PIETA LEHTINEN

Pediatric Inflammatory Bowel Disease in Finland

Incidence and long-term outcomes
PIETA LEHTINEN

Pediatric Inflammatory Bowel Disease in Finland

Incidence and long-term outcomes

ACADEMIC DISSERTATION
To be presented, with the permission of the Board of the School of Health Sciences of the University of Tampere, for public discussion in the Main auditorium of building B, School of Medicine, Medisiinarinkatu 3, Tampere, on 17 June 2016, at 12 o’clock.

UNIVERSITY OF TAMPERE
PIETA LEHTINEN

Pediatric Inflammatory Bowel Disease in Finland

Incidence and long-term outcomes
Supervised by
Professor Anssi Auvinen
University of Tampere
Finland
Docent Kaija-Leena Kolho
University of Helsinki
Finland

Reviewed by
Docent Pekka Arikoski
University of Eastern Finland
Finland
Professor Marjo-Riitta Järvelin
Imperial College London
United Kingdom

The originality of this thesis has been checked using the Turnitin OriginalityCheck service in accordance with the quality management system of the University of Tampere.

Copyright ©2016 Tampere University Press and the author

Cover design by
Mikko Reinikka

Distributor:
verkkokauppa@juvenesprint.fi
https://verkkokauppa.juvenes.fi

Acta Universitatis Tamperensis 2174
ISBN 978-952-03-0133-0 (print)
ISSN-L 1455-1616
ISSN 1455-1616

Acta Electronica Universitatis Tamperensis 1673
ISBN 978-952-03-0134-7 (pdf)
ISSN 1456-954X
http://tampub.uta.fi

Suomen Yliopistopaino Oy – Juvenes Print
Tampere 2016
Abstract

Background:

The incidence of inflammatory bowel disease (IBD) has been increasing among children especially in Western countries over the past decades. Crohn’s disease (CD) predominates over ulcerative colitis (UC) in most countries. The factors behind this increase are mainly unknown. Environmental factors influence, however, unquestionably the pathogenesis of IBD. The disease course in pediatric IBD is suggested to be more severe compared to adults which may have particularly impact on child development. The possible long-term sequelae of pediatric onset disease include growth impairment, risk of surgery and reduced quality of life.

Objectives:

This epidemiological study aimed to evaluate the incidence of IBD among Finnish children between the years 1987-2003. The role of environmental determinants (pediatric population density, agricultural industry, paper mills or sea shore close to the place of residence, north-south gradient and chemical concentrations of tap water) in the spatial variations of pediatric IBD was explored. Further, medical record data were applied in the characterization of the clinical picture. The long-term outcome of pediatric IBD patients was assessed by conducting a questionnaire survey among the patients diagnosed at Helsinki and Tampere university hospitals between years 1987-2003.

Materials and methods:

All children aged 0-17 years diagnosed with IBD in Finland between years 1987-2003 were identified through the Social Insurance Institution special reimbursement database. Information on residence was obtained from the
Population Register Centre and population size data from Statistics Finland. Annual incidence rates per 100,000 pediatric population and 95% confidence intervals (CI) were calculated assuming a Poisson distribution. The surface area of Finland was divided into squares of 250 x 250 m and regional differences were assessed. The databases of the two largest university hospitals in Finland were searched to collect the information on the clinical picture of the pediatric IBD diagnosed between years 1987-2003. In addition, a questionnaire on the health status was sent to the patients identified from the hospital files and to age- and sex-matched controls randomly selected from the Population Register Centre.

Results:

In total, 1880 children at the age of <18 years were diagnosed with IBD in Finland during the 17-year study period. The incidence of pediatric IBD increased threefold from 4.8/100,000 in 1987 to 15.0/100,000 in 2003. The annual increase was on average 6.5% (95% CI 5.4%-7.5%). The analysis by IBD subtype was conducted only for years 1992-2003 due to incompleteness of the earlier data. The annual incidence of UC increased from 4 to 9 per 100,000 and that of CD from 2 to 5 per 100,000 during years 1992-2003. UC was more common than CD during the entire period. The average annual increase in CD was, however, higher compared to UC (8.4% versus 5.2%). There was no statistically significant north-south gradient in the incidence rates. In addition, chemical concentrations of tap water, agricultural industry and the closeness of the paper mill or seaside were not associated the incidence rates of pediatric IBD within the geographic units. Nevertheless, the incidence rates were significantly higher in the districts with sparse compared to dense child population.

Of the patients identified from the hospital databases, the majority (52%, n=317) was diagnosed with UC. The proportion of CD was 34% (n=203) and IBD-unclassified 14% (n=83) respectively. Altogether 45% of these children with IBD had received glucocorticoids as primary medication and 21% were operated before age 18. Participation proportion of the questionnaire survey was 67% (368/550) among patients and 37% (646/1760) among controls. As much as 83% of these patients had received systemic glucocorticoids during the disease course. The most common extraintestinal manifestation among the patients was a joint disease (in 5% of the patients who completed the questionnaire). According to
questionnaire responses, the patients with pediatric onset IBD had lower scores in all four questions assessing quality of life compared to the healthy controls although the difference was statistically significant only in overall quality of life and physical functioning. Moreover, the male patients were shorter and weighted less than the healthy controls.

Conclusions:

The incidence of pediatric IBD has substantially increased in Finland during 1987-2003. Moreover, the incidence rate of pediatric IBD was higher in the areas with low density of child population than in areas with high density of child population. The disease course of IBD among children is aggressive; systemic glucocorticoid therapy and surgical operations are frequent. In consequence, pediatric onset IBD reduces overall quality of life even in early adulthood when compared to overall quality of life in their healthy peers.
Tiivistelmä

Tausta:


Tavoitteet:


Menetelmät:

Kaikki vuosina 1987–2003 Suomessa 0-17 vuoden iässä IBD diagnoosin saaneet lapset identifioitiin Kansaneläkelaitoksen tietokannasta. Asuinpaikkatiedot saatiin Väestörekisterikeskukselta, ja väestötiedot Tilastokeskukselta. Vuosittaiset ilmantoiminnallisuudet laskettiin 100 000 lasta kohden, ja 95 %:n luottamusväli (CI) arvioitiin Poissonin jakauman perusteella. Suomi jaettiin 250

**Tulokset:**

Yhteensä 1880 lasta sai IBD-diagnoosin alle 18 vuoden iässä Suomessa 17-vuotisen tutkimusjakson aikana. Lasten IBD:n ilmantoipuus nousi 1987 vuonna 4,8/100 000 vuonna 2003. Keskimääräinen vuosittainen kasvu olisi 6,5% (95% CI 5,4% -7,5%). Alatypyppäiset analyysit tehtiin vain vuosien 1992 ja 2003 välillä, koska tutkimusjakson alkuperäisiä diagnoositiedot olivat puutteellisia. UC:n vuosittainen ilmantoipuus suureni 4-9 100 000 kohti ja CD:n ilmantoipuus 2-5 100 000 kohti. UC oli yleisin diagnoosi koko jakson ajan. CD:n ilmantoipuus yleistyikin kuitenkin UC-ryhmän nopeammin (8,4% verrattuna 5,2%). UC:n ja CD:n ilmantoipuvuudessa ei ollut merkittävää eroa pohjois-eteläsuunnassa. Lisäksi vesijohtoveden kemikaalipitoisuuksilla, maanviljelyjen määrällä ja merenrannan tai paperitehtaiden läheisyydellä ei ollut vaikutusta lasten IBD:n ilmantoipuuteen. Kuitenkin ilmantoipuvuus oli korkeampaa alueilla, joissa oli matala lapsiväestötiheyys, verrattuna korkean lapsiväestötiheyden alueisiin. Suurimmalla osalla (52%, n=317) sairaaloiden potilasrekistereiden kautta identifioiduista potilaista diagnoosina oli UC. CD:n osuus oli 34% (n=203) ja luokittelemattoman IBD:n vastaavasti 14% (n=83). Kokonaisuudessaan 45% näistä lapsista oli saanut ensilinjan lääkityksenä systeemistä glukokortikoidia ja 21% oli leikattu alle 18 vuoden iässä. Kyselytutkimuksen osallistumisprosentti oli potilailla 67% (368/550) ja verrokeilla 37% (646/1760). Jopa 83% näistä potilaista oli saanut systeemistä glukokortikoidia sairauden kulussa. Nivelsairaudet olivat yleisimpää liitännäissairauksia potilaiden keskuudessa (5%:lla kyselyyn vastanneista potilaista). Potilaat, joilla on lapsuusiässä diagnoosito IBD, saivat matalamman pistemääriän kaikissa neljässä elämän tunnelaa, mitaavassa kysymyksessä terveisiin ikätovereihin verrattuna kyselytutkimuksen perusteella. Ero oli tilastollisesti merkitsevä kokonaiselämänlaadun lisäksi...
fyysistä toimintaa mittaavassa kysymyksessä. Lisäksi miespuoliset potilaat olivat lyhempä ja painoivat vähemmän kuin terveet verrokit.

**Johtopäätökset:**

Abstract ...................................................................................................................................................... 3

Tiivistelmä ................................................................................................................................................... 7

List of Original Publications .......................................................................................................................... 15

Abbreviations .................................................................................................................................................. 17

1 Introduction .................................................................................................................................................. 19

2 Review of Literature .................................................................................................................................... 21
  2.1 Definitions ............................................................................................................................................. 21
  2.2 Diagnostic procedure .............................................................................................................................. 21
    2.2.1 Blood tests ........................................................................................................................................... 22
    2.2.2 Fecal markers ...................................................................................................................................... 23
  2.3 Diagnostic classification .......................................................................................................................... 23
    2.3.1 Serology .............................................................................................................................................. 24
  2.4 Incidence of pediatric IBD ...................................................................................................................... 25
  2.5 Etiology .................................................................................................................................................... 33
    2.5.1 Genetic factors ..................................................................................................................................... 37
    2.5.2 Environmental factors ....................................................................................................................... 38
      2.5.2.1 Urban and rural environments ................................................................................................. 38
      2.5.2.2 The north-south gradient ........................................................................................................... 38
      2.5.2.3 Gut microbiota and antibiotics ................................................................................................. 39
      2.5.2.4 Drinking water ............................................................................................................................ 40
  2.6 Disease characteristics and clinical picture of pediatric onset IBD ....................................................... 40
    2.6.1 Symptoms .......................................................................................................................................... 40
    2.6.2 Disease location ................................................................................................................................... 41
    2.6.3 Growth retardation ............................................................................................................................ 41
    2.6.4 Extraintestinal manifestations .......................................................................................................... 42
    2.6.5 Early-onset IBD ................................................................................................................................ 43
    2.6.6 Reproduction ..................................................................................................................................... 43
    2.6.7 Malignancy and mortality in children with IBD ............................................................................... 44
  2.7 Management of IBD in Children ........................................................................................................... 44
    2.7.1 Disease activity assessment .............................................................................................................. 44
    2.7.2 Medication ....................................................................................................................................... 45
2.7.2.1 Systemic glucocorticoids ............................................. 45
2.7.2.2 Exclusive enteral nutrition and nutrition support ............................................. 46
2.7.2.3 Aminosalicytes ................................................................. 46
2.7.2.4 Immunomodulators ........................................................... 47
2.7.2.5 Biological agents ............................................................... 48
2.7.2.6 Antibiotics ................................................................. 48
2.7.2.7 Thalidomide ................................................................. 49
2.7.3 Surgery ................................................................................. 49
2.8 Quality of life in children with IBD .................................................. 50
2.9 Summary ................................................................................ 52
3 Aims of the Study ......................................................................... 53
4 Materials and Methods ..................................................................... 54
4.1 Data collection ............................................................................. 55
4.1.1 The SII database (Studies III & IV) ............................................. 55
4.1.1.1 IBD subtypes ........................................................................... 56
4.1.2 Demographics ........................................................................... 57
4.1.3 Environmental data (Study IV) ...................................................... 57
4.1.4 Hospital databases (Study I) ......................................................... 57
4.1.5 Questionnaire survey (Study II) ..................................................... 58
4.2 Statistical Analysis ......................................................................... 59
4.3 Ethical issues ................................................................................ 61
5 Summary of the Results ................................................................. 62
5.1 Incidence of pediatric IBD (Studies III & IV) ........................................ 62
5.1.1 Incidence rates and trends ............................................................ 64
5.1.2 Regional differences (Study III) ..................................................... 66
5.1.3 Spatial variations of pediatric IBD in Finland (Study IV) ......................... 66
5.2 Hospital-based study (Study I) ......................................................... 71
5.2.1 Diagnostic classification .............................................................. 72
5.2.2 Diagnostic procedure ................................................................. 73
5.2.3 Disease distribution ..................................................................... 74
5.3 Questionnaire survey (Study II) ......................................................... 74
5.3.1 Participation ................................................................................ 74
5.3.2 Characteristics of the patient group ................................................. 75
5.3.3 Family history with IBD .............................................................. 76
5.3.4 Reproductive history ..................................................................... 76
5.3.5 Chronic diseases ........................................................................... 76
5.3.6 Anthropometric Measures ............................................................ 78
5.3.7 Quality of life ................................................................................. 78
5.4 Reclassifications of the diagnoses (Studies I & II) ................................. 80
5.5 Medication (Studies I & II) ................................................................. 81
5.6 Surgery (Studies I & II) ........................................................................ 81

6 Discussion .................................................................................................. 83
6.1 Data sources ............................................................................................ 83
6.2 Incidence of pediatric IBD ....................................................................... 85
6.3 Environmental factors related to incidence of IBD ............................... 87
   6.3.1 North-south gradient ..................................................................... 88
   6.3.2 Vitamin D ...................................................................................... 88
   6.3.3 Population density ......................................................................... 89
   6.3.4 Drinking water ............................................................................... 89
   6.3.5 Gut microbiota and antibiotics ....................................................... 90
   6.3.6 Paper industry and seaside ............................................................. 91
6.4 Disease characteristics and clinical picture ......................................... 92
   6.4.1 Medication ..................................................................................... 92
   6.4.2 Disease location ............................................................................ 92
   6.4.3 Surgery ......................................................................................... 92
   6.4.4 Disease reclassification ................................................................. 93
   6.4.5 Extraintestinal manifestations ....................................................... 93
   6.4.6 Growth retardation ...................................................................... 94
   6.4.7 Long-term sequelae ..................................................................... 94
   6.4.8 Quality of life ............................................................................... 94
   6.4.9 Fertility ........................................................................................ 95
6.5 Future directions ..................................................................................... 95

7 Summary and Conclusions ....................................................................... 97

8 Acknowledgements .................................................................................. 99

References .................................................................................................... 101

Appendix 1 ................................................................................................. 119

Appendix 2 ................................................................................................. 131
List of Original Publications


<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-ASA</td>
<td>5-aminosalicyte acid</td>
</tr>
<tr>
<td>ASCA</td>
<td>Anti-Saccharomyces cerevisae antibody</td>
</tr>
<tr>
<td>BCG</td>
<td>Bacilli Calmette-Guerin</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
</tr>
<tr>
<td>CD</td>
<td>Crohn’s disease</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>CRP</td>
<td>C-reactive protein</td>
</tr>
<tr>
<td>EEN</td>
<td>Exclusive enteral nutrition</td>
</tr>
<tr>
<td>EGD</td>
<td>Esophagogastroduodenoscopy</td>
</tr>
<tr>
<td>FC</td>
<td>Fecal calprotectin</td>
</tr>
<tr>
<td>GI</td>
<td>Gastrointestinal</td>
</tr>
<tr>
<td>GT</td>
<td>Glutamyltransferase</td>
</tr>
<tr>
<td>GWAS</td>
<td>Genome-wide association scanning</td>
</tr>
<tr>
<td>HRQOL</td>
<td>Health-related quality of life</td>
</tr>
<tr>
<td>IBD</td>
<td>Inflammatory bowel disease</td>
</tr>
<tr>
<td>IBDU</td>
<td>IBD-unclassified</td>
</tr>
<tr>
<td>IC</td>
<td>Indeterminate colitis</td>
</tr>
<tr>
<td>MRE</td>
<td>Magnetic resonance enterography</td>
</tr>
<tr>
<td>OR</td>
<td>Odds ratio</td>
</tr>
<tr>
<td>pANCA</td>
<td>Perinuclear antineutrophil cytoplasmic antibody</td>
</tr>
<tr>
<td>PCDAI</td>
<td>Pediatric Crohn’s Disease Activity Index</td>
</tr>
<tr>
<td>PET</td>
<td>Positron emission tomography</td>
</tr>
<tr>
<td>PSC</td>
<td>Primary sclerosing cholangitis</td>
</tr>
<tr>
<td>PUCAI</td>
<td>Pediatric Ulcerative Colitis Activity Index</td>
</tr>
<tr>
<td>RR</td>
<td>Rate ratio</td>
</tr>
<tr>
<td>SII</td>
<td>Social Insurance Institution</td>
</tr>
<tr>
<td>TNF</td>
<td>Tumor necrosis factor</td>
</tr>
<tr>
<td>UC</td>
<td>Ulcerative colitis</td>
</tr>
<tr>
<td>WCE</td>
<td>Wireless capsule endoscopy</td>
</tr>
</tbody>
</table>
1 Introduction

Inflammatory bowel disease (IBD) is a chronic disease of unknown etiology. It has three subtypes. The two major clinical subtypes are Crohn’s disease (CD) and ulcerative colitis (UC). The third type of IBD is IBD-unclassified (IBDU). The incidence of IBD has been rising during the last decades particularly in Western countries (Molodecky et al. 2012). This increasing trend in IBD incidence has been noticeable also among children (Benchimol et al. 2011). The increase has been steepest in CD (Benchimol et al. 2011).

