 | 0.95 (0.91–1.00) 886/4966 |
| From a municipality with < 20,000 inhabitants | 0.94 (0.78–1.14) 118/630 | 0.77 (0.57–1.05) 43/287 | 1.08 (0.86–1.37) 75/343 |
| From a municipality with 20,000–149,999 inhabitants | 0.97 (0.93–1.01) 1299/7030 | 1.01 (0.95–1.07) 569/2786 | **0.94 (0.90–0.99)** 730/4244 |
| From a municipality with ≥150,000 inhabitants | 1.15 (0.96–1.38) 138/600 | 1.16 (0.87–1.53) 59/254 | 1.14 (0.89–1.45) 79/346 |
| Moving to a municipality with ≥150,000 inhabitants | 0.99 (0.95–1.04) 937/4793 | 0.99 (0.93–1.06) 398/2045 | 0.99 (0.94–1.05) 539/2748 |
| From a municipality with < 20,000 inhabitants | 1.01 (0.74–1.38) 44/217 | 1.10 (0.68–1.76) 19/86 | 0.96 (0.64–1.44) 25/131 |
| From a municipality with 20,000–149,999 inhabitants | 1.06 (0.86–1.31) 106/499 | 1.10 (0.79–1.52) 44/200 | 1.04 (0.79–1.36) 62/299 |
| From a municipality with ≥150,000 inhabitants | 0.99 (0.95–1.04) 782/3998 | 0.98 (0.92–1.06) 332/1732 | 1.00 (0.94–1.06) 450/2266 |
| Population density | | | |
| Moving to a municipality with < 50 inhabitant/km$^2$ | 0.97 (0.94–1.00) 1645/8920 | 0.99 (0.94–1.04) 738/3776 | **0.95 (0.91–0.99)** 907/5144 |
| From a municipality with < 50 inhabitant/km$^2$ | 0.97 (0.93–1.00) 1423/7747 | 0.99 (0.94–1.05) 646/3274 | **0.95 (0.90–0.99)** 777/4473 |
| From a municipality with 50–399 inhabitant/km$^2$ | 0.90 (0.75–1.09) 123/687 | 0.89 (0.66–1.18) 51/290 | 0.91 (0.72–1.16) 72/397 |
| From a municipality with ≥400 inhabitant/km$^2$ | 1.12 (0.90–1.40) 93/411 | 1.00 (0.72–1.41) 37/184 | 1.23 (0.92–1.64) 56/227 |
| Moving to a municipality with 50–399 inhabitant/km$^2$ | 1.01 (0.97–1.05) 1049/5116 | 1.03 (0.96–1.10) 442/2062 | 1.00 (0.95–1.05) 607/3054 |
| From a municipality with < 50 inhabitant/km$^2$ | 0.96 (0.80–1.15) 129/675 | 0.90 (0.68–1.20) 53/296 | 1.00 (0.79–1.27) 76/379 |
| From a municipality with 50–399 inhabitant/km$^2$ | 1.01 (0.97–1.06) 834/4013 | 1.04 (0.97–1.12) 353/1581 | 1.00 (0.94–1.06) 481/2432 |
| From a municipality with ≥400 inhabitant/km$^2$ | 1.09 (0.86–1.38) 82/376 | 1.10 (0.77–1.57) 36/163 | 1.08 (0.79–1.47) 46/213 |
| Moving to a municipality with ≥400 inhabitant/km$^2$ | 0.96 (0.92–1.01) 745/4150 | 0.97 (0.90–1.04) 316/1721 | 0.95 (0.89–1.02) 429/2429 |
| From a municipality with < 50 inhabitant/km$^2$ | 1.07 (0.81–1.41) 55/256 | 0.92 (0.59–1.46) 19/104 | 1.17 (0.82–1.67) 36/152 |
| From a municipality with 50–399 inhabitant/km$^2$ | 1.16 (0.87–1.54) 54/230 | 1.28 (0.82–1.99) 23/88 | 1.08 (0.75–1.57) 31/142 |
| From a municipality with ≥400 inhabitant/km$^2$ | 0.95 (0.90–1.00) 631/3585 | 0.96 (0.89–1.04) 271/1497 | 0.94 (0.88–1.01) 360/2088 |
| Relocation intensity | | | |
| Moving to a municipality with low relocation intensity | 0.98 (0.95–1.01) 2063/10780 | 1.00 (0.95–1.05) 894/4483 | 0.97 (0.93–1.01) 1169/6297 |
| From a municipality with low relocation intensity | 0.99 (0.96–1.02) 1813/9336 | 1.01 (0.96–1.06) 787/3855 | 0.97 (0.93–1.02) 1026/5481 |
| From a municipality with medium relocation intensity | **0.84 (0.71–0.99)** 172/1014 | 0.81 (0.63–1.04) 73/447 | 0.87 (0.70–1.08) 99/567 |
| From a municipality with high relocation intensity | 0.91 (0.72–1.15) 78/430 | 0.94 (0.66–1.34) 34/181 | 0.89 (0.65–1.21) 44/249 |
| Moving to a municipality with medium relocation intensity | 0.95 (0.90–1.00) 792/4398 | 1.01 (0.93–1.09) 366/1799 | **0.91 (0.84–0.98)** 426/2599 |
| From a municipality with low relocation intensity | 0.87 (0.73–1.04) 148/848 | 0.90 (0.69–1.16) 68/378 | 0.85 (0.67–1.08) 80/470 |
| From a municipality with medium relocation intensity | 0.95 (0.89–1.01) 522/3091 | 1.02 (0.94–1.12) 259/1225 | **0.89 (0.82–0.97)** 293/1866 |
| From a municipality with high relocation intensity | 1.00 (0.80–1.25) 92/459 | 0.99 (0.70–1.40) 39/196 | 1.01 (0.75–1.35) 53/263 |
| Moving to a municipality with high relocation intensity | 1.01 (0.95–1.07) 569/2802 | 0.98 (0.89–1.08) 229/1195 | 1.02 (0.95–1.11) 340/1607 |
| From a municipality with low relocation intensity | 0.96 (0.79–1.17) 117/607 | 0.84 (0.62–1.15) 45/269 | 1.06 (0.83–1.37) 72/338 |