Research on the factors behind this increase has been active. It is evident that genetic predisposition is linked to the risk of IBD (Van Limbergen, Radford-Smith & Satsangi 2014). Nevertheless, inheritable characteristics in the population do not alter within a time span of decades. The role of the environment in the increasing incidence of IBD is, undeniably, substantial. Urban environment with high population density is one of those factors associated with pediatric IBD (El-Matary, Moroz & Bernstein 2014). Moreover, modern westernized diet containing refined sugars may increase the risk of IBD (Ng et al. 2014, Danese, Sans & Fiocchi 2004) and chemical concentrations of drinking water for example iron content have been linked to IBD (Aamodt et al. 2008a). Recurrent use of antibiotics affects the gut flora and has been associated with the development of pediatric CD (Virta et al. 2012). Altogether, the role of the intestinal microbiota in the pathogenesis of IBD has been demonstrated. For example, statistically significant differences in average amounts of Escherichia/Shigella- and Faecalibacterium-components in stool samples between of UC patients and controls have been indicated (Thorkildsen et al. 2013).

Since IBD is more common in the northern parts of the globe, ultraviolet radiation and insufficient levels of vitamin D have been proposed as possible etiologic factors (Bernstein 2012). Low levels of vitamin D have been linked to multiple chronic diseases such as asthma and atopic dermatitis (Cheon et al. 2015, Somashekar, Prithvi & Gowda 2014). Ultraviolet radiation and north-south gradient are interesting subjects owing to the northern location of Finland.

Pediatric IBD is a chronic disease with commonly severe disease course (Levine 2009). Even if mortality directly due to IBD is minor, the disease impacts
on the quality of life in children with IBD. As a whole, the quality of life is at a lower level among children with IBD compared to the healthy peers (Greenley et al. 2010). Furthermore, pediatric onset IBD has many long-term effects on the patients’ lives. Hospitalizations, extraintestinal manifestations and growth failures are common during the subsequent years from the diagnosis (Abraham, Mehta & El-Serag 2012).

The data on the incidence rates of IBD especially among pediatric population have been missing almost completely earlier in Finland. A previous Finnish study described an annual CD incidence of 1.0/100,000 with no increase between years 1986-1992 among Finnish children aged 0-14 years (Pebody, Paunio & Ruutu 1998). Whether the incidence of pediatric IBD has an increasing trend also in Finland has been unclear. A public healthcare system and national health insurance with an accessible database enables comprehensive nationwide, long-term studies in Finland.

The main objective of the present study was to estimate the incidence rate of pediatric IBD nationwide and its evolution in Finland between the years 1987-2003. The possible influence of the environmental factors such as pediatric population density and chemical concentrations of the tap water on the incidence rates of IBD among children was assessed. Additionally, this study aimed to learn more about the long-term outcomes of pediatric onset IBD. The objective of the literature review was to clarify the present knowledge of the pediatric IBD with emphasis on the studies concerning incidence, environmental factors and long-term outcomes. The current review focuses on the studies conducted since year 2000, although this is not a systematic review.

As a limitation, it was not possible to include the whole lifelong exposure data. There were constraints in terms of what environmental and other potential exposure factors were available from data sources employed (the Social Insurance Institution special reimbursement database, the Population Register Centre, Statistics Finland, Corine Land Cover 2000 raster data and water works of municipalities). Hence the information on potential explanatory factors such as vitamin D levels, sunlight exposure and socioeconomic status is missing. Additionally, individual-level data on water consumption was not included in this study. A part of information which could have been obtained from the questionnaires and the hospital databases for example birth weight and gestational age was not included in the analyses of the present study.
2 Review of Literature

2.1 Definitions

The three subtypes of IBD are UC, CD and IBDU, which is defined as IBD subtype that cannot be classified as CD or UC (Geboes et al. 2008). This third subtype of IBD was previously called indeterminate colitis (IC) (Geboes et al. 2008). Contemporary recommendations state, however, that the term of IC should be only used if the diagnosis is based on colectomy specimen (Geboes et al. 2008, Silverberg et al. 2005).

2.2 Diagnostic procedure

Fundamentally, IBD is a chronic inflammation of the gastrointestinal (GI) tract. All other causes of the inflammation need to be ruled out especially in children under two years of age with the possibility of primary immune deficiency kept in mind (Levine et al. 2013b). Consequently, endoscopic evaluation of colon and terminal ileum by ileocolonoscopy and assessment of upper GI tract by esophagogastroduodenoscopy (EGD) with histological examination of multiple mucosal biopsies form the basis for the diagnosis of IBD. The small bowel assessment is recommended to be performed during the diagnostic procedure of all suspected IBD cases with the exception of the patients with typical UC (Levine et al. 2013b). Magnetic resonance enterography (MRE) can accurately identify macroscopic small intestinal involvements in pediatric CD patients (Piekkala et al. 2012). By performing MRE, the entire gut and the potential extraluminal disease can be evaluated (Mentzel et al. 2014). Nevertheless, the usage of MRE can be limited by inadequate compliancy of the youngest pediatric patients (Mentzel et al. 2014). MRE is preferable to fluoroscopy due to avoided radiation exposure and better specificity (Levine et al. 2013b). In the imaging of the small bowel, wireless capsule endoscopy (WCE) is a valuable alternative to MRE particularly in the youngest children (Levine et al. 2013b).
Potential but less frequently used diagnostic modalities comprise technetium-labeled white blood cell scintigraphy, contrast-enhanced ultrasonography and positron emission tomography (PET). These modalities cannot, however, replace the endoscopies but may be considered in some cases if there is local expertise in these techniques (Lemberg et al. 2005, Charron, Di Lorenzo & Kocoshis 2000, Bremner et al. 2006, Levine et al. 2013b). Ultrasonography is an effective alternative to assess the transmural and perivisceral inflammatory lesions in CD especially in the terminal ileum (Levine et al. 2013b, Migaleddu et al. 2011). One possible application of ultrasonography could be useful in ruling out possible IBD (Charron, Di Lorenzo & Kocoshis 2000) but its routine use is limited by radiation exposure. Further, 18F-fluorodeoxyglucose-PET (FDG-PET) has high diagnostic accuracy for inflammatory lesions of the bowel but involves substantial exposure to radiation and is less frequently available (Berthold et al. 2013). Balloon assisted enteroscopy is recommended only in special situations as a complementary diagnostic tool (Levine et al. 2013b, Pasha et al. 2008). The technique is invasive.

2.2.1 Blood tests

Important blood tests in the early stages of the diagnostic procedure are full blood count, albumin, transaminases, glutamyltransferase (GT), erythrocyte sedimentation rate and C-reactive protein (CRP) (Levine et al. 2013b). Nevertheless, the results of the screening laboratory tests often are within normal limits at the time of the diagnosis especially in patients with mild disease (Mack et al. 2007). Thus, IBD can never be excluded merely by the blood tests. Specific antibodies to microbial and leukocyte antigens for example the anti-Saccharomyces cerevisae antibodies (ASCA) and Perinuclear antineutrophil cytoplasmic antibodies (pANCA) are detected more commonly in pediatric IBD patients compared to children without IBD but the serologic testing is mainly suggested as an additional tool in the differentiation of CD from UC (Zholudev et al. 2004). Occasionally further laboratory tests such as transaminases are indicated in order to discover possible extraintestinal manifestations of IBD (Levine et al. 2013b).
2.2.2 Fecal markers

Calprotectin is a protein occurring mainly in neutrophil granulocytes and its levels in stools are elevated in bowel inflammations due to the infiltration of neutrophils in the intestinal mucosa (Konikoff, Denson 2006). In comparison to standard blood tests, fecal calprotectin (FC) is unequivocally better in distinguishing children with IBD (Henderson et al. 2012, Sidler, Leach & Day 2008, Quail et al. 2009). Moreover, FC has a high sensitivity in detecting patients with IBD among children with suspected IBD (Henderson, Anderson & Wilson 2013, Kostakis et al. 2013). FC is not, however, specific to IBD (Henderson et al. 2012). Of the other fecal markers, lactoferrin and fecal S100A12 (Ca-binding protein) can detect gastrointestinal inflammation with a specificity of more than 90% (Sidler, Leach & Day 2008, Sipponen et al. 2008), while other fecal tests are not recommended for routine use (Levine et al. 2013b). New promising fecal markers are, however, explored constantly and for example matrix metalloproteinase 9 (MMP-9) has shown to be almost comparable to FC in detection of UC among children (Kolho et al. 2014).

2.3 Diagnostic classification

The differentiation of CD, UC and IBDU from each other is challenging despite all the diagnostic methods. In up to 9% of the pediatric IBD cases, the diagnosis is reclassified within one year after initial diagnosis (Stordal et al. 2004). The diagnosis changes mainly from IBDU to CD (Abraham, Mehta & El-Serag 2012). The classic characteristics of UC are diffuse and continual inflammation of the mucosa in the colon (North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition et al. 2007). Histological characteristics of both active and chronic inflammation are present in typical UC (North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition et al. 2007). Nevertheless, UC patients may have abnormalities in the distal ileum termed backwash ileitis. Changes of the terminal ileum among UC patients are usually of mild degree and parallel to the severity of the colitis (Haskell et al. 2005). In addition, rectal sparing, upper GI tract involvement and histological patchiness (normal mucosa between two segments with mucosal inflammation) can be detected in a minority of children with UC (Rajwal et al. 2004, Tobin et al. 2001, Glickman et al. 2004, Levine et al. 2013a). Cecal patch (periappendiceal and cecal inflammation in presence of colitis constricted to the left side of the colon) is also an atypical
feature of UC found in 2% of pediatric UC patients (Levine et al. 2013a, North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition et al. 2007). Gastritis with granulomas and further true (nonpericrypt) granulomas in the GI tract are a marker of CD (North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition et al. 2007). Focally enhanced gastritis (inflammation of the stomach with discrete inflammatory foci) is not specific for CD although it is more common in children with CD than in UC (Ushiku, Moran & Lauwers 2013).

CD can occur in any segment of the GI tract (de Bie et al. 2013). Classical histological findings in CD include chronic discontinuous inflammation of the colon and/or the ileum with granulomas, fissuring ulceration, stricturing of bowel and fistula (North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition et al. 2007). Perianal fistulas or abscesses are found in 9% of children with CD at the time of the diagnosis (de Bie et al. 2013). Moreover, FC levels in the feces do not differ notably between subtype groups of IBD (Henderson et al. 2012).

The Montreal classification for IBD (Silverberg et al. 2005) and the Paris classification (a pediatric modification of the Montreal criteria) (Levine et al. 2011) provide recommendations for classification of IBD in practice. The Paris classification takes into account special needs of the pediatric IBD. It groups CD according to the age at diagnosis, the anatomic distribution, the behavior (stricturing or penetrating) and the presence of growth delay. Respectively, UC is divided according to extent and severity of the disease.

2.3.1 Serology

Serologic testing provides further information on the differential diagnostics between CD and UC, although no serological markers are absolute in diagnostic classification (Levine et al. 2013b). Compared to children with UC, ASCA antibodies are more common among children with CD and especially among CD patients with ileal disease (Zholudev et al. 2004). ASCA positivity is also marker of severe CD (Russell et al. 2009). Furthermore, pANCA antibodies are more prevalent in UC than in CD (Zholudev et al. 2004). A combination of these serologic markers increases diagnostic accuracy (Hoffenberg, Fidanza & Sauaia 1999, Mainardi et al. 2007, Reese et al. 2006). The absence of ASCA and pANCA refers to IBDU (Joossens et al. 2002, Russell et al. 2009). Anti-OmpC (anti-outer membrane protein C of Escherichia coli), anti-I2 (antibody to the Pseudomonas
fluorescens-associated sequence I2) and other novel serologic markers can be best utilized in combination with other serologic markers (Davis et al. 2007, Zholudev et al. 2004, Ashorn et al. 2009, Iltanen et al. 2006).

2.4 Incidence of pediatric IBD

Overall, the incidence rate of pediatric IBD has been increasing since the 1970s (Benchimol et al. 2011), although also stable incidence rates have been reported (Adamiak et al. 2013, Agnarsson et al. 2013, Ahmed et al. 2006, Grieci, Butter 2009). The increasing incidence has mainly been due to pediatric CD (Malaty et al. 2010, Hildebrand et al. 2003, Kolek et al. 2004, Armitage et al. 2001). The increase of UC incidence has been more moderate (Orel et al. 2009, Malmborg et al. 2013, Abramson et al. 2010). Further, stable and even decreasing incidence rates of pediatric UC have been reported in some populations (Perminow et al. 2009, Auvin et al. 2005, Barton, Gillon & Ferguson 1989, Benchimol et al. 2009, Grieci, Butter 2009). A summary of the studies describing the incidence rates of pediatric IBD is compiled in Table 1. As a whole, an increasing trend in the incidence of pediatric IBD is observed in these studies. There is, however, a wide divergence of overall incidence rates which can at least partly be explained by differences in the age limits and study periods.

CD is the most common subtype of pediatric IBD globally (Benchimol et al. 2011). Nevertheless, UC is the most common diagnosis in some countries including Italy, Denmark, Iceland and Poland (Castro et al. 2008, Jakobsen et al. 2011, Agnarsson et al. 2013, Karolewska-Bochenek et al. 2009). IBDU is an infrequent diagnosis in adolescents but it encompasses as much as 22% of the new IBD diagnosis among children aged 0-5 years (Aloi et al. 2014, Hope et al. 2012, Agnarsson et al. 2013, Auvin et al. 2005, Winter et al. 2015).

The incidence rates among children are approximately half of those in adults: The highest reported incidence rates of pediatric IBD are 13.9/100,000 in Canada for CD and 13.3/100,000 in Denmark for UC (Benchimol et al. 2011), while the highest rates among adults are 29.3/100,000 in Australia for CD and 27.4/100,000 in Finland for UC (Jussila et al. 2012, Molodecky et al. 2012). The incidence of IBD among adults is likewise increasing noticeably in most populations, though in few countries the trends are stable or even decreasing (Molodecky et al. 2012). Adult studies from Denmark, the Netherlands and Northern France have shown
statistically significant decrease in the incidence of UC, but none in CD (Molodecky et al. 2012).

The highest rates for pediatric IBD incidence are reported in Europe and North America (Benchimol et al. 2011). Incidence rates of pediatric IBD in Australia and in New Zealand are also increasing in a similar fashion (Gearry et al. 2006, Yap et al. 2008, Phavichitr, Cameron & Catto-Smith 2003, Ponsonby et al. 2009). Adequate information on the pediatric IBD incidence is missing in the majority of developing countries, and therefore it is difficult to assess the global distribution of the IBD incidence (Gasparetto, Guariso 2013, Benchimol et al. 2011). A survey from Libya, North Africa showed significantly increasing trend in pediatric IBD incidence (Ahmaida, Al-Shaikhi 2009), otherwise no epidemiological data on pediatric IBD from Africa is available (Benchimol et al. 2011). In the epidemiological studies on IBD among adults in Africa, the incidence rates have been increasing over time (Molodecky et al. 2012). Further, recent studies from Asia indicate an increasing trend of childhood IBD incidence, although the figures are lower compared to the Western countries (El Mouzan et al. 2014, Tsai et al. 2004, Kim et al. 2010, Shen et al. 2011, Wang et al. 2013). Adult studies from Asia demonstrate parallel results (Ng et al. 2013, Molodecky et al. 2012).