(*continued on next page*)

**Table 3** (*continued*)

| | IBD | CD | UC |
|---|---|---|---|
| | OR (95% CI) number of movements, cases/controls | OR (95% CI) number of movements, cases/controls | OR (95% CI) number of movements, cases/controls |
| From a municipality with medium relocation intensity | 0.97 (0.77–1.22) 85/437 | 1.06 (0.75–1.50) 37/174 | 0.91 (0.68–1.24) 48/263 |
| From a municipality with high relocation intensity | 1.02 (0.95–1.10) 367/1758 | 0.99 (0.88–1.12) 147/752 | 1.04 (0.95–1.14) 220/1006 |
| Rurality | | | |
| Moving to an urban municipality | 0.99 (0.97–1.02) 2481/12572 | 1.02 (0.97–1.06) 1073/5166 | 0.98 (0.94–1.02) 1408/7406 |
| From an urban municipality | 1.00 (0.97–1.03) 2295/11569 | 1.02 (0.98–1.07) 998/4739 | 0.98 (0.94–1.02) 1297/6830 |
| From a rural municipality | 1.03 (0.88–1.19) 177/860 | 0.96 (0.76–1.22) 71/371 | 1.07 (0.88–1.31) 106/489 |
| Moving to a rural municipality | **0.94 (0.90–0.98)** 958/5614 | 0.95 (0.89–1.02) 423/2393 | **0.93 (0.88–0.99)** 535/3221 |
| From an urban municipality | 0.90 (0.78–1.05) 193/1078 | 0.87 (0.70–1.10) 79/459 | 0.93 (0.76–1.12) 114/619 |
| From a rural municipality | **0.94 (0.89–0.99)** 759/4473 | 0.96 (0.89–1.03) 341/1908 | **0.92 (0.87–0.99)**4 18/2565 |

OR = odds ratio; CI = confidence interval.
Bold indicates significant findings on the 95% confidence limit.

for UC, whereas such an effect was not observed in CD. Children who had lived abroad showed a lower risk for IBD onset, with similar estimates for both disease subtypes.

We evaluated five indicators characterizing the departure and destination areas. Mobility and population mixing have been used as proxies for unmeasured contact with microbial agents in population-level cancer research [31]. In the context of IBD, a variety of surrogates have been utilized to examine the association of childhood microbial exposure with the disease onset [15–19,32]. A recent umbrella review summarized that several proxies are linked with IBD, such as urban living (increasing the risk) and bed sharing (decreasing the risk, specifically of CD) [33]. Although the review reported direct associations with microbes from Helicobacter species, the findings are not directly applicable in the Finnish setting, as *Helicobacter pylori* infections are rare in Finland, especially among children with IBD [34], K.L. Kolho, personal communication, January 13, 2023. To our knowledge, no previous study has assessed overall patterns of residential mobility in relation to IBD in children, or among adults.

We used the number of residential movements as an indicator for population mixing and for encountering novel pathogens in the environment. Population density in Finland is low (on average 18.25 person/km$^2$) [35], and distances between population centers can be long. Hence, it offers a good setting to study the effect of residential mobility.

Microbial exposure has been a long-standing focus of research in the etiology of IBD, with two hypotheses proposed to explain its effect. Some reviews have suggested a “triggering” role of early exposure to an array of microbes that can survive immune mechanisms and result in chronic inflammation [2,8,10,11,36,37]. The “hygiene hypothesis”, on the other hand, postulates that lack of microbial exposure during childhood can disrupt immune-regulatory mechanisms controlling autoimmune responses [7,8,10,12,38]. Our results are consistent with the proposition that encountering new environments and potentially microbial profiles at a young age may decrease the risk of childhood IBD. Nonetheless, the effect seems rather small and points to a more complex picture than an exclusive link with specific microbes. Alternatively, this might imply that a triggering agent requires a longer period of contact (approximated by less mobility) to increase the disease risk, although we were unable to directly assess this hypothesis. The findings, limited largely to UC alone, suggest a difference in the pathogenesis and etiological factors between the two main subtypes.

Our results may indicate that more frequent residential changes can influence UC onset in children; for each additional move, OR was reduced by 4%. Nevertheless, this should be interpreted with appropriate caution.

Comparable decrease in OR was found when the analysis was restricted to subjects aged under 2 and 6 years, indicating similar protective effect for IBD in different pediatric age groups. Our findings also showed that mobility during the latest years before the index date was associated with reduced ORs of IBD, as cases were less likely to change their dwellings in the period immediately preceding the diagnosis. Unexpectedly, overall movements between dwellings of less than 50 km apart were associated with a lower IBD risk, but moving further away was not. Moving to further areas increases the chances of exposure to new pathogens, yet we did not observe a trend in effect size when analyzing distance of movements in kilometers. On the other hand, categorizing movements based on none versus within Finnish municipalities, between Finnish municipalities, or abroad showed different risk estimates. Children who had lived abroad reported lower IBD risk compared with those who only moved within Finland. Nevertheless, the number of children in the former category was very small. These findings are contradictory and partly inconsistent with our proposition of an effect related to potential exposure to novel microbes.

We characterized locations based on population density, population size, relocation intensity, and rurality and analyzed the effect of moving to locations in those categories. Effect estimates were generally lower, but no clear differences were found in relation to specific characteristics analyzed. When separately investigating the disease subtypes, the protective effect was shown in UC, but not CD. This likely denotes midpoint estimates in IBD between those of UC and CD. A more extensive examination of movements between areas with different population sizes, population densities, and relocation intensities exhibited complicated results, without consistent patterns. Moving between similar areas was more common than to areas with different population characteristics, which resulted in more precise estimates. Nonetheless, we were unable to provide a clear interpretation of the findings related to area characteristics but hope a common denominator could be discovered through future research.

Our findings are partly consistent with previous studies, which used different proxies for early microbial exposures in childhood IBD. Strisciuglio et al. (2017) [19] examined multiple indicators and reported a significantly reduced risk for pet ownership in CD and UC, as well as for family history of intestinal parasitosis in UC. They also found that the number of siblings was inversely associated with the risk of both disease subtypes. In addition, Radon et al. (2007) [18] showed an inverse association of CD with a large number of siblings and found a lower risk in CD and UC for contact with farm animals in the first year of life. By contrast, some reports showed higher risks with infection and poor hygiene. Jakobsen et al. (2013) [17] found that children who shared their bedrooms were significantly more likely to be diagnosed with IBD before the age of 15 years. Baron et al. (2005) [16] also described a similar trend among young individuals with UC. This, however, is in contrast with an umbrella review that summarized a reduced risk of CD associated with bed sharing, although the findings were not limited to the child population [33]. Overall, the conflicting results may reflect limitations due to proxies with low sensitivity and/or specificity. Most of the abovementioned studies used questionnaires for data collection on a number of potential risk determinants, which might lead to information bias and chance findings. Furthermore, control selection was not population-based and participation varied between cases and controls, which could have induced selection bias.