In addition, the incidence rates of pediatric IBD may vary between different ethnic groups even within a geographical area. The risk of IBD has been shown to increase among adults who emigrate from areas with low IBD incidence to high-risk areas (Molodecky et al. 2012). In Canada, the incidence of pediatric IBD was higher among children of South Asian origin compared with non-South Asian children (Pinsk et al. 2007). A study from the British Isles also demonstrated a substantially elevated risk of IBD among children of Asian origin (Sawczenko et al. 2001). Furthermore, the incidence of IBD was higher among white children compared to African Americans and Hispanics according to a study from Texas (Malaty et al. 2010). Nevertheless, also similar occurrence in ethnic groups has been reported in the USA (Adamiak et al. 2013, Kugathasan et al. 2003).
Table 1. Incidence rates of IBD, UC and CD in children across the world. A summary of all available pediatric studies published between years 2000-2014.

<table>
<thead>
<tr>
<th>Reference, district/country</th>
<th>Study period</th>
<th>Age range (years)</th>
<th>Overall incidence (/100,000 children) and trend</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>IBD</td>
</tr>
<tr>
<td>Abramson et al. 2010,</td>
<td>1996-2006</td>
<td>0-17</td>
<td>-</td>
</tr>
<tr>
<td>Northern California/USA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adamiak et al. 2013,</td>
<td>2000-2007</td>
<td>0-17</td>
<td>9.5 ↔</td>
</tr>
<tr>
<td>Wisconsin/USA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Agnarsson et al. 2013,</td>
<td>1951-2010</td>
<td>0-16</td>
<td>5.0 ↑</td>
</tr>
<tr>
<td>Ahmaida et al. 2009,</td>
<td>1997-2006</td>
<td>0-14</td>
<td>0.9 ↑</td>
</tr>
<tr>
<td>Eastern Libya</td>
<td></td>
<td></td>
<td>(year 2006)</td>
</tr>
<tr>
<td>Ahmed et al. 2006,</td>
<td>1996-2003</td>
<td>0-15</td>
<td>5.4 ↔</td>
</tr>
<tr>
<td>South Wales/UK</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Armitage et al. 2001,</td>
<td>1981-1995</td>
<td>0-16</td>
<td></td>
</tr>
<tr>
<td>Scotland</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Auvin et al. 2005,</td>
<td>1988-1999</td>
<td>0-16</td>
<td>3.1</td>
</tr>
<tr>
<td>Northern France</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reference, district/country</td>
<td>Study period</td>
<td>Age range (years)</td>
<td>Overall incidence (/100,000 children) and trend</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>--------------</td>
<td>-------------------</td>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>IBD</td>
</tr>
<tr>
<td>Benchimol et al. 2014, Ontario/Canada</td>
<td>1999-2008</td>
<td>0-9</td>
<td>2.9 ↑</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10-19</td>
<td>21.5 ↑</td>
</tr>
<tr>
<td>Castro et al. 2008, Italy</td>
<td>1996-2003</td>
<td>0-17</td>
<td>1.39 ↑*</td>
</tr>
<tr>
<td>Grieci et al. 2009, Southwestern Ontario</td>
<td>1997-2006</td>
<td>0-17</td>
<td>13.3 ↓ NS</td>
</tr>
<tr>
<td>Hassan et al. 2000, Wales</td>
<td>1995-1997</td>
<td>0-16</td>
<td>2.6</td>
</tr>
<tr>
<td>Reference, district/country</td>
<td>Study period</td>
<td>Age range (years)</td>
<td>Overall incidence (/100,000 children) and trend</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>--------------</td>
<td>-------------------</td>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>IBD</td>
</tr>
<tr>
<td>Herrinton et al. 2008, Northern California/USA</td>
<td>1996-2002</td>
<td>0-18</td>
<td>-</td>
</tr>
<tr>
<td>Hildebrand et al. 2003, Stockholm/Sweden</td>
<td>1990-2001</td>
<td>0-15</td>
<td>7.4↑</td>
</tr>
<tr>
<td>Hope et al. 2012, Ireland</td>
<td>2000-2010</td>
<td>0-15</td>
<td>3.9↑</td>
</tr>
<tr>
<td>Jakobsen et al. 2011, Eastern Denmark</td>
<td>2007-2009</td>
<td>0-14</td>
<td>6.4↑**</td>
</tr>
<tr>
<td>Karolewska-Bochenek et al. 2009, Poland</td>
<td>2002-2004</td>
<td>0-18</td>
<td>2.7</td>
</tr>
<tr>
<td>Kolek et al. 2004, Moravia/Czech Republic</td>
<td>1990-2001</td>
<td>0-15</td>
<td>2.24↑</td>
</tr>
<tr>
<td>Kugathasan et al. 2003, Wisconsin/USA</td>
<td>2000-2001</td>
<td>0-17</td>
<td>7.05</td>
</tr>
<tr>
<td>Reference, district/country</td>
<td>Study period</td>
<td>Age range (years)</td>
<td>Overall incidence (/100,000 children) and trend</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>--------------</td>
<td>-------------------</td>
<td>---------------------------------------------</td>
</tr>
<tr>
<td>Malmborg et al. 2013, Stockholm/Sweden</td>
<td>2002-2007</td>
<td>0-15</td>
<td>12.8 ↔ 2.8 ↑ 9.2 ↔</td>
</tr>
<tr>
<td>Mouzan et al. 2014, Saudi Arabia</td>
<td>2003-2012</td>
<td>0-14</td>
<td>0.47 ↑ 0.2 ↑ 0.27 ↑</td>
</tr>
<tr>
<td>Orel et al. 2009, Central and Western Slovenia</td>
<td>1994-2005</td>
<td>0-18</td>
<td>4.03 ↑ 1.14 ↑ 2.42 ↑ NS</td>
</tr>
<tr>
<td>Perminow et al. 2009, Southeastern Norway</td>
<td>2005-2007</td>
<td>0-17</td>
<td>10.9 3.6 6.8</td>
</tr>
</tbody>
</table>
Table 1. (Continued)

<table>
<thead>
<tr>
<th>Reference, district/country</th>
<th>Study period</th>
<th>Age range (years)</th>
<th>Overall incidence (/100,000 children) and trend</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>IBD</td>
</tr>
<tr>
<td>Pinsk et al. 2007, British Columbia/Canada</td>
<td>1996-2001</td>
<td>0-16</td>
<td>5.19</td>
</tr>
<tr>
<td>Pozler et al. 2006, Czech Republic</td>
<td>1990-2001</td>
<td>0-14</td>
<td>-</td>
</tr>
<tr>
<td>Sawczenko et al. 2001, British Isles</td>
<td>1998-1999</td>
<td>0-15</td>
<td>5.2 (UK)</td>
</tr>
<tr>
<td>Schildkraut et al. 2013, Victoria/Australia</td>
<td>1950-2009</td>
<td>0-16</td>
<td>-</td>
</tr>
<tr>
<td>Stordal et al. 2004, Southeastern Norway</td>
<td>1990-1993</td>
<td>0-15</td>
<td>4.7</td>
</tr>
<tr>
<td>Reference, district/country</td>
<td>Study period</td>
<td>Age range (years)</td>
<td>Overall incidence (/100,000 children) and trend</td>
</tr>
<tr>
<td>-------------------------------------------------</td>
<td>--------------</td>
<td>-------------------</td>
<td>--------------------------------------------------</td>
</tr>
<tr>
<td>van der Zaaag-Loonen et al. 2004, Netherlands</td>
<td>1999-2001</td>
<td>0-17</td>
<td>IBD: 5.2, UC: 1.6, CD: 2.1</td>
</tr>
<tr>
<td>Yap et al. 2008, New Zealand</td>
<td>2002-2003</td>
<td>-</td>
<td>IBD: 2.9, UC: 0.5, CD: 1.9</td>
</tr>
</tbody>
</table>

**Abbreviations:**
NS = non-significant change
UK = United Kingdom
↑ = increasing trend in pediatric incidence
↓ = decreasing trend in pediatric incidence
↔ = stable trend in pediatric incidence
* no information on statistical significance of the time trend
**the increasing trend is from years 1998-2009, combined data from different cohorts
2.5  Etiology

The pathogenesis of IBD is multifactorial and is not completely comprehended. The hygiene hypothesis states that the modern, hygienic life has led to the increasing rates of IBD (Lakatos 2009). Several factors including pathogenic microbes, gut flora, inheritable characteristics and exogenous factors such as passive smoking in children have been associated with the increasing incidence rates of IBD (Lakatos 2009, Lashner et al. 1993). In adults, smoking is a risk factor of CD but protective against UC (Lakatos 2009).

On the contrary, pets, appendectomy and large families are associated with a lower risk of IBD (Baron et al. 2005, Bernstein et al. 2006). Many dietary factors including the substantial supply of dietary fiber and long chain omega-3 fatty acids have been demonstrated to be protective factors for pediatric CD (Amre et al. 2007). In addition, breast feeding has shown to be protective against IBD in several studies (Ng et al. 2014, Lakatos 2009), though a contradictory finding has been reported (Baron et al. 2005). The exogenous factors associated with the pediatric IBD are presented in Table 2.
Table 2. A summary of the studies on exogenous factors associated with the risk of childhood onset IBD published since 2000.

<table>
<thead>
<tr>
<th>Protective factors</th>
<th>OR (unless otherwise indicated)</th>
<th>Reference, district/country, the type of the study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(95% CI)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>IBD</td>
<td>UC</td>
</tr>
<tr>
<td>High amount of vegetables</td>
<td>0.69 (0.33-1.44)</td>
<td>Amre et al. 2007, Canada, a case-control study</td>
</tr>
<tr>
<td>LCN-omega-3 fatty acid</td>
<td>0.44 (0.19-1.00)</td>
<td></td>
</tr>
<tr>
<td>Fish</td>
<td>0.46 (0.20-1.06)</td>
<td></td>
</tr>
<tr>
<td>Dietary fiber</td>
<td>0.12 (0.04-0.37)</td>
<td></td>
</tr>
<tr>
<td>Drinking tap water</td>
<td>0.56 (0.3-1.0)</td>
<td>Baron et al. 2005, Northern France, a case-control study</td>
</tr>
<tr>
<td>Appendectomy</td>
<td>0.06 (0.01-0.36)</td>
<td></td>
</tr>
<tr>
<td>Daily vegetable consumption</td>
<td>0.3 (0.1-0.7)</td>
<td>Jakobsen et al. 2013, Denmark, a case-control study</td>
</tr>
<tr>
<td>Daily wholemeal bread consumption</td>
<td>0.5 (0.3-0.9)</td>
<td></td>
</tr>
<tr>
<td>Breast feeding</td>
<td>0.5 (0.3-1.0)</td>
<td></td>
</tr>
<tr>
<td>(&gt;3 months)</td>
<td>0.5 (0.2-1.0)</td>
<td></td>
</tr>
<tr>
<td>Risk factors</td>
<td>OR (unless otherwise indicated) (95% CI)</td>
<td>Reference, district/country, the type of the study</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>----------------------------------------</td>
<td>---------------------------------------------------</td>
</tr>
<tr>
<td></td>
<td>IBD</td>
<td>UC</td>
</tr>
<tr>
<td>Breast feeding</td>
<td>2.1 (1.3-3.4)</td>
<td></td>
</tr>
<tr>
<td>BCG vaccination</td>
<td>3.6 (1.1-11.9)</td>
<td></td>
</tr>
<tr>
<td>High ratio of LCN omega-6/omega-3 fatty acids</td>
<td>1.63 (1.01-2.64)</td>
<td></td>
</tr>
<tr>
<td>Pneumonia by age 5 years</td>
<td>2.74 (1.04-7.21)</td>
<td></td>
</tr>
<tr>
<td>Antibiotic use ≥1 antibiotic course in the childhood</td>
<td>1.84 (RR) (1.08-3.15)</td>
<td>1.21 (RR) (0.61-2.38)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.93 (RR) (1.34-6.40)</td>
</tr>
<tr>
<td>Antibiotic use &gt;6 antibiotic courses in the childhood</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bedroom sharing</td>
<td>2.1 (1.0-4.3)</td>
<td>3.6 (1.3-9.4)</td>
</tr>
<tr>
<td>Daily candy consumption</td>
<td>1.5 (1.0-2.4)</td>
<td></td>
</tr>
</tbody>
</table>
Table 2. (Continued)

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>OR (unless otherwise indicated) (95% CI)</th>
<th>Reference, district/country, the type of the study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IBD</td>
<td>UC</td>
</tr>
<tr>
<td>Antianaerobic antibiotic use by age 1 year</td>
<td>5.51 (HR)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(1.66-18.28)</td>
<td></td>
</tr>
<tr>
<td>Birth by cesarean section</td>
<td>1.14 (0.97-1.34)</td>
<td></td>
</tr>
<tr>
<td>Urban environment</td>
<td>1.66 (RR)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(1.28-2.16)</td>
<td></td>
</tr>
<tr>
<td>Living in urban environment</td>
<td>1.46 (HR)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(1.07-1.99)</td>
<td></td>
</tr>
<tr>
<td>Birth by elective cesarean section</td>
<td>1.67 (HR)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(1.17-2.39)</td>
<td></td>
</tr>
<tr>
<td>High socioeconomic status</td>
<td>1.47 (HR)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(1.04-2.07)</td>
<td></td>
</tr>
<tr>
<td>Old maternal age (33 years or over)</td>
<td>1.41 (HR)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(0.97-2.05)</td>
<td></td>
</tr>
<tr>
<td>Antibiotic use (≥1 course in their first year of life)</td>
<td>2.9 (1.2-7.0)</td>
<td>0.9 (0.2-4.2)</td>
</tr>
</tbody>
</table>
### Table 2. (Continued)

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>OR (unless otherwise indicated) (95% CI)</th>
<th>Reference, district/country, the type of the study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IBD</td>
<td>UC</td>
</tr>
<tr>
<td>Otitis media by age 1 year</td>
<td>2.77 (1.50-5.12)</td>
<td>3.31 (1.15-9.48)</td>
</tr>
<tr>
<td>Otitis media by age 5 years</td>
<td>2.80 (1.50-5.23)</td>
<td>3.02 (1.07-8.50)</td>
</tr>
<tr>
<td>Measles vaccination</td>
<td>1.51 (0.53-4.29)</td>
<td></td>
</tr>
<tr>
<td>Antibiotic use in the study period</td>
<td>1.11 (0.71-1.76)</td>
<td>2.06 (0.97-4.36)</td>
</tr>
<tr>
<td>Cephalosporin use in the study period</td>
<td></td>
<td>2.82 (1.65-4.81)</td>
</tr>
</tbody>
</table>

Abbreviations:
CI = confidence interval
BCG = bacilli Calmette-Guerin
HR = hazard ratio
LCN = long chain
OR = odds ratio
RR = rate ratio
UK = United Kingdom

#### 2.5.1 Genetic factors

Genetic factors contribute without doubt to the pathogenesis of IBD. Family history with IBD increases the risk of this disease. Within monozygotic twins the concordance for CD is 36% compared to 16% in UC indicating a larger influence of genetic factors for CD than for UC. Further, the concordance for dizygotic
twins is 4% for both CD and UC (Russell, Satsangi 2004). Nevertheless, the clinical picture is similar in familial and sporadic IBD cases (Halme et al. 2002). Recently, genome-wide association scanning (GWAS) has increased knowledge of IBD genetics and more than 160 susceptibility loci have been recognized by the year 2014 (Van Limbergen, Radford-Smith & Satsangi 2014). NOD2 (nucleotide-binding oligomerization domain-containing protein) variants have a strongest association with CD (Van Limbergen, Radford-Smith & Satsangi 2014). They regulate the intestinal microbiota and mucosal immune response (Van Limbergen, Radford-Smith & Satsangi 2014). In the light of present knowledge, pediatric-onset and adult-onset IBD have similar genetic susceptibility although the phenotypic characteristics differ (Henderson et al. 2011). The hereditary factors involved in CD and UC overlap to some extent (Van Limbergen, Radford-Smith & Satsangi 2014).