We found a small but significant reduction in IBD risk among children who frequently changed their dwellings in rural areas, yet the duration of living in neither rural areas nor urban exhibited an effect. Rural population is more likely to be exposed to farm animals and dust and potentially more diverse microbial profiles [10,39,40]. By contrast, urban environments often involve better hygiene standards [10,23], which has been suggested to influence the maturity of immune cells and tolerance to microbiota [7,8,10,12,23,38–40]. Frequent movers in rural areas might potentially encounter a wider variation of risk factors as opposed to people with fewer residential changes. Dwellers who tend to settle in a limited number of houses could be exposed to a narrower variety of pathogens, even if the duration of staying in a single rural house was long. This suggests that the frequency of residential changes, even if they occur in local areas, might influence IBD onset more than the duration of residence in a certain region per se. Nevertheless, most study participants (86.8%) lived only in either urban or rural areas for the entire period before the index date, and hence, our dataset does not allow analyses of the effect of residential duration on IBD risk. Previous studies have reported urban upbringing as a potential risk factor and rural residence as protective. Benchimol et al. (2017) [39] showed a decreased incidence of childhood IBD related to rural residence during early years of life. Similar to our study, the protective effect was stronger in UC than CD. Furthermore, Elten et al. (2021) [41] found lower risk of childhood IBD, especially for UC, related to green space in residential areas (estimated by normalized difference vegetation index) with a linear gradient. Radon et al. (2007) [18] reported higher IBD risk for living in urban areas among children aged 6–18 years. Two other studies also found increased childhood CD risk associated with urban upbringing [32,42]. Similarly, a summary of meta-analyses reported a higher risk of IBD and CD onset among people living in urban areas [33]. Nevertheless, people living in urban environments are likely to use more healthcare services, which might explain at least partly the higher disease occurrence [43,44]. Additionally, environmental factors related to rurality cannot solely be reduced to more diverse microbial profiles and higher exposure to them. Other unidentified factors may explain this association.

Previous immigration studies have reported mixed effects of mobility on IBD risk. Children of immigrant background in Ontario had a lower risk for developing CD and UC [25]. A study that examined Faroes movers to Denmark, including both children and adults, found that subjects exhibited lower UC risk after 10 years of relocation [27]. By contrast, childhood IBD was more likely among South Asian immigrants to British Columbia than the host population [29]. UK-born individuals from Indian and Pakistani backgrounds were shown to have higher risk to develop IBD before the age of 26 years [28]. Also, two studies covering pediatric and adult populations reported increased UC risk for moving to more developed countries [20,26]. A potential explanation of those findings, with ours included, could be that the risk of IBD, and especially UC, may be related to exposure to novel environments, with increased or decreased risk depending on the changes encountered.

We used comprehensive nationwide registers, which constitutes a major strength to our study. The dataset covered the entire Finnish child population over a 40-year period, with a large sample size and accurate information on each residence enabling us to construct full residential histories of the study subjects. The controls were randomly selected from the population base and individually matched. The coverage of the special reimbursement register for the pediatric population has been shown to reach 94%, with 98% of the cases meeting modern diagnostic criteria, indicating high sensitivity and specificity [30]. Additionally, the time gap between the date of diagnosis and approval of reimbursement is short (mean 2.3 ± 6.9 months) [30]. A small number of patients with mild symptoms might not require medication and they could be missing from our dataset, yet such cases are exceptional in the pediatric patient population.

The current study also has some weaknesses. We used a proxy to indirectly measure environmental exposures, which may not be of sufficient sensitivity and validity for specific aspects of them. Small population size, low population density, and rural location of a municipality do not necessarily imply low frequency of contacts. Our findings may be hampered by imperfect proxies and not accounting for multiple testing. Moreover, having no access to data about several potential confounders is a main drawback in the study. Finally, much of the population may be living in close proximity within small areas due to uneven population distribution, even in a large municipality. This means that there is substantial variation for the population within a municipality comprising both urban and suburban, and even rural areas.

## Conclusions

Residential movement was associated with a small but significant reduction in the risk of childhood IBD, particularly UC. The protective effect was mainly shown for mobility to nearby and rural areas. Further research is required to elucidate the findings and to explore their replicability.

## Funding

This work was supported by the Pediatric Research Foundation (KLK), Helsinki University Hospital (Grant numbers TYH2018212 and TYH2020217 [KLK]). The funding source had no involvement in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the article for publication.

## CRediT authorship contribution statement

**Wafa Alimam:** Validation, Formal analysis, Data curation, Writing – original draft, Visualization. **Atte Nikkilä:** Conceptualization, Methodology, Formal analysis, Data curation, Writing – review & editing. **Jani Raitanen:** Validation, Formal analysis, Data curation, Writing – review & editing, Visualization. **Kaija-Leena Kolho:** Conceptualization, Resources, Writing – review & editing, Supervision, Project administration, Funding acquisition. **Anssi Auvinen:** Conceptualization, Methodology, Writing – review & editing, Supervision, Project administration.

## References


[1] Kaplan GG, Ng SC. Understanding and preventing the global increase of inflammatory bowel disease. Gastroenterology 2017;152:313–321.e2. https://doi.org/10.1053/j.gastro.2016.10.020

[2] Malmborg P, Hildebrand H. The emerging global epidemic of paediatric inflammatory bowel disease - causes and consequences. J Intern Med 2016;279:241–58. https://doi.org/10.1111/joim.12413

[3] Roberts SE, Thorne K, Thapar N, Broekaert I, Benninga MA, Dolinsek J, et al. A systematic review and meta-analysis of paediatric inflammatory bowel disease incidence and prevalence across Europe. J Crohn's Colitis 2020;14:1119–48. https://doi.org/10.1093/ecco-jcc/jjaa037

[4] Sýkora J, Pomahačová R, Kreslová M, Cvalínová D, Štych P, Schwarz J. Current global trends in the incidence of pediatric-onset inflammatory bowel disease. World J Gastroenterol 2018;24:2741–63. https://doi.org/10.3748/wjg.v24.i25.2741

[5] Virta LJ, Saarinen MM, Kolho K-L. Inflammatory bowel disease incidence is on the continuous rise among all paediatric patients except for the very young: a nationwide registry-based study on 28-year follow-up. J Crohn's Colitis 2016;11:150–6. https://doi.org/10.1093/ecco-jcc/jjw148

[6] Benchimol EI, Bernstein CN, Bitton A, Carroll MW, Singh H, Otley AR, et al. Trends in epidemiology of pediatric inflammatory bowel disease in Canada: distributed network analysis of multiple population-based provincial health administrative databases. Am J Gastroenterol 2017;112:1120–34. https://doi.org/10.1038/ajg.2017.97

[7] Ananthakrishnan AN. Epidemiology and risk factors for IBD. Nat Rev Gastroenterol Hepatol 2015;12:205–17. https://doi.org/10.1038/nrgastro.2015.34

[8] De Souza HSP, Fiocchi C. Immunopathogenesis of IBD: current state of the art. Nat Rev Gastroenterol Hepatol 2016;13:13–27. https://doi.org/10.1038/nrgastro.2015.186

[9] Kaplan GG. The global burden of IBD: from 2015 to 2025. Nat Rev Gastroenterol Hepatol 2015;12:720–7. https://doi.org/10.1038/nrgastro.2015.150

[10] Molodecky NA, Kaplan GG. Environmental risk factors for inflammatory bowel disease. Gastroenterol Hepatol 2010;6:339–46.

[11] Ananthakrishnan AN, Bernstein CN, Iliopoulos D, Macpherson A, Neurath MF, Ali RAR, et al. Environmental triggers in IBD: a review of progress and evidence. Nat Rev Gastroenterol Hepatol 2018;15:39–49. https://doi.org/10.1038/nrgastro.2017.136

[12] Aujnarain A, Mack DR, Benchimol EI. The role of the environment in the development of pediatric inflammatory bowel disease. Curr Gastroenterol Rep 2013;15:326. https://doi.org/10.1007/s11894-013-0326-4

[13] Mentella MC, Scaldaferri F, Pizzoferrato M, Gasbarrini A, Miggiano GAD. Nutrition, IBD and gut microbiota: a review. Nutrients 2020;12:944. https://doi.org/10.3390/nu12040944

[14] Ng SC, Bernstein CN, Vatn MH, Lakatos PL, Loftus EV, Tysk C, et al. Geographical variability and environmental risk factors in inflammatory bowel disease. Gut 2013;62:630–49. https://doi.org/10.1136/gutjnl-2012-303661