2.5.2 Environmental factors

2.5.2.1 Urban and rural environments

Urban environment has been associated with a higher risk of adult IBD in several studies (Aamodt et al. 2008b, Blanchard et al. 2001, Green et al. 2006, Soon et al. 2012). In a Spanish study, the risk of adult CD was greater in the urban region, whereas among UC patients the results were opposite (Mate-Jimenez et al. 1994). Similarly, children from urban environments have been shown to be at higher risk of IBD compared to children from rural districts (Ponsonby et al. 2009, Orel et al. 2009, Phavichitr, Cameron & Catto-Smith 2003, El-Matary, Moroz & Bernstein 2014). Conversely, the relative risk of CD among adults was higher within rural and periurban areas than in the urban areas in the Northern France (Declercq et al. 2010). An American study on pediatric IBD demonstrated a similar IBD incidence in densely and sparsely populated areas (Kugathasan et al. 2003).

2.5.2.2 The north-south gradient

In addition to differences between urban and rural regions, a north-south gradient in incidence rates of pediatric IBD has been demonstrated within the countries in
the Northern hemisphere (Karolewska-Bochenek et al. 2009, Kappelman et al. 2007, Armitage et al. 2004). This finding is also evident in the adult studies (Nerich et al. 2006, Shivananda et al. 1996, Sonnenberg, McCarty & Jacobsen 1991). The gradient is noticeable worldwide in the Northern hemisphere with the highest incidence rates of pediatric IBD in Northern Europe and Canada (Benchimol et al. 2011). However, in the Southern hemisphere the gradient is reverse. Especially among adults, regions with one of the highest incidence figures are found in Australia and New Zealand (Molodecky et al. 2012). Consequently, the distance from the equator and hence exposure to sunlight has been suggested as a key factor underlying the north-south gradient in the northern hemisphere (Bernstein 2012). Low levels of sunlight and ultraviolet exposure among adults have been associated with higher risk of CD and increased rates of hospitalizations and operations among IBD patients (Limketkai et al. 2014, Nerich et al. 2011). Furthermore, ultraviolet radiation of the sun is the foremost environmental source of the vitamin D and higher plasma levels of 25(OH)D show the association with a lower risk of IBD particularly CD among American women (Ananthakrishnan et al. 2012). There is also some evidence for an association of some polymorphisms in vitamin D receptor gene with IBD (Xue et al. 2013).

2.5.2.3 Gut microbiota and antibiotics

Despite numerous investigations, no single microorganism to cause IBD has been identified (Lakatos 2009). However, intestinal flora and its changes are related to the pathogenesis of IBD and further, fecal microbiota in newly diagnosed untreated IBD patients differs from controls’ microbiota (Danese, Sans & Fiocchi 2004, Thorkildsen et al. 2013). Additionally, disparities between CD and UC patients’ gut microbiota have been reported (Thorkildsen et al. 2013). Interestingly, a negative association between Helicobacter pylori infection and IBD has been discovered (Castano-Rodriguez et al. 2015). In contrast, related enterohepatic Helicobacter species and Campylobacter species increase the risk of IBD (Castano-Rodriguez et al. 2015). Antibiotics influence the development of the normal enteral flora (Gevers et al. 2014). Antibiotic use and having infections commonly treated with antibiotics in the early childhood have shown to be risk factors for pediatric IBD especially for CD (Hviid, Svanstrom & Frisch 2011, Shaw, Blanchard & Bernstein 2010, Shaw, Blanchard & Bernstein 2013, Hildebrand et al. 2008, Virta et al. 2012, Kronman et al. 2012). In UC group, the
association is weaker (Hviid, Svanstrom & Frisch 2011, Shaw, Blanchard & Bernstein 2010, Virta et al. 2012). This interconnection is evident primarily among children (Ungaro et al. 2014).

2.5.2.4 Drinking water

Drinking water and its contaminants may affect gut flora. Therefore, the relation between water supply and IBD has been researched. An association between well water drinking and increased risk of CD has been observed in adults (Van Kruiningen et al. 2005). In children, tap water consumption in comparison with drinking bottled or well water has been shown to be protective against CD but not against UC (Baron et al. 2005). Moreover, a Norwegian study has reported a relation between high iron content in drinking water and an increased risk of adulthood IBD (Aamodt et al. 2008a).

2.6 Disease characteristics and clinical picture of pediatric onset IBD

Twenty five percent of the IBD cases occur in childhood or adolescence. This statement is commonly used in literature concerning IBD. True or false, the fact is that the incidence of pediatric IBD is increasing worldwide (Benchimol et al. 2011). Among children less than 18 years of age, IBD is most commonly diagnosed at the age of >10 years (de Bie et al. 2012, Benchimol et al. 2014). Generally, there can be observed male predominance in pediatric-onset CD while in adult CD the distribution of males and females is reverse (Van Limbergen et al. 2008). In UC, the gender distribution is equal in both childhood-onset and adult-onset disease (Van Limbergen et al. 2008).

2.6.1 Symptoms

Clinical features in pediatric IBD appear to parallel those among adult IBD patients (Glickman et al. 2004, Levine 2009). Classic symptoms in pediatric UC are rectal bleeding and diarrhea (North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition et al. 2007). Respectively, in pediatric CD the abdominal pain is the most common symptom (Griffiths 2004).
Other classic symptoms of CD include diarrhea and weight loss together with oral aphthae, fever, perianal fistula and abscess.

2.6.2 Disease location

The disease location of pediatric IBD differs from that of adult-onset IBD. Over half of the pediatric UC patients present with pancolitis at the time of the diagnosis compared to one third of adult UC patients (Levine 2009). In line with that in the large European multicenter study on pediatric IBD, pancolitis was seen 69% of the patients with UC (Levine et al. 2013a). Proctitis is an unusual finding among children with UC, occurring in only 5% of patients (Levine et al. 2013a). Rectal sparing and histological patchiness are more likely to occur in pediatric UC than in adult-onset UC (Glickman et al. 2004).

Disease location in pediatric-onset CD is age-related. Isolated colitis is more prevalent among small children (Levine et al. 2007). Comparing disease distribution between pediatric-onset and adult-onset CD, isolated ileal disease is less common among children, as it occurs in only 3% of the pediatric patients with CD (Van Limbergen et al. 2008). At the time of the diagnosis, stricturing or penetrating diseases are rare among children with CD (de Bie et al. 2013). Nevertheless, after few years’ follow-up, disease location is similar to adults with one third of the patients having stricturing and/or penetrating phenotype (Van Limbergen et al. 2008).

2.6.3 Growth retardation

The major feature of pediatric CD is growth retardation present in 15%-40% of the patients with pediatric-onset IBD (Newby et al. 2005). On occasion, it may be the first sign of imminent IBD (Shamir, Phillip & Levine 2007). Despite good disease control, growth failure may persist during the follow-up (Pfefferkorn et al. 2009) and up to one fifth of the patients with childhood-onset CD fail to achieve their target height (Sawczenko et al. 2006). In contrast, growth failure is unusual in UC (Griffiths 2004). Young age at the time of the diagnosis and male gender are related to higher risk of growth retardation (Vasseur et al. 2010). Malnutrition and proinflammatory cytokines from the affected bowel lie behind the mechanism of growth failure (Walters, Griffiths 2009). In addition, medications in particular systemic glucocorticoids may induce growth retardation.
Among children with IBD body mass index (BMI) is generally lower compared to healthy controls because of malnutrition, which is affected by insufficient caloric intake, increased nutritional needs, malabsorption and stool losses (Thayu et al. 2007, Hyams 2005, Kugathasan et al. 2007). Like growth retardation, low BMI is more common among pediatric CD patients than among children with UC (Kugathasan et al. 2007). Additionally, malnutrition and other determinants including immunological factors affect pubertal development and delayed puberty is a complication seen in children with CD (Gasparetto, Guariso 2014). At the same time, overweight is a growing problem among children in general. In a North American study, 10% of the patients with pediatric-onset CD and even one third of the patients with pediatric-onset UC had BMI ≥85% (at risk of overweight or overweight) at the time of the diagnosis (Kugathasan et al. 2007).

2.6.4 Extraintestinal manifestations

At the time of the IBD diagnosis, 6-20% of the pediatric IBD patients have at least one extraintestinal manifestation (Jose et al. 2009, Dotson et al. 2010, Orel et al. 2009). The frequency reaches up to 29% after 15 years’ follow-up (Jose et al. 2009). The proportion is similar in both pediatric- and adult-onset IBD (Sauer, Kugathasan 2009). Arthritis/arthralgia, aphthous stomatitis and osteopenia/osteoporosis are the most commonly diagnosed extraintestinal manifestations among children (Jose et al. 2009, Dotson et al. 2010). In addition, erythema nodosum, pancreatitis and primary sclerosing cholangitis (PSC) are diagnosed in 1-3% of the pediatric IBD patients (Dotson et al. 2010).

In general, no association between age, gender, IBD subtype or race with the occurrence of extraintestinal manifestations can be found (Jose et al. 2009). When comparing IBD subtypes, aphthous stomatitis and erythema nodosum are more common among pediatric CD patients than in UC (Dotson et al. 2010). Respectively, PSC is more commonly seen among pediatric UC patients than in CD (Dotson et al. 2010). In UC, severe disease course and pancolitis are related to the increased risk of developing extraintestinal manifestations (Dotson et al. 2010).
2.6.5 Early-onset IBD

Although IBD is more common in children over ten years of age, 4-15% of the pediatric IBD patients are diagnosed at the age of five years or younger (early-onset IBD) (Aloi et al. 2014, Oliva-Hemker et al. 2015). Early-onset IBD has been associated with monogenic defects especially interleukin-10 and interleukin-10R deficiencies (Carneiro-Sampaio, Coutinho 2015). Among children with early-onset IBD, IBDU is more common compared to the older pediatric IBD patients (Mamula et al. 2002, Aloi et al. 2014). Furthermore, the diagnosis is reclassified during the disease course in up to 15% of the children with early-onset IBD reflecting difficulties in diagnostic classification (Mamula et al. 2002). Rectal bleeding is more common in children with early-onset IBD (Aloi et al. 2014, Gupta et al. 2008). The disease presentation in pediatric IBD patients aged 0-5 years is peculiar and more extensive. Pancolitis in UC and isolated colitis in CD are more common compared with older pediatric IBD patients (Gupta et al. 2008, Aloi et al. 2014, Oliva-Hemker et al. 2015). The prevalence of extraintestinal manifestations and growth failure are similar between early- and later-onset pediatric IBD patients (Aloi et al. 2014).

2.6.6 Reproduction

Childhood-onset IBD can affect reproduction. Sexual function is fairly similar among men with IBD compared to controls especially years after the diagnosis (Timmer et al. 2007b). Nonetheless, sexual function in women with IBD is impaired and almost 50% of the women reported sexual dysfunction after ileoanal anastomosis (Timmer et al. 2007a, Ogilvie et al. 2008). On the other hand, proctocolectomy with ileoanal anastomosis does not influence sexual function when comparing UC patients with or without childhood proctocolectomy (Koivusalo et al. 2009).

IBD does not influence fertility in men (Heetun et al. 2007). Furthermore, overall fertility in women with IBD is good but active CD and restorative proctocolectomy in women decreases fertility (Heetun et al. 2007, Cornish et al. 2007b, van der Woude et al. 2014). Disease activity can affect the outcome of pregnancy and increase the risk of preterm and low birth weight babies (Heetun et al. 2007, Lin et al. 2010, Cornish et al. 2007a, van der Woude et al. 2014).
2.6.7 Malignancy and mortality in children with IBD

Cancer and mortality in children with IBD are infrequent (de Ridder et al. 2014). Over half of the malignancies are lymphomas or leukemia (de Ridder et al. 2014). The risk of these malignancies is slightly increased in patients treated with immunosuppressive agents compared to other pediatric IBD patients (Ashworth et al. 2012, de Ridder et al. 2014). However, anti-tumor necrosis factor agents are not associated with the increased risk of lymphoma among pediatric IBD patients according to a systematic review (Dulai et al. 2014). Mortality in pediatric IBD is mainly caused by infections which are also related to immunomodulators, although complications of IBD or treatments have also been observed as cause of deaths (de Ridder et al. 2014). The risk of colorectal cancer, small bowel cancer and lymphoma is significantly higher in adults with IBD than in general population (Burisch, Munkholm 2015). Among adults with CD, the overall mortality is even 50% higher compared to the background population (Burisch, Munkholm 2015, Wolters et al. 2006). However, the mortality risk has not increased in adults with UC.

2.7 Management of IBD in Children

2.7.1 Disease activity assessment

All treatment in pediatric IBD is aimed to avoid or reduce the manifestations of the disease, and hence its adverse consequences including growth failure and reduced quality of life (Ruemmele et al. 2014). The essential goal of the medical treatment is mucosal healing (“deep/complete remission”), which improves the disease course and reduces the need for operative treatment (Ruemmele et al. 2014, Turner et al. 2012). Nevertheless, repeated endoscopies should be avoided in children unless essential due to severe symptoms (Turner et al. 2012). Thus non-invasive methods to evaluate the activity of the disease are needed. A Pediatric Ulcerative Colitis Activity Index (PUCAI) and a Pediatric Crohn’s Disease Activity Index (PCDAI) are tools for measuring the severity of the disease and assist with decisions about management of IBD (Hyams et al. 1991, Turner et al. 2007b). In addition, FC levels are another noninvasive tool for assessment of mucosal inflammation and clinical activity of IBD in children (Sipponen et al. 2008, Kolho, Turner 2013). Serum inflammatory markers
including high-sensitivity CRP are unreliable in the disease activity assessment in pediatric IBD (Turner et al. 2012, Sidoroff et al. 2010).

2.7.2 Medication

While medical therapy in pediatric IBD is in many ways similar to adults, differences also exist. Among children, the disease course is commonly more severe. Consequently, children need more often immunosuppressive agents compared to adults (Ruemmele, Turner 2014). Moreover, the maintenance therapy is indicated at least to all children with UC (Turner et al. 2012). The medical therapy is in outline similar for early- and later-onset pediatric IBD, though the need for glucocorticoids is more common in IBD patients aged 0-5 years (Aloi et al. 2014).

2.7.2.1 Systemic glucocorticoids

Especially in children, systemic glucocorticoids can cause many harmful side effects. Accordingly, those are not recommended for maintenance therapy (Turner et al. 2012, Ruemmele et al. 2014). However, systemic glucocorticoids are effective and generally recommended as an alternative for inducing remission in pediatric UC and luminal CD with moderate to severe symptoms (Ruemmele et al. 2014, Turner et al. 2012). As a side effect, steroid-dependency is observed even in 45% of the pediatric UC patients after one year (Hyams et al. 2006). Even recommended doses of systemic glucocorticoids may induce adverse effects including glaucoma, cataract and growth retardation in pediatric patients (Uchida et al. 2006). In addition, glucocorticoids suppress bone turnover as long as the therapy continues, predisposing children to osteoporosis (Vihinen et al. 2008). Oral budesonide is an option to systemic glucocorticoids (prednisone, prednisolone) in mild to moderate ileal pediatric CD, with slightly lower or similar effectiveness and less complications (Levine et al. 2003). When used, it is combined with other medicines (Otley et al. 2012) and not indicated for long-term use (Ruemmele et al. 2014, Turner et al. 2012). The use of intravenous glucocorticoids is restricted to acute severe pediatric IBD (Turner et al. 2011, Ruemmele et al. 2014).
2.7.2.2 Exclusive enteral nutrition and nutrition support

Exclusive Enteral Nutrition (EEN) is equally or nearly as efficient for inducing remission with fewer side effects as systemic glucocorticoids in pediatric CD (Heuschkel et al. 2000, Dziechciarz et al. 2007, Wilson et al. 2010, Levine et al. 2014a, Ruuska et al. 1994). According to the new European guideline, it is recommended as first-line therapy to pediatric CD patients with luminal active disease (Ruemmele et al. 2014). In contrast, EEN is not effective as a treatment modality in pediatric UC (Turner et al. 2012).