[15] Amre DK, Lambrette P, Law L, Krupoves A, Chotard V, Costea F, et al. Investigating the hygiene hypothesis as a risk factor in pediatric onset Crohn's disease: a case-control study. Am J Gastroenterol 2006;101:1005–11. https://doi.org/10.1111/j.1572-0241.2006.00526.x

[16] Baron S, Turck D, Leplat C, Merle V, Gower-Rousseau C, Marti R, et al. Environmental risk factors in paediatric inflammatory bowel diseases: a population based case control study. Gut 2005;54:357–63. https://doi.org/10.1136/gut.2004.054353

[17] Jakobsen C, Paerregaard A, Munkholm P, Wewer V. Environmental factors and risk of developing paediatric inflammatory bowel disease - a population based study 2007-2009. J Crohn's Colitis 2013;7:79–88. https://doi.org/10.1016/j.crohns.2012.05.024

[18] Radon K, Windstetter D, Poluda AL, Mueller B, Von Mutius E, Koletzko S, et al. Contact with farm animals in early life and juvenile inflammatory bowel disease: a case-control study. Pediatrics 2007;120:354–61. https://doi.org/10.1542/peds.2006-3624

[19] Strisciuglio C, Giugliano F, Martinelli M, Cenni S, Greco L, Staiano A, et al. Impact of environmental and familial factors in a cohort of pediatric patients with inflammatory bowel disease. J Pediatr Gastroenterol Nutr 2017;64:569–74. https://doi.org/10.1097/MPG.0000000000001297

[20] Barreiro-de Acosta M, Alvarez Castro A, Souto R, Iglesias M, Lorenzo A, Dominguez-Munoz JE. Emigration to western industrialized countries: a risk factor for developing inflammatory bowel disease. J Crohn's Colitis 2011;5:566–9. https://doi.org/10.1016/j.crohns.2011.05.009

[21] Ko Y, Butcher R, Leong RW. Epidemiological studies of migration and environmental risk factors in the inflammatory bowel diseases. World J Gastroenterol 2014;20:1238–47. https://doi.org/10.3748/wjg.v20.i5.1238

[22] Misra R, Faiz O, Munkholm P, Burisch J, Arebi N. Epidemiology of inflammatory bowel disease in racial and ethnic migrant groups. World J Gastroenterol 2018;24:424–37. https://doi.org/10.3748/wjg.v24.i3.424

[23] Song C, Yang J, Ye W, Zhang Y, Tang C, Li X, et al. Urban–rural environmental exposure during childhood and subsequent risk of inflammatory bowel disease: a meta-analysis. Expert Rev Gastroenterol Hepatol 2019;13:591–602. https://doi.org/10.1080/17474124.2018.1511425

[24] Nikkilä A, Auvinen A, Kolho K-L. Clustering of pediatric onset inflammatory bowel disease in Finland: a nationwide register-based study. BMC Gastroenterol 2022;22:1–5. https://doi.org/10.1186/s12876-022-02579-1

[25] Benchimol EI, Mack DR, Guttmann A, Nguyen GC, To T, Mojaverian N, et al. Inflammatory bowel disease in immigrants to Canada and their children: a population-based cohort study. Am J Gastroenterol 2015;110:553–63. https://doi.org/10.1038/ajg.2015.52

[26] Carr I, Mayberry JF. The effects of migration on ulcerative colitis: a three-year prospective study among Europeans and first- and second-generation South Asians in Leicester (1991–1994. Am J Gastroenterol 1999;94:2918–22. https://doi.org/10.1016/S0002-9270(99)00494-3

[27] Hammer T, Lophaven SN, Nielsen KR, von Euler-Chelpin M, Weihe P, Munkholm P, et al. Inflammatory bowel diseases in Faroese-born Danish residents and their offspring: further evidence of the dominant role of environmental factors in IBD development. Aliment Pharmacol Ther 2017;45:1107–14. https://doi.org/10.1111/apt.13975

[28] Montgomery SM, Morris DL, Pounder RE, Wakefield AJ. Asian ethnic origin and the risk of inflammatory bowel disease. Eur J Gastroenterol Hepatol 1999;11:543–6. https://doi.org/10.1097/00042737-199905000-00013