Partial enteral nutrition or high-energy supplements are recommended only to pediatric UC patients with poor nutritional status (Turner et al. 2012). In children with CD, partial enteral nutrition is one alternative, which can be used together with other medications in maintenance therapy (Ruemmele et al. 2014). Probiotics may be indicated in very mild pediatric UC, if 5-aminosalicyte acid (5-ASA) preparations are not tolerated, or as a part of the maintenance therapy (Turner et al. 2012). On the other hand, there is no firm evidence of the probiotics’ usefulness in pediatric CD (Ruemmele et al. 2014).

Otherwise, regular varied diet based on general references is adequate for most pediatric IBD patients (Kleinman et al. 2004). The intake of calcium and vitamin D is often inadequate and need to be ensured on demand as supplements (Turner et al. 2012, Ruemmele et al. 2014). Nonetheless, over half of the adolescents with IBD use complementary alternative medicine regularly and a similar proportion of patients use special diets such as non-dairy or gluten-free (Nousiainen et al. 2014).

2.7.2.3 Aminosalicytes

5-ASA is a recommended and safe preparation for inducing and maintaining remission in pediatric UC and should be used as first-line therapy in mild or moderate UC (Wilson et al. 2010, Quiros et al. 2009, Turner et al. 2012, Zeisler et al. 2013). In addition, rectal 5-ASA is indicated in proctitis or in combination with oral 5-ASA (Turner et al. 2012). In childhood CD, 5-ASA is warranted merely for children with mild colitis as an adjuvant therapy for remission induction (Wilson et al. 2010, Ruemmele et al. 2014). Monotherapy with 5-ASA in CD is associated with elevated FC levels despite clinical remission, which may indicate continual mucosal inflammation (Levine et al. 2014b).
Thiopurines (azathioprine and 6-mercaptopurine) are effective in maintaining remission in pediatric IBD (Markowitz et al. 2000, Jaspers et al. 2006, Riello et al. 2011, Hyams et al. 2011). Thus they are recommended for maintenance therapy in pediatric UC patients with intolerance to or failure of 5-ASA and in children with moderate to severe CD (Ruemmele et al. 2014, Turner et al. 2012). Nevertheless, side effects to azathioprine and 6-mercaptopurine occur in as many as 46% of the pediatric IBD patients (Kirschner 1998). The majority of those are, however, transient and the medication can be continued after dose reduction (Kirschner 1998). In 12-18% of the patients, thiopurine medication need to be discontinued due to adverse events such as pancreatitis, continual infections/fever, nausea, gastrointestinal symptoms and rash (Riello et al. 2011, Kirschner 1998). Consequently, regular blood tests are needed to detect possible toxicities including myelosuppression and hepatotoxicity (Ruemmele et al. 2014). Moreover, thiopurine methyltransferase genotype or phenotype is recommended to be defined to rule out myelotoxicity and the homozygous or remarkably low enzyme activity are contraindications to thiopurine usage (Riello et al. 2011, Ruemmele et al. 2014, Turner et al. 2012).

Methotrexate is recommended as an alternative for maintenance therapy in pediatric CD (Ruemmele et al. 2014, Willot, Noble & Deslandres 2011). In pediatric UC, there is less evidence of methotrexate’s efficacy and it is indicated only to patients with no other medication alternatives (Turner et al. 2012). Approximately half of the children treated with methotrexate experience side effects, most commonly nausea (Turner et al. 2007a, Willot, Noble & Deslandres 2011). Hepatotoxicity is noticed in every tenth child receiving methotrexate and almost half of them need cessation of the medication (Valentino et al. 2014). Consequently, routine checks of liver enzymes are required during methotrexate treatment (Ruemmele et al. 2014).

Children with acute severe UC may require short-term medical rescue therapy with cyclosporine if medication with glucocorticoids is unsuccessful (Turner et al. 2011). There is only little evidence of tacrolimus’s efficacy in children and it may be used exclusively in acute severe UC (Turner et al. 2011). Otherwise these medications are not recommended in pediatric IBD (Turner et al. 2012).
2.7.2.5 Biological agents

Anti-tumor necrosis factor (TNF) agents are recommended for treatment in active or steroid-dependent pediatric UC (Turner et al. 2012). Correspondingly, anti-TNF medication is advisable in luminal CD not responding to the first-line medication and in active fistulising CD in conjunction with surgical treatment (Ruemmele et al. 2014). In pediatric CD, both infliximab and adalimumab are used in a similar fashion, while in UC infliximab is the first choice anti-TNF agent. Other biological agents including vedolizumab and certolizumab pegol are currently under research (Lahad, Weiss 2015). Remission rate in induction therapy vary between 50%-85% in pediatric CD and 33%-36% in pediatric UC (Hyams et al. 2012a, Walters et al. 2014, Ruemmele et al. 2009, Hyams et al. 2010). Long-term results are parallel or even better (Nuti et al. 2013, Hyams et al. 2012a, Walters et al. 2014, Hyams et al. 2012b, Hyams et al. 2010). Serum levels and antibodies of infliximab and adalimumab can be measured in order to optimize drug doses or decide to stop the medication (Ruemmele et al. 2014). In induction therapy, lower serum infliximab levels are associated with inadequate response to infliximab medication (Hämäläinen, Sipponen & Kolho 2013). Adverse effects with anti-TNF therapy occur in 12%-95% of the pediatric IBD patients (Nuti et al. 2013, Hyams et al. 2012a, Kolho, Sipponen 2014). The most common side effects include infusion reactions caused by anti-bodies to anti-TNF agents and infections (Nuti et al. 2013, Ruemmele et al. 2014). Antibodies may also indicate the loss of drug’s effect (Ruemmele et al. 2014).

2.7.2.6 Antibiotics

In pediatric CD patients with perianal fistulising disease, antibiotics (metronidazole or ciprofloxacin) are a recommended alternative for remission induction (Ruemmele et al. 2014). In luminal CD and in pediatric UC, the evidence of antibiotics’ effectiveness is still deficient (Turner et al. 2012, Ruemmele et al. 2014). However, in a small study the combination of azithromycin and metronidazole was efficient in inducing remission in children with luminal CD (Levine, Turner 2011). Combination of different broad-spectrum antibiotics appears to be efficient in proportion of the children with moderate to severe UC according to preliminary results (Turner et al. 2014). Pouchitis after the proctocolectomy is an indication for antibiotic therapy in pediatric UC (Turner et al. 2012).
2.7.2.7 Thalidomide

Thalidomide therapy among children with IBD is limited to refractory CD with failed anti-TNF therapy (Ruemmele et al. 2014). Despite its effectiveness, multiple adverse events, including peripheral neuropathy occurring in up to half of the children using thalidomide, block wider usage of this medication among pediatric IBD (Lazzerini et al. 2013, Felipez et al. 2012).

2.7.3 Surgery

Surgery is a potential alternative for pediatric IBD patients with active disease in spite of maximum medication especially with prolonged glucocorticoid usage (Turner et al. 2012, Ruemmele et al. 2014). There is an increased risk of colorectal cancer among children and adolescents with IBD and therefore dysplasia is an obvious indication for surgery (Oliva-Hemker et al. 2008, Turner et al. 2012). In pediatric UC, the inflammation is mainly restricted to the colon area and consequently colectomy enables most children to discontinue strong medical therapy (Oliva-Hemker et al. 2008). In pediatric CD, surgery is never a cure for the disease and should always be considered carefully (Oliva-Hemker et al. 2008). Nevertheless, surgery is an inviting option particularly in CD patients with limited ileal disease or stricturing of the bowel unresponsive to medication (Ruemmele et al. 2014).

In pediatric UC, operations are almost invariably colectomies (Adamiak et al. 2013). The operation is generally performed in two stages with temporary stoma at the first stage followed later by its closure (Turner et al. 2012). Functional outcomes are, however, similar also in the one-stage operation without ileostomy (Weston-Petrides et al. 2008). Due to the higher risk of complications, the one-stage procedure is advisable only for selected UC patients without complicating factors such as malnutrition (Weston-Petrides et al. 2008). Although not yet common, laparoscopic surgery is a safe and potential alternative for children with IBD (Huang, Koleilat & Lee 2013). In pediatric CD, the most common type of operation is a partial resection of the bowel followed by abscess incision, fistulotomy and colectomy (Adamiak et al. 2013).

The surgery rates vary substantially between studies with 10%-72% in pediatric-onset CD and 0%-50% in pediatric UC (Abraham, Mehta & El-Serag 2012). Furthermore, up to 70-90% of the patients with CD undergo at least one operation during the disease course (Oliva-Hemker et al. 2008). In contrast to a
stable surgery rate in UC, the intestinal resection rate among pediatric CD patients has been increasing substantially during the last decade according to a nationwide American study (Debruyn et al. 2013). Risk factors of surgery among children with CD include growth failure, hypoalbuminemia, fistula, abscess and stricture (Gupta et al. 2006). The fact whether the use of surgery is higher in pediatric CD or UC, differs between surveys. For example, operations are more common in CD compared to UC according to a systematic review (Abraham, Mehta & El-Serag 2012). In line with that, surgery was more frequent in pediatric CD than in pediatric UC in an American study (Adamia et al. 2013). In contrast, children with UC were more likely to undergo an operation compared to children with CD in Scotland (Van Limbergen et al. 2008). The proportion of patients undergoing an operation during the disease course is similar in early- and later onset IBD (Aloi et al. 2014).

Three out of four operated pediatric IBD patients experience at least one surgical complication and over half of the children undergo a reoperation within ten years after the primary surgery (Piekkala et al. 2013, Pakarinen et al. 2009). Additionally, disease activation is common after the primary surgery in children with CD. Disease relapses occur in 77%-94% of the cases within ten years after the primary resection (Hansen et al. 2015, Piekkala et al. 2013). The most common complications include adhesive bowel obstruction and anastomotic stricture/stenosis. Nevertheless, 82%-96% of the operated children with IBD are at least moderately content with the operation results.

### 2.8 Quality of life in children with IBD

Health-related quality of life (HRQOL) is comprised of several components including physical welfare, social anchorage, mental condition, medical attention and symptoms caused by the disease (Bousvaros et al. 2006). The major problem concerning studies on HRQOL in children is the fact that in many cases parents complete the questionnaires on behalf of their children. The concordance between answers of parents and pediatric patients is moderate, and both under- and overestimation is observed (Gallo et al. 2014, Väistö et al. 2010).

A significantly lower level of HRQOL among children and adolescents with IBD compared to healthy controls has been observed in several studies (De Boer et al. 2005, Marcus et al. 2009, Greenley et al. 2010). This finding is comparable to the surveys on HRQOL among children with other chronic diseases.

In patients with pediatric IBD, HRQOL is influenced by varying factors including age, disease severity and self-esteem (De Boer et al. 2005, Otley et al. 2006, Perrin et al. 2008). Nonetheless, HRQOL significantly improves in all domains during the first year after the diagnosis when treatment is commenced (Otley et al. 2006). Furthermore, in a Swiss study, only physical well-being was decreased among children with IBD, while mental well-being and social support values of pediatric IBD patients increased above controls’ values (Rogler et al. 2013). Pediatric IBD patients’ self-reported psychosocial functioning is altogether corresponding to the values of controls (Väistö et al. 2010, Mackner, Crandall 2005). Basically, pediatric patients with IBD are at risk to confront problems in psychosocial functioning especially in domains of behavior/emotions, social competence and self-regard. Yet, such difficulties do not affect all pediatric patients (Mackner, Crandall & Szegethy 2006).

The disease burden in children and adolescents with IBD can affect all the areas of their lives. In particular, their school work can deteriorate because of the disease (Mackner, Bickmeier & Crandall 2012). Comparing to pediatric patients with non-acute juvenile idiopathic arthritis IBD patients have signs of mild verbal memory problems, but other domains of cognitive functioning are comparable (Castaneda et al. 2013). Additionally, pediatric IBD patients report lower levels of physical activity (Werkstetter et al. 2012).

It is widely believed that depression among children with IBD is common. The results are, however, contradictory. Depending on the study, pediatric patients with IBD have been reported to show more or less depressive symptoms compared to healthy controls or adolescents with other chronic disorders (Reed-Knight et al. 2014, Castaneda et al. 2013, Greenley et al. 2010). However, emotional problems including depressed mood are more common among children with IBD compared to their peers according to parents reports (Väistö et al. 2010). Difficult disease course is associated with depressive symptoms and a small proportion of children with IBD need medical attention for their depression (Reed-Knight et al. 2014).

HRQOL in children and adolescents with IBD can be improved. Important factors are support from family, acceptance of IBD in everyday life, self-management and spiritual growth (Karwowski, Keljo & Szegethy 2009). Moreover, involving young patients in medical decisions has positive effects on
their lives. Finally, enteral nutrition impacts also favorably HRQOL according a Japanese study (Kuriyama et al. 2009).

2.9 Summary

Even if the research on pediatric IBD has been active especially after year 2000, there are still many unsolved issues. In summary, the incidence of childhood onset IBD is still increasing and as a departure from the earlier, the pediatric IBD incidence has an increasing trend also in Asia. The environmental factors associated with pediatric IBD include for example low levels of vitamin D, urban environment, gut microbiota changes and antibiotic use. Nevertheless, many exogenous factors like drinking water and their association with IBD are inadequately comprehended particularly among children.

The disease course in pediatric IBD is partially different to adults’ one. Due to incomplete growth in children, childhood onset IBD can lead to growth retardation in consequence of malnutrition, immunological factors and the use of systemic glucocorticoids. Furthermore, disease symptoms, absences from school and side-effects of treatments may result in lowered quality of life.

Genetic factors attribute also to the pathogenesis of IBD and study results from other countries cannot therefore be completely utilized in Finland. Previously, the epidemiological information on Finnish children with IBD has been inadequate.
3 Aims of the Study

This study aimed to characterize occurrence, clinical features and patient outcomes of pediatric IBD in Finland from year 1987 to year 2003. The specific objectives of the present study are the following:

1. To evaluate the incidence of IBD and its temporal trends in Finnish children under 18 years of age in years 1987-2003 (Studies I & III).

2. To explore the regional distribution of pediatric-onset IBD in Finland with an emphasis on pediatric population density (Studies III & IV).

3. To assess potential environmental factors behind the spatial variations of pediatric IBD incidence in Finland (Study IV).

4. To characterize the clinical picture of pediatric IBD in two large university hospital districts in Finland (Study I).

5. To evaluate long-term outcomes in pediatric IBD and to describe health-related quality of life in adolescents and young adults with childhood-onset IBD compared to age-matched peers (Study II).
4 Materials and Methods

In Finland, the total population was 5.5 million in 2013 with 16.4% of the population aged 0-14 years (895,021 inhabitants) and 20.0% of the population aged 0-17 years (1,076,680 inhabitants) (Statistics Finland 2014d). The mean population density was 17.9/km² in 2013 (Statistics Finland 2014d). Nevertheless, even if the mean population density is among the lowest in Europe, there are considerable regional variations. Within the 19 counties in Finland the population density ranges from 2/km² in Lapland to 174/km² in Uusimaa (Statistics Finland 2014d). Finland is divided into five university hospital districts. Two largest university hospital districts (Helsinki and Tampere) constitute the area with a population of 3.0 million (589,426 inhabitants aged 0-17 years, 19.7%) (Statistics Finland 2014d).
4.1 Data collection

**Hospital databases**
(Helsinki and Tampere University Hospitals)

**Study I**
• 604 pediatric IBD patients aged 0-17 years

**SII database**

**Study III**
• 1880 pediatric IBD patients aged 0-17 years

**Study II**
• 550 pediatric IBD patients aged 0-17 years

**Study IV**
• 1040 pediatric IBD patients aged 0-14 years

**Figure 1.** Flow chart illustration of the study procedure. Study IV covers the ages 0-14 years while other studies cover the ages 0-17 years. In total, 36 patients were missing from the SII database and thus were excluded from the study II. Additionally, 18 patients’ postal addresses were unavailable. SII= The Social Insurance Institution of Finland

4.1.1 The SII database (Studies III & IV)

As a part of the comprehensive national health insurance, a medication reimbursement system subsidizes the costs of prescribed medicines in Finland. The Social Insurance Institution of Finland (SII) is the organization controlling this reimbursement system under supervision of the Finnish parliament. There are three categories of reimbursements: basic (35% of the costs), lower special (65% of the costs) and higher special (100% of the costs). Ten diseases including IBD fall into the lower special reimbursement category. In order to be eligible for the reimbursements, a medical certificate is required confirming that the diagnostic criteria are met. In IBD, these include endoscopy and histological verification. Generally, every newly-diagnosed patient with pediatric onset IBD needs medication and is entitled to reimbursement. Therefore, the SII database, where the entitlement decisions are filed, comprises a comprehensive source of all Finnish pediatric patients with IBD. No reimbursement is available for the medication received in hospitals or other institutions.
In addition, to verify the diagnostic criteria a total of 50 reimbursement reports from two hospital districts with the highest incidence rates were randomly chosen for re-evaluation. These reimbursement reports from both hospital districts were reviewed by a pediatric gastroenterologist (Kaija-Leena Kolho) focusing on the diagnostic modalities used in diagnostic procedure and on the findings.

The age at the time of the diagnosis was calculated on the assumption that the date of approval for reimbursement corresponds with the date of the diagnosis. To assess the delay, a comparison between the dates of diagnosis in the hospital files and reimbursement decision was made. We included in this assessment 518 patients who were included also in our hospital record-based study. The median interval between the diagnosis and the date of the reimbursement decision was 2 months (mean 2.3 ± SD 6.9 months).

Data for the nationwide study of the pediatric IBD incidence were obtained from the SII database. At first, all patients diagnosed with IBD at <18 years of age in 1987-2003 were included. Selection criteria were diagnostic codes of the International Classification of Diseases corresponding IBD (K50 and K51). Further, data on the date of approval for eligibility, gender, birth date and place of residence at the time of the reimbursement approval was obtained. In general, the population data from Statistics Finland is organized as per five-year categories. Therefore, the analyses of pediatric IBD incidence in relation to the pediatric population density at the next phase, were performed by using age limit of 0-14 years. The information on children diagnosed with IBD at the age of 0-14 years between years 1987-2003 was also obtained from the SII database.

4.1.1.1 IBD subtypes

Data on the subtypes of IBD (i.e. UC and CD) was also obtained from the SII database. The information on diagnosis of UC and CD was available only for 70.3% of the cases (1322 out of 1880). However, during 2000-2003 detailed diagnosis was available for 99.7% of the cases in contrast to the years 1987-1989 when detailed diagnosis was available only for 1.7% of the cases. Thus, the completeness of the information on IBD subtypes increased over time. Therefore, the analysis by the IBD subtype was conducted from year 1992 onward, including only the years with detailed diagnosis available at least for 50% of the patients. Additional analysis was performed from year 1994 onwards (the coverage of the information on detailed diagnosis at least 75%).
4.1.2 Demographics

The data on address, municipality and coordinates of the residence at the time of the diagnosis was acquired from the Population Register Centre. Information on the size of the pediatric population by sex and gender (age limit varying between 0-17 and 0-14 years depending on the analysis) in Finland for years 1987-2003 was obtained from Statistics Finland. Finland is divided into 21 central hospital districts and the data on the size of the child population in these districts was obtained for the analysis of geographical variation. Data on the size of the pediatric population and the number of children belonging to the occupational group of farmers for each 250 x 250 m square of the area was also obtained from Statistics Finland.

4.1.3 Environmental data (Study IV)

The EUREF-FIN coordinate system (consistent with World Geodetic System WGS84) was used in the analysis of geographical variation. The location of each central hospital was used as the population center of the hospital district. The geographic coordinates for each central hospital were acquired from the National Land Survey of Finland. The distance from the sea was obtained from the Corine Land Cover 2000 raster data (SYKE (Finnish Environment Institute) 2011). Additionally, the chemical and metal concentrations of tap water were retrieved from the water works of municipalities and information on locations of paper industry units in Finland was obtained from Wikipedia (Wikipedia 2014).

4.1.4 Hospital databases (Study I)

In Finland, hospital databases cover both outpatient clinic visits and hospitalizations. Lists of all pediatric patients diagnosed with IBD at the age of <18 years at Helsinki University Hospital or at Tampere University Hospital between years 1987-2003 were obtained. Before the year 1987, the coverage of the hospital databases was incomplete. Diagnostic codes of the International Classification of Diseases (national adaptation) corresponding IBD with the separate codes for UC, CD and IBDU (ICD-10 classification K50.0-51.8) were used. Medical records of all pediatric patients diagnosed with IBD during the
study period were reviewed by two investigators (Pieta Lehtinen in Tampere and Kaija-Leena Kolho in Helsinki). The IBD diagnoses were re-evaluated according to the Lennard-Jones criteria (Lennard-Jones 1989). Incorrect or unreliable diagnosis was an exclusion criterion. Information on age at diagnosis, macroscopic localization of the inflammatory changes in the intestine, the distribution of the chronic inflammatory changes in histological examination of the gastrointestinal biopsies, diagnostic procedures, medical treatment and operations was collected. Additionally, the information on the last control visit at <18 years of age was retrieved.

4.1.5 Questionnaire survey (Study II)

The patients diagnosed with IBD at the age of <18 years at Helsinki University Hospital and at the Tampere University Hospital were also selected for the questionnaire survey. In total, postal addresses for 97% of the patients (550/568) with a confirmed diagnosis of IBD were obtained from the Population Register Centre. Furthermore, age- and sex-matched controls with the same place of residence as patients’ were randomly chosen from the Population Register Centre. Three primary controls and one secondary control were selected for each case (see below). The questionnaire contained questions about anthropometric measures, number of siblings and offspring, family history of IBD, chronic diseases (asthma, liver, kidney, heart, joint, bile duct and thyroid diseases), abdominal operations and current medication (Appendix 1 and 2). In addition, information on the original and the current diagnosis and the use of systemic glucocorticoids during the disease course was also asked in the patient group (Appendix 1). The questionnaire included also assessment of the quality of life similar for both the patients and the controls. A generic method was developed for assessing HRQOL with a visual analog scale scoring from 1 to 7 with 4 questions assessing overall quality of life, social functioning, physical and emotional well-being. The data collected from the hospital databases earlier was applied to acquire information on the age at the diagnosis and operations. The pretesting of the questionnaire was conducted among a small group of adolescents in order to confirm simplicity and suitability of the questionnaire for adolescents and children.

At first the questionnaire was sent to the patients (n=550) and to three primary controls of each patient (n=1650). In the second stage, the questionnaire was mailed to the patients and the controls without primary response. The
questionnaire was mailed to the secondary (fourth) controls of the patients only if none of the three primary controls of the patient replied. In total, 3.7% of the returned questionnaires (39/1053) were excluded from the analysis. Five were returned without adequate identification information (2 patient and 3 control forms). In addition, 34 controls had by mistake filled the information regarding their offspring instead of themselves.

4.2 Statistical Analysis

The age was grouped into three-year categories (0-2 years, 3-5 years, 6-8 years, 9-11 years, 12-14 years and 15-17 years) or five-year categories (0-4 years, 5-9 years and 10-14 years) depending on the upper age limit employed and differences in incidence rates were analyzed accordingly. Annual incidence rates were computed per 100,000 pediatric population. The 95% confidence intervals (CI) were calculated assuming that the number of cases followed the Poisson distribution. All incidences were age-adjusted by three-or five-year age categories.

The hospital databases included information on IBD subtypes. Thus, the analyses based on these data were done separately for CD, UC and IBDU. However, information on IBD subtypes was limited in the data obtained from the SII database. Consequently in the analysis by IBD subtypes, the number of cases within each diagnostic subgroup was evaluated by allocating the cases with unknown subtype to each diagnostic subgroup assuming a similar distribution as in the patients with known subtype (imputing missing diagnosis). In other words, if half of the cases with detailed diagnosis had UC, also half of the patients with unknown subtypes were presumed to have UC. In the subtype analysis by the pediatric population density, only the patients with defined subtypes were included.

The latitude and longitude were both divided into four segments and the geographical differences were estimated accordingly. The surface area of Finland was divided into squares of 250 x 250 m (0.0625 km²) for the spatial analysis. Further, the pediatric population density for each square was calculated. The squares were classified accordingly into seven categories: 0-10, 11-20, 21-50, 51-200, 201-500, 501-800 and >800 children per square and incidence rates for each category were computed. In the analysis by the subtype, pediatric population density categories were assigned to be consistent to the classification of the main
analysis (0-7, 8-14, 15-35, 36-150, 151-350, 351-500 and >500 person years per 250 x 250 m square of the area). The pediatric death rate is low in Finland (20 per 100,000 in 2013). Therefore, it was ignored in the calculations (Statistics Finland 2014c).

Categories for the regions including only farmer’s offspring and the regions including at least one person year of farmer’s offspring were composed and the incidences were estimated accordingly. The distance from the seaside was divided into six categories (<1, 1-2, 2-5, 5-10, 10-50 and >50 km) and the incidence rates were calculated for each category. Further, incidence rates for 31 municipalities with paper industry units were analyzed. The incidence rates were compared in relation to exposures applying Poisson regression analysis. Trend tests across exposure categories were performed by entering the grouping variable as a linear (continuous) term in the regression model.

The results of the water quality analyses were obtained from 19 cities and towns (eight with high level of incidence, nine with intermediate level of incidence and two with low level of incidence). The data included information on routinely measured concentrations of eight chemical compounds (iron, manganese, 1,2-dichloroethane, aluminum, ammonium, nitrite, trihalomethanes and tetra- and trichloroethenes) from years 2002-2007. The yearly measurements were performed in several different locations within these 19 cities. The averages of the tap water metal and chemical concentrations for each city were computed and categorized into three groups according to the concentration levels. The data on 1,2-dichloroethane and tetra- and trichloroethenes was not available for one city and data on trihalomethanes for three cities. The concentration levels of 1,2-dichloroethane from every city were low and came all under one concentration category rendering it unanalyzable. Information on water quality measurements prior to year 2002 was unavailable. Thus, the mean incidence rates in those 19 cities were computed for the years 1999-2003 in order to correspond better with the water data.

Poisson regression analysis was applied to estimate the incidence trends with the number of cases as the dependent variable and the population size as the offset variable. The calendar year was used as a continuous variable in the estimation of the mean change per year. To evaluate departure from linearity, a term for categorical three-year period was added into a model with the linear term and the improvement in fit was compared by a likelihood ratio test. Furthermore, Poisson regression analysis was applied to compare the incidence rates between the
diagnostic subgroups and between the categories of chemical concentrations in the water analysis.

Time to the first operation was computed using the Kaplan-Meier method. The outcomes among the groups of IBD subtypes were analyzed by log rank test. A Pearson chi-square test was applied to evaluate frequencies between groups (patients versus controls, UC versus CD, controls replying to the questionnaire at the first stage versus controls replying at the second stage). Fisher’s exact test was used to compare differences in bile duct diseases between patient and control groups because of the small number of cases. The analysis was performed without matching to maximally utilize the information in the data by including also subjects without matched IBD case or any control. Differences in the overall quality of life between operated and nonoperated patients, between controls replying fast and controls replying slowly, and differences in anthropometric data between groups of CD and UC were analyzed by the Mann-Whitney test (2-sample rank sum test). A chi-square test was used to assess the homogeneity between the seasons when IBD symptoms had first started. Moreover, both the t-test and the Pearson chi-square test were applied to evaluate the differences between patients who responded to the questionnaire and who did not. Statistical analyses were performed using SPSS (version 13.0, Chicago, IL) and Stata (v.8 and v.12, College Station, TX) software. Additionally, spatial analysis were conducted using ArcGIS 9 software (GIS, Geographical Information System).

4.3 Ethical issues

The study protocol of this research project was reviewed by the ethical committees of Tampere and Helsinki University Hospitals. The study on the long-term outcomes in pediatric IBD was based on the information received from questionnaires from the participants. All of the participants who returned the questionnaire gave also a written consent to participate in the study. In case of children under 18 years of age their legal guardian signed the consent. Three other studies were register-based studies without contact with the participants and no written consent was needed in accordance with the Finnish regulations. The institutions whose registers were employed in this research project gave permission to obtain the data. In addition, the Ministry of Social Affairs and Health in Finland authorized the usage of the patient documents from the records of Tampere and Helsinki University Hospitals.
5 Summary of the Results

5.1 Incidence of pediatric IBD (Studies III & IV)

During 1987-2003, altogether 1880 children were diagnosed with IBD at the age <18 years in Finland (Table 3). The median age at diagnosis was 14.4 years (IQR 11.3-16.5). There was a predominance of boys with a male:female ratio of 1:0.84.
Table 3. Finnish children diagnosed with IBD at the age <18 years between years 1987 and 2003. The information on the IBD subtypes and the age at the time of the diagnosis is included. Percentage values of IBD subtypes is presented of the cases with detailed diagnosis.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Total no. of cases (%)</th>
<th>Boys no. of cases (%)</th>
<th>Girls no. of cases (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cases</td>
<td>1880 (54.3% of all cases)</td>
<td>1020 (54.3% of all cases)</td>
<td>860 (45.7% of all cases)</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>UC</td>
<td>840 (63.5)</td>
<td>441 (60.9)</td>
</tr>
<tr>
<td></td>
<td>CD</td>
<td>449 (34.0)</td>
<td>270 (37.3)</td>
</tr>
<tr>
<td></td>
<td>IBDU</td>
<td>33 (2.5)</td>
<td>13 (1.8)</td>
</tr>
<tr>
<td></td>
<td>Unknown</td>
<td>558 (29.7% of all cases)</td>
<td>296 (26.4% of all girls)</td>
</tr>
<tr>
<td>Age (year)</td>
<td>&lt;3</td>
<td>44 (2.3)</td>
<td>22 (2.2)</td>
</tr>
<tr>
<td></td>
<td>3-&lt;6</td>
<td>90 (4.8)</td>
<td>43 (4.2)</td>
</tr>
<tr>
<td></td>
<td>6-&lt;9</td>
<td>151 (.0)</td>
<td>79 (7.7)</td>
</tr>
<tr>
<td></td>
<td>9-&lt;12</td>
<td>272 (14.5)</td>
<td>141 (13.8)</td>
</tr>
<tr>
<td></td>
<td>12-&lt;15</td>
<td>504 (26.8)</td>
<td>285 (27.9)</td>
</tr>
<tr>
<td></td>
<td>15-&lt;18</td>
<td>819 (43.6)</td>
<td>450 (44.1)</td>
</tr>
</tbody>
</table>

Abbreviations: UC=ulcerative colitis; CD=Crohn’s disease; IBDU=IBD-unclassified
5.1.1 Incidence rates and trends

The overall incidence of IBD in children aged <18 years was 9.6/100,000 (95% CI 9.2-10.1). The annual incidence was 4.8/100,000 (95% CI 3.6-6.3) in 1987 compared with 15.0/100,000 (95% CI 12.8-17.4) in 2003. The average annual increase was 6.5% (95% CI 5.4%-7.5%) (Figure 2). The highest annual incidence was in 2002 (15.4/100,000, 95% CI 13.2-18.0). There was no statistically significant deviation from linearity in the time trend (p=0.088) as adding a squared calendar year term did not improve the fit. The rising trend in the incidence was noticeable among both boys and girls (average annual increase 6.9%, 95% CI 5.6%-8.3% for boys and 5.9%, 95% CI 4.4%-7.4% for girls). There was no significant difference in the incidence trends by 3-year age group (p=0.62 for the interaction term age*year, p>0.5 for both boys and girls) or hospital district (p=0.96 for the interaction term hospital district*year, p>0.5 for both boys and girls).
Figure 2. The incidence of IBD (n/100,000 person years) among Finnish children aged <18 years between years 1987-2003. The incidences of UC and CD are shown from year 1992 onward due to incompleteness of the data.

For Finnish children aged <15 years, the overall incidence of IBD was 6.5/100,000 (95% CI 6.1-6.9) during the study period, 1897-2003. The overall incidence for boys in this age group was 6.8/100,000 (95% CI 6.3-7.4) and 6.1/100,000 (95% CI 5.6-6.7) for girls, but the difference was not statistically significant. The incidence trend was increasing in both groups over the study period.

The annual incidence of UC was higher than that of CD during the years 1992-2003. The incidence of UC increased from 4.1/100,000 (95% CI 3.0-5.5) in 1992 to 9.1/100,000 (95% CI 7.4-11.1) in 2003. The corresponding figures for CD were 2.2/100,000 (95% CI 1.5-3.3) in 1992 and 5.3/100,000 (95% CI 4.1-5.9) in 2003. The incidence of CD increased faster in relative terms (average annual increase 5.2%, 95% CI 3.3%-7.2% for UC versus 8.4%, 95% CI 5.6%-11.2% for CD)
Moreover, between years 1994-2003 the average annual increase was 3.9% for UC and 7.2% for CD.