[29] Pinsk V, Lemberg DA, Grewal K, Barker CC, Schreiber RA, Jacobson K. Inflammatory bowel disease in the South Asian pediatric population of British Columbia. Am J Gastroenterol 2007;102:1077–83. https://doi.org/10.1111/j.1572-0241.2007.01124.x

[30] Lehtinen P, Ashorn M, Iltanen S, Jauhola R, Jauhonen P, Kolho KL, et al. Incidence trends of pediatric inflammatory bowel disease in Finland, 1987-2003, a nationwide study. Inflamm Bowel Dis 2011;17:1778–83. https://doi.org/10.1002/ibd.21550

[31] Law GR, Feltbower RG, Taylor JC, Parslow RC, Gilthorpe MS, Boyle P, et al. What do epidemiologists mean by "population mixing"? Pediatr Blood Cancer 2008;51:155–60. https://doi.org/10.1002/pbc.21570

[32] Ponsonby A-L, Catto-Smith AG, Pezic A, Dupuis S, Halliday J, Cameron D, et al. Association between early-life factors and risk of child-onset Crohn's disease among Victorian children born 1983–1998: a birth cohort study. Inflamm Bowel Dis 2009;15:858–66. https://doi.org/10.1002/ibd.20842

[33] Piovani D, Danese S, Peyrin-Biroulet L, Nikolopoulos GK, Lytras T, Bonovas S. Environmental risk factors for inflammatory bowel diseases: an umbrella review of meta-analyses. Gastroenterology 2019;157:647–659.e4. https://doi.org/10.1053/j.gastro.2019.04.016

[34] Kolho K-L, Rautelin H, Lindahl H, Savilahti E. *Helicobacter pylori*-positive gastritis in pediatric patients with chronic inflammatory bowel disease. J Pediatr Gastroenterol Nutr 1998;27:292–5. https://doi.org/10.1097/00005176-199809000-00004

[35] Finland Population 2023 (Live), ⟨https://worldpopulationreview.com/countries/finland-population⟩; 2023 [accessed January 28, 2023].

[36] Irving PM, Gibson PR. Infections and IBD. Nat Clin Pract Gastroenterol Hepatol 2008;5:18–27. https://doi.org/10.1038/ncpgasthep1004

[37] Ohkusa T, Nomura T, Sato N. The role of bacterial infection in the pathogenesis of inflammatory bowel disease. Intern Med 2004;43:534–9. https://doi.org/10.2169/internalmedicine.43.534

[38] Mak WY, Zhao M, Ng SC, Burisch J. The epidemiology of inflammatory bowel disease: east meets west. J Gastroenterol Hepatol 2020;35:380–9. https://doi.org/10.1111/jgh.14872

[39] Benchimol EI, Kaplan GG, Otley AR, Nguyen GC, Underwood FE, Guttmann A, et al. Corrigendum: Rural and urban residence during early life is associated with a lower risk of inflammatory bowel disease: a population-based inception and birth cohort study. Am J Gastroenterol 2017;112:1485. https://doi.org/10.1038/ajg.2017.271

[40] Timm S, Svanes C, Janson C, Sigsgaard T, Johannessen A, Gislason T, et al. Place of upbringing in early childhood as related to inflammatory bowel diseases in

adulthood: a population-based cohort study in Northern Europe. Eur J Epidemiol 2014;29:429–37. https://doi.org/10.1007/s10654-014-9922-3
[41] Elten M, Benchimol EI, Fell DB, Kuenzig ME, Smith G, Kaplan GG, et al. Residential greenspace in childhood reduces risk of pediatric inflammatory bowel disease: a population-based cohort study. Am J Gastroenterol 2021;116:347–53. https://doi.org/10.14309/ajg.0000000000000990
[42] Phavichitr N, Cameron DJS, Catto-Smith AG. Increasing incidence of Crohn's disease in Victorian children. J Gastroenterol Hepatol Aust 2003;18:329–32. https://doi.org/10.1046/j.1440-1746.2003.02975.x
[43] M'koma AE. Inflammatory bowel disease: an expanding global health problem. Clin Med Insights Gastroenterol 2013;6:33–47. https://doi.org/10.4137/CGast.S12731
[44] Soon IS, Molodecky NA, Rabi DM, Ghali WA, Barkema HW, Kaplan GG. The relationship between urban environment and the inflammatory bowel diseases: a systematic review and meta-analysis. BMC Gastroenterol 2012;12:51. https://doi.org/10.1186/1471-230X-12-51