The main analyses were performed assuming a similar distribution of IBD subtypes among the cases with unknown subtype as among cases with defined subtype. Sensitivity analyses were conducted in order to evaluate the potential effect of the missing data on the results. The maximal incidence of subtype was estimated for the early years by hypothesizing that all of the patients with undefined subtype had CD and none UC, or vice versa. The increasing trend in UC was noticeable despite the extreme assumption while in CD group the increasing trend disappeared because of smaller number of CD patients. Nevertheless, such extreme assumptions seem unrealistic.

5.1.2 Regional differences (Study III)

In the analysis by hospital district, the highest pediatric incidence was noticed in Kainuu hospital district in northeastern Finland with an overall mean incidence of 16.5/100,000 (95% CI 12.5-21.2). Respectively, the lowest incidence was observed in Itä-Savo hospital district in southeastern Finland (4.9/100,000, 95% CI 2.6-8.6). All 25 randomly selected reimbursement reports in Lapland (hospital district with the second highest incidence) were acceptable and the diagnoses were confirmed. Moreover, in the re-evaluation process of 25 reimbursement reports in Kainuu the diagnosis was questionable in only one case. In temporal trends, no statistically significant geographical difference was observed in the analysis by latitude and longitude (p=0.22 and p=0.79 for the interaction terms with calendar year).

5.1.3 Spatial variations of pediatric IBD in Finland (Study IV)

The incidence rates of IBD among children aged 0-14 years were significantly higher in the areas with low density of child population compared to the areas with high density of child population (trend p=0.046; Table 4). In very sparsely populated areas (≤10 children per 250 x 250 m square) the incidence of pediatric IBD was 9.2/100,000 (95% CI 6.3-13.1) and in the areas with the highest population density (>800 children per 250 x 250 m square) 5.6/100,000 (95% CI 4.8-6.4). The incidence of pediatric IBD decreased 1.5% (95% CI 0.0%-3.1%) for every increase of pediatric population density by 100 children per 250 x 250 m
Further, this pattern was notable in boys (trend p<0.001) but not in girls (trend p= 0.59). For UC group, the incidence rate was slightly higher in the sparsely inhabited areas than in the densely inhabited areas, but the trend was non-significant (trend p=0.09; Original article IV, Table 2). In the CD group, the differences were minimal (trend p=0.77).

Table 4. Incidence of pediatric IBD in Finland in relation to pediatric population density and rate ratio (based on total incidences) by pediatric population density groups (reference >800 children per unit area).

<table>
<thead>
<tr>
<th>Pediatric population density (children per 250m x 250m)</th>
<th>Incidence (/100,000) (95% CI) (n=1040)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-10</td>
<td>9.2 (6.3-13.1)</td>
<td>1.6 (1.1-2.4)</td>
</tr>
<tr>
<td>11-20</td>
<td>7.6 (5.6-10.1)</td>
<td>1.4 (1.0-1.9)</td>
</tr>
<tr>
<td>21-50</td>
<td>6.6 (5.5-7.8)</td>
<td>1.2 (1.0-1.5)</td>
</tr>
<tr>
<td>51-200</td>
<td>6.1 (5.3-7.0)</td>
<td>1.1 (0.9-1.3)</td>
</tr>
<tr>
<td>201-500</td>
<td>6.6 (5.8-7.4)</td>
<td>1.2 (1.0-1.4)</td>
</tr>
<tr>
<td>501-800</td>
<td>7.1 (6.1-8.3)</td>
<td>1.3 (1.0-1.6)</td>
</tr>
<tr>
<td>&gt; 800</td>
<td>5.6 (4.8-6.4)</td>
<td>1 (reference)</td>
</tr>
</tbody>
</table>

Abbreviations: CI=confidence interval
RR=rate ratio
In the districts all children belonging to the occupational group of farmers, the incidence rate was almost two-fold higher compared to the areas with no children belonging to the occupational group of farmers (11.7/100,000, 95% CI 6.5-19.3 versus 6.5/100,000, 95% CI 5.1-8.0, trend p=0.22). Moreover, the incidence rates were similar in areas by the seaside (<1 km from seaside 6.0/100,000, 95% CI 4.9-7.3) and >50 km from the seaside (6.3/100,000, 95% CI 5.7-7.0; trend p=0.62).

The additional analyses were performed including only a high-incidence area in Western Finland which covers eight hospital districts (Original article IV, Figure 1). Even though Lapland is a high incidence district, it is almost completely sparsely populated and was omitted from these analyses. The overall incidence in Western Finland was 8.0/100,000 (95% CI 7.2-8.7). In very sparsely populated area (≤10 children per 250 x 250 m square), the overall incidence was 11.8/100,000 (95% CI 6.7-19.1) in comparison with 7.8/100,000 (95% CI 5.9-10.0) in densely populated areas (>800 children per 250 x 250 m square) in Western Finland, but the difference was not statistically significant (trend p=0.70). Moreover, the incidence of IBD in boys was higher in seaside compared to the areas further from seaside (< 1 km 10.5/100,000, 95% CI 6.9-15.1 and 1-2 km from seaside 12.2/100,000, 95% CI 7.7-18.5 versus 7.3/100,000, 95% CI 5.7-9.1 > 50 km from seaside, trend p=0.04). The results were similar in the UC group but not for CD (trend p=0.03 and trend p=1.0, respectively). Additionally, the risk of IBD among boys was particularly high within areas <2km from the sea containing farmers’ households compared with districts by the seaside without farmers’ offspring (trend p=0.19). This finding was not comparable among girls.

There were no statistically significant associations between the chemical concentrations of tap water and the incidence of pediatric IBD. However, there was a tendency for higher incidence rates in the cities with intermediate or high levels of iron in tap water compared with the low-level cities (Table 5). The closeness of the paper mills had no effect on the risk of IBD among children (RR=1.0, 95% CI 0.9-1.2 compared with the overall incidence of pediatric IBD in Finland). This finding was similar in UC and CD groups as well (RR=0.91, 95% CI 0.70-1.2 for UC and RR=1.1, 95% CI 0.79-1.6 for CD).
Table 5. The chemical and metal concentrations in tap water in relation to IBD incidence among Finnish children.

<table>
<thead>
<tr>
<th>Concentration categories</th>
<th>Incidence (/100,000) (95% CI)</th>
<th>Trend test</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Iron (µg/l)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10</td>
<td>6.8 (4.2-10.2)</td>
<td></td>
</tr>
<tr>
<td>10-50</td>
<td>13.6 (9.5-19.0)</td>
<td></td>
</tr>
<tr>
<td>&gt;50</td>
<td>7.2 (5.5-9.2)</td>
<td>p=0.64</td>
</tr>
<tr>
<td><strong>Manganese (µg/l)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;0.001</td>
<td>8.6 (1.0-31.2)</td>
<td></td>
</tr>
<tr>
<td>0.001-10</td>
<td>8.2 (6.7-9.9)</td>
<td></td>
</tr>
<tr>
<td>&gt;10</td>
<td>9.3 (3.7-19.2)</td>
<td>p=0.80</td>
</tr>
<tr>
<td><strong>Aluminum (µg/l)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;0.001</td>
<td>10.5 (6.6-15.9)</td>
<td></td>
</tr>
<tr>
<td>0.001-10</td>
<td>8.4 (6.5-10.6)</td>
<td></td>
</tr>
<tr>
<td>&gt;10</td>
<td>6.8 (4.5-9.8)</td>
<td>p=0.13</td>
</tr>
<tr>
<td><strong>Ammonium (mg/l)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;0.009</td>
<td>9.0 (6.8-11.6)</td>
<td></td>
</tr>
<tr>
<td>0.009-0.05</td>
<td>9.0 (5.3-14.2)</td>
<td></td>
</tr>
<tr>
<td>&gt;0.05</td>
<td>7.1 (5.1-9.7)</td>
<td>p=0.26</td>
</tr>
</tbody>
</table>
Table 5. (Continued)

<table>
<thead>
<tr>
<th>Concentration categories</th>
<th>Incidence (/100,000) (95% CI)</th>
<th>Trend test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitrite (mg/l)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;0.009</td>
<td>9.0 (6.8-11.6)</td>
<td>p=0.60</td>
</tr>
<tr>
<td>0.009-0.10</td>
<td>7.0 (4.6-10.3)</td>
<td></td>
</tr>
<tr>
<td>&gt;0.10</td>
<td>8.1 (5.6-11.4)</td>
<td>p=0.99</td>
</tr>
<tr>
<td>Trihalomethanes (µg/l)a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;0.001</td>
<td>7.8 (5.7-10.5)</td>
<td>p=0.99</td>
</tr>
<tr>
<td>0.001-10</td>
<td>8.1 (5.9-10.9)</td>
<td></td>
</tr>
<tr>
<td>&gt;10</td>
<td>7.6 (4.3-12.6)</td>
<td></td>
</tr>
<tr>
<td>Tetra- and trichloroethenes (µg/l)b</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;0.001</td>
<td>8.1 (6.5-10.0)</td>
<td>p=0.44</td>
</tr>
<tr>
<td>0.001-1.0</td>
<td>2.6 (0.3-9.3)</td>
<td></td>
</tr>
<tr>
<td>&gt;1.0</td>
<td>10.5 (6.8-15.7)</td>
<td></td>
</tr>
</tbody>
</table>

aConcentration levels of three cities were unavailable.
bConcentration levels of one city were unavailable.
Abbreviations: CI, confidence interval
5.2 Hospital-based study (Study I)

Between years 1987-2003, a total of 604 children were diagnosed with IBD at ages 0-17 years within two largest university hospitals districts (Helsinki and Tampere) in Finland (Table 6).

<table>
<thead>
<tr>
<th></th>
<th>IBD</th>
<th>CD</th>
<th>UC</th>
<th>IBDU</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of cases (%)</td>
<td>604*</td>
<td>203 (33.6)</td>
<td>317 (52.5)</td>
<td>83 (13.7)</td>
</tr>
<tr>
<td>Boys, n (%)</td>
<td>298 (49.3)</td>
<td>102 (50.2)</td>
<td>157 (49.5)</td>
<td>39 (47)</td>
</tr>
<tr>
<td>Median age at the diagnosis, years (IQR)</td>
<td>12.0 (8.6-14.2)</td>
<td>12.5 (9.7-14.6)</td>
<td>11.8 (8.2-14.0)</td>
<td>11.7 (6.9-14.8)</td>
</tr>
<tr>
<td>Total colitis, n (%)</td>
<td>350 (57.9)</td>
<td>109 (53.7)</td>
<td>194 (61.2)</td>
<td>47 (56.6)</td>
</tr>
</tbody>
</table>

*In one case diagnosis unsettled because of missing data.

Almost all of the patients had been followed up after the initial diagnosis in the hospitals with the median length of the follow-up being 3.1 years. The follow-up time was shorter in older children (the median length 5.9 years in children <3 years of age compared to 2.8 years in children 12-14 years of age). In patients 15-17 years of age, the follow-up time was inadequate (the median length 1.3 years) due to transfers to adult gastroenterologists.
Increasing trend in incidence of pediatric IBD over the study period was observed with the average annual increase of 5% (95% CI 4%-7%) in the districts of these two university hospitals. Further, the overall annual incidence was 3.9/100,000 (95% CI 2.5-5.8) in 1987 compared to 7.0/100,000 (95% CI 5.0-9.4) in 2003 (p<0.001). The increasing trend was significant in all three subtypes of IBD (p<0.001 for both CD and UC and p=0.011 for IBDU).

5.2.1 Diagnostic classification

UC was the most common diagnosis, also in every age group. It represented 52.5% (317/604) of the cases (Table 6). Further, 33.6% (203/604) and 13.7% (83/604) of the patients were diagnosed with CD and IBDU respectively. The proportion of the patients diagnosed at the age of <3 years was 5.1% (31/604), while one third of the patients (200/604) were diagnosed at the ages 12-14 years. IBDU was more common diagnosis, proportionally, in children <6 years compared to older children (Figure 3).
Figure 3. Age distribution of the children diagnosed with IBD at the time of the diagnosis. Numbers of UC, CD and IBDU cases are indicated separately.

5.2.2 Diagnostic procedure

All patients had undergone endoscopic evaluation of the colon by colonoscopy with histological examination of mucosal biopsies. Videoendoscopy was not in use in the early part of the study period. Therefore, the terminal ileum had been reached in 17.2% of the cases diagnosed in 1987-1989 compared to 65.5% of those diagnosed during 1998-2003. Additionally, 68.5% of the patients had undergone assessment of the upper GI tract by EGD. The proportion was 79.3% in CD, 62.1% in UC and 67.5% of the IBDU cases. In 11.3% of the patients, small bowel follow-through was a part of diagnostic procedure. Moreover, 17.3% of the patients in whom terminal ileum had not been reached and 6.3% of the patients
without EGD had undergone small bowel follow-through. Technetium scan was infrequently used.

5.2.3 Disease distribution

Pancolitis was seen in 57.9% (350/604) of the patients on the basis of histological examination. In total, 41.9% (13/31) of the patients <3 years of age and 53.7% (109/203) of the cases with CD presented with pancolitis. Furthermore, of the CD patients in whom terminal ileum had been reached by endoscopy, ileal disease was seen in 58.1% (72/124) and both ileal and colonic disease in 37.9% (47/124). An atypical feature of CD was a sole manifestation of the upper GI tract found only in 3.7% (6/161) of the patients who had undergone EGD.

5.3 Questionnaire survey (Study II)

5.3.1 Participation

The final participation proportion was 66.9% (368/550) among the patients and 36.7% (646/1760) among the controls (Table 7).
Table 7. Demographic characteristics of the patient and the control groups

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of cases</td>
<td>368</td>
<td>646</td>
</tr>
<tr>
<td>Age, median (years, minimum-maximum)</td>
<td>20.0 (5.1-36.7)</td>
<td>19.0 (2.7-35.7)</td>
</tr>
<tr>
<td>Female/male ratio</td>
<td>1:0.82*</td>
<td>1:0.74*</td>
</tr>
</tbody>
</table>

*p=0.47

Item non-response was low among the patients and the controls with 1% missing values per question. However, there was variation between questions. Differences between responders and non-responders were assessed by a dropout analysis in order to evaluate possible selection bias. The patients who replied were slightly younger compared to the non-responders (mean age 21.5 ± 6.2 [SD] years versus 23.5 ± 5.6 years) and more frequently female (54.9% versus 42.3%). The proportions of operated and non-operated patients (data obtained from the hospital database) who completed the questionnaire were equal. Thus, the patients with complicated disease course did not presumably reply more often or vice versa. Comparing rapid and slow-responders among controls, no significant differences in reported symptoms or the scores for overall quality of life were observed.

5.3.2 Characteristics of the patient group

At the time of the diagnosis, the median age was 11.8 years (minimum to maximum 0.8-17.8 years). There was a slight predominance of girls with the female:male ratio of 1:0.82. Of the patients, 58.2% (214/368) were initially
diagnosed with UC. Moreover, CD was diagnosed in 34.8% (128/368) of the patients and IBDU in 7.1% (26/368) of the cases. At the time of the survey, the median duration of the disease was 8.3 years (range 2.4-19.3).

5.3.3 Family history with IBD

In contrast to the controls, more than one third of the patients (34.8%, 128/368) had at least one relative (first-degree or other) with IBD. The corresponding proportion among controls was less than one eighth (12.2%, 79/646, RR=2.8, 95% CI 2.2-3.7). Additionally, a first-degree relative with IBD was reported by 18.5% (68/368) of the patients compared to 6.7% (43/646) of the controls (RR=2.8, 95% CI 1.9-4.0). Comparing the number of siblings between patients and controls, no significant differences were discovered. Furthermore, the proportion without any siblings was rather similar between patients and controls (11.4%, 42/368 versus 9.6%, 62/646).

5.3.4 Reproductive history

Among the patient group, 9.8% (15/153) had children compared with 16.9% (40/237) of the controls when including only participants >20 years of age at the time of the questionnaire (RR=0.58, 95% CI 0.33-1.0). Of the girls >20 years of age (born before 1985), 11.7% (11/94) among the patient group and 15.7% (24/153) among the control group had children (p=0.45). Moreover, of the patients with a history of abdominal surgery and being >20 years of age, 17% (10/60) had children. The corresponding figure among non-operated patients of the same age was 5% (5/93). The operations had taken place before giving birth.

5.3.5 Chronic diseases

Joint diseases including various arthritis and other joint symptoms were more common in the patient group compared to the age and sex matched control group (5.4% versus 0.2%, RR 35.1, 95% CI 4.7-260.5) (Table 8 and original article II, Table 2). In 70% (14/20) of the cases, the joint disease was diagnosed after IBD, with the mean time lag of 4.1 years. In addition, bile duct diseases (mainly PSC) were reported more frequently by patients than by controls (2.7% versus 0.3%,
RR 8.8, 95% CI 1.9-39.8). Other chronic diseases were equally common among patients and controls (Table 8).

Table 8. Frequencies of chronic disease among patients and controls at the time of the questionnaire.

<table>
<thead>
<tr>
<th>Chronic disease</th>
<th>Patients (%)</th>
<th>Controls (%)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=368</td>
<td>n=646</td>
<td></td>
</tr>
<tr>
<td>Joint disease</td>
<td>20 (5.4)</td>
<td>1 (0.2)</td>
<td>35.1 (4.7-260.5)</td>
</tr>
<tr>
<td>Bile duct disease</td>
<td>10 (2.7)</td>
<td>2 (0.3)</td>
<td>8.8 (1.9-39.8)</td>
</tr>
<tr>
<td>Asthma</td>
<td>33 (9.0)</td>
<td>48 (7.4)</td>
<td>1.2 (0.8-1.8)</td>
</tr>
<tr>
<td>Kidney disease</td>
<td>2 (0.5)</td>
<td>3 (0.5)</td>
<td>-</td>
</tr>
<tr>
<td>Heart disease</td>
<td>4 (1.1)</td>
<td>6 (0.9)</td>
<td>-</td>
</tr>
<tr>
<td>Liver disease</td>
<td>3 (0.8)</td>
<td>1 (0.2)</td>
<td>-</td>
</tr>
<tr>
<td>Thyroid disease</td>
<td>5 (1.4)</td>
<td>3 (0.5)</td>
<td>-</td>
</tr>
</tbody>
</table>
5.3.6  Anthropometric Measures

The male patients ≥18 years of age were shorter and weighed less compared with their controls (p=0.028 for height and p=0.004 for weight; Original article II, Table 3). Moreover, the male patients with CD had lower self-reported weight and height figures than those with UC (Original article II, Table 3). In the female group, no statistically significant differences in anthropometric indices were observed. The anthropometric measures among controls were equivalent to the ±0 SD in population-based growth charts.

5.3.7  Quality of life

As a whole, the mean scores of the patient group in all four quality of life dimensions were a slightly lower than those of controls (Table 9); although not statistically significantly different except for overall quality of life and physical functioning. Furthermore, operated patients had slightly lower mean scores in every quality of life dimension compared to non-operated patients (Table 10). The mean scores of quality of life were comparable among CD and UC patients.
Table 9. Mean scores of quality of life dimensions among patients and controls at the time of the questionnaire. Visual analog scale scoring from 1 to 7 (1=terrible, 7=very good).

<table>
<thead>
<tr>
<th></th>
<th>Patients (mean ± SD)</th>
<th>Controls (mean ± SD)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall quality of life</td>
<td>5.7 ± 1.2</td>
<td>6.0 ±1.0</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Physical functioning</td>
<td>5.7 ± 1.3</td>
<td>5.9 ± 1.0</td>
<td>0.004</td>
</tr>
<tr>
<td>Emotional functioning</td>
<td>5.6 ± 1.2</td>
<td>5.7 ± 1.0</td>
<td>0.255</td>
</tr>
<tr>
<td>Social functioning</td>
<td>5.9 ± 1.1</td>
<td>6.0 ± 0.9</td>
<td>0.815</td>
</tr>
</tbody>
</table>
Table 10. Mean scores for operated and non-operated IBD patients by quality of life dimensions at the time of the questionnaire. Visual analog scale scoring from 1 to 7 (1=terrible, 7=very good).

<table>
<thead>
<tr>
<th></th>
<th>Operated patients (mean ± SD)</th>
<th>Non-operated patients (mean ± SD)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=101</td>
<td>n=263</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall quality of life</td>
<td>5.5 ± 1.4</td>
<td>5.8 ± 1.1</td>
<td>0.07</td>
</tr>
<tr>
<td>Physical functioning</td>
<td>5.6 ± 1.3</td>
<td>5.7 ± 1.2</td>
<td>0.76</td>
</tr>
<tr>
<td>Emotional functioning</td>
<td>5.5 ± 1.3</td>
<td>5.7 ± 1.1</td>
<td>0.08</td>
</tr>
<tr>
<td>Social functioning</td>
<td>5.7 ± 1.2</td>
<td>6.0 ± 1.1</td>
<td>0.16</td>
</tr>
</tbody>
</table>

5.4 Reclassifications of the diagnoses (Studies I & II)

The diagnosis had been reclassified in 13.0% (48/368) of the patients who completed the questionnaire at a median of 8.3 years after the diagnosis. In comparison, reclassification of the diagnosis had been performed in 9.8% (57/584) of the patients followed up through the hospital databases at a median of 3.1 years from the diagnosis. To be precise, 8.4% (18/218) and 3.8% (12/317) of the UC patients had been reclassified as CD in the questionnaire survey and in the hospital database study respectively. Furthermore, of the IBDU patients in the hospital database study, 16% (13/83) and 39% (32/83) had been specified as CD and UC respectively. 11.1% (41/368) of the patients who replied to the questionnaire had no medication at the time of the questionnaire. Further, 0.86%
(5/584) of the patients from the hospital-based study had been able to discontinue medication at the end of the follow-up.

5.5 Medication (Studies I & II)

In total, 273 (45.2%) of the patients from hospital-based study had received systemic glucocorticoids as primary therapy. At the end of the follow-up, 17.3% (101/584) of the patients were using systemic glucocorticoids and 17.8% (104/584) (31.6% with CD and 10.3% with UC) were using other immunosuppressive agents (azathioprine, cyclosporin and methotrexate). The proportion of children initially treated with glucocorticoids increased over time (34.4%, 44/128 of the patients diagnosed in 1987-1991 versus 51.5%, 151/293 in 1998-2003, p=0.001). The proportion of patients receiving other immunosuppressive agents at the end of the follow-up increased during the study period. Only 4.9% of the patients diagnosed between years 1987 and 1991 were using these medications in contrast to 25.8% of the children diagnosed between years 1998 and 2003 (p<0.001). In addition, 82.6% (304/368) of the patients who completed the questionnaire (at a median of 8.3 years from the diagnosis) had received systemic glucocorticoids during the disease course. The proportions of patients treated with glucocorticoids were rather similar between patients with of CD and UC.

5.6 Surgery (Studies I & II)

More than one fifth of the patients (21%, 121/584) had been operated on by the age of <18 years. Operations were more common among UC patients compared with other subtypes (p=0.03 for CD versus UC and p=0.003 for IBDU versus UC, Table 6). The majority of the primary operations were total colectomies (81%, 86/121). Nonetheless, among CD patients the most common operation was ileal resection constituting 41% (14/34) of all operations according to the hospital database study. Colectomy was the most commonly reported operation and as many as 24% (51/214) of the patients with UC had been colectomized. However, 16% (8/51) of them had later been reclassified as CD. Partial resections of the intestine comprise most of the operations among the patients initially diagnosed with CD according to the questionnaire survey.
The majority of the operations were performed within 3 years after the diagnosis (74%, 90/121, of the primary operations from the hospital databases) with the median interval between the diagnosis and the first operation being 1.8 years. Moreover, the median time interval was 1.7 years in children with UC compared to 2.0 years in the CD group. The difference in the outcomes between IBD subtypes was statistically significant (p=0.007; Original article I, Figure 4).

Most of the operated patients underwent the intestinal surgery at the age of <18 years (84%, 86/102, of the operations reported through questionnaires). Of the patients ≥18 years of age at the time of the questionnaire, 27% (61/226) had been operated on by the age of 18 years compared with 7% (16/226) operated on after the age 18 years. The probability of the operation during the following years from the diagnosis was similar in all age groups (Original article II, Figure 1). The patients diagnosed <6 years of age seemed, however, to be less likely to undergo intestinal surgery compared with the oldest age group (p=0.24 for UC, p=0.36 for CD and p=0.058 for IBD).
6 Discussion

This dissertation describes the incidence of pediatric IBD and its changes in Finland between years 1987-2003. During the study period, the incidence of IBD among Finnish children tripled reaching a level comparable to the rates reported from the high-incidence areas in North America and other Northern European countries. In addition, the results suggest higher incidence rates in the areas with sparse pediatric population compared to the areas with dense pediatric population. The spatial variations in the incidence rates, however, did not associate with chemical concentrations of tap water, seaside residence or nearby paper industry. This study, which was conducted before the era of the biological agents, demonstrates a frequent need for an operation and systemic glucocorticoids within few years after the diagnosis, indicating an aggressive disease course of IBD among children. Further, the quality of life among patients with pediatric onset IBD was somewhat lower than among their healthy peers.

6.1 Data sources

The main source of the patient data was the SII database, which provides comprehensive information on IBD patients diagnosed in Finland. This register covers whole Finland enabling a nationwide, population-based study. The comprehensive national health insurance and public healthcare systems of Finland and rigorous criteria for reimbursements are the two factors behind the completeness of this database. In order to verify the accordance and validity of the reimbursement criteria, 25 representative reports from the both Lapland and Kainuu hospital districts (two districts with the highest incidence rates) were re-examined. Only in one case (from Kainuu) the diagnosis procedure was not completely sufficient. This demonstrates the accuracy and the uniformity of the diagnostic criteria in all parts of Finland.

Another major database used in this study was Helsinki and Tampere University Hospitals’ discharge and medical records. The major strength in using these records is the possibility for reconsideration of the diagnoses and
consequently minimization of misclassification. However, there are some limitations in utilization of the medical record databases. Firstly, some patients with mild symptoms may have not undergone endoscopic evaluation, which are centralized to the university hospitals, and thus could be missed. Secondly, a proportion of adolescents over 15 years of age are treated at adult clinics especially in Helsinki region, and hence the number of patients at that age group is likely underestimated. In Finland, diagnostic procedure and treatment of pediatric IBD is concentrated in public health care. Thus it is unlikely that pediatric patients would solely be treated in private clinics.

It is possible that if the symptoms are very mild and no medication is needed, some patients can be omitted from the SII database. As this study demonstrated, it is, however, infrequent to be able to cope without regular medication. A comparison between the SII database and hospital databases reveals that the number of patients in the SII database exceeds that of hospital database by up to 50%, whereas only 6% of the cases identified from hospital databases were missing from the SII database. For this reason, the sensitivity of the case ascertainment through the SII database is likely to be very high.

As a limitation, the information on the IBD subtypes obtained from the SII database was incomplete. Nevertheless, the completeness increased with time. Hence, the study period used in the subtype analyses was shorter. The time period selected was the years 1992-2003 with over 50% completeness of the subtype information. The increasing trend in the incidence of UC was notable in sensitivity analysis even for the most extreme presumption of the subtype distribution, whereas in CD group with a smaller number of cases the increasing trend disappeared when all cases with missing subtype were assumed to have UC. Additionally, the information on tap water contaminants was available only for the years 2002-2007. Consequently, as closely matching study period was used in the water analyses as possible (1999-2003).

The study on the long-term outcomes in pediatric IBD was questionnaire-based. The long duration of disease at the time of the questionnaire (the median duration of 8.3 years) enabled an extensive assessment of long-term sequelae in pediatric-onset IBD including its influence on reproduction. The response proportion of 67% among patients is comparable to other corresponding surveys (Galea, Tracy 2007, Hille et al. 2005, Korkeila et al. 2001). Controls may probably have lower motivation to reply due to missing impact of IBD on their lives, and hence the response proportion was lower (37%) among them. Asthma prevalence among controls who replied (7.4%) was comparable to the previous
Finnish studies (6.2%-8%) indicating similar medical condition between responders and non-responders (Pallasaho et al. 2002, von Hertzen et al. 2006). Furthermore, the mean heights of male and female controls aged ≥ years were comparable to the Finnish mean adult heights (166 cm in female controls versus 167 cm in Finnish female population and 179 cm in male controls versus 181 cm in Finnish male population (Saari et al. 2011). Hence, the presence of substantial selection bias is unlikely. Similarly, no signs of more severe clinical picture among patients who replied than among non-responders were observed. In comparison with women, among men the participation proportion is in general lower (Eaker et al. 1998). This sex difference was notable also in our study.

One advantage of using various data sources is the possibility to collect a wide variety of information, and cross-check validity of information. The study based on medical records was not nationwide, but the more restricted study population enables to collect more specific data and in-depth. The questions in the questionnaire concerned mainly present features or major issues including operations. Therefore, the presence of major recall bias is unlikely. The social class is associated with self-assessed health among adults in Finland (Kunst et al. 2005). As a limitation, we had no information on the socioeconomic status of the patients or the controls. Nonetheless, some studies suggest no association between the health and the socioeconomic status of the parents among Finnish children (Siponen et al. 2011). Further, the place of residence and family size were similar between the groups indicating no major differences in demographic factors.

Internal and international migration is low in Finland. In 2003, the proportion of the pediatric population (aged 0-14 years) with foreign background was 5.8% (14359/246401) in Uusimaa and 1.0% (320/32200) in Lapland (Statistics Finland 2015). Additionally, the internal net migration was -1142 children in Uusimaa and +111 in Lapland (Statistics Finland 2015). Hence, these factors are unlikely to have a noticeable impact on the spatial analyses.

### 6.2 Incidence of pediatric IBD

This study showed a substantially increasing trend in the incidence of pediatric IBD with the incidence figures among the highest reported incidence rates of pediatric IBD. In Canada, an incidence as high as 13.3/100,000 among children aged 0-17 years has been reported (Grieci, Butter 2009) compared to the overall
incidence of 9.6/100,000 in Finland. Another Finnish study described a significantly increasing incidence of IBD for the entire Finnish population between years 2000-2007 with the overall incidence of 34.0/100,000 (Jussila et al. 2011). According to that study, children aged 0-15 years encompass 6% of all the IBD patients in Finland.

However, the incidence rates of different studies are not always comparable. The diagnostic criteria may vary between countries and hospitals, and also completeness of case ascertainment may vary. The incidence of IBD increases substantially after the age of 10 and peaks at the age of 20-30 years (Benchimol et al. 2014). Accordingly, the age limit chosen affects crucially the incidence rates. In this study, the overall incidence rate during 1987-2003 was considerably lower in children aged 0-14 years in comparison with children aged 0-17 years (6.5/100,000 versus 9.6/100,000). Yet, even the lower figure is high in international comparison (Benchimol et al. 2011). The studies reporting the highest UC and CD incidence rates among children (13.3/100,000 in Denmark and 13.9/100,000 in Canada respectively) used age limit <20 years in contrast to the most pediatric studies using age limit of ≤15 years (Langholz et al. 1991, Lowe et al. 2009, Benchimol et al. 2011). Nevertheless, the choice of the age limit did not influence trends of incidence over the years in the current study, as the age groups were unchanged through the study period and the incidence trends were comparable for all age groups.

The increasing trend in IBD incidence among children is in line with most other studies. According to a large review article, almost 80% of the studies analyzing time trends in the incidence reported an increase in the course of time, while no declining trends were reported (Benchimol et al. 2011). A decrease of the age at diagnosis does not appear to explain this increase (Braegger et al. 2011). Even if the incidence rates of pediatric IBD are increasing as a whole, a few countries including Iceland and South Wales have demonstrated plateauing incidence rates after an increase (Agnarsson et al. 2013, Ahmed et al. 2006). As a limitation, this study demonstrates the incidence trend of pediatric IBD only until 2003. More recent studies have, however, revealed the continuation of the increasing trend in pediatric IBD (Benchimol et al. 2014, Agnarsson et al. 2013).

In the present study, the increasing incidence trend was noticeable in both UC and CD. In contrast, several pediatric studies have indicated increasing incidence rates exclusively for CD with the predominance of CD over UC (Hildebrand et al. 2003, Malaty et al. 2010, Auvin et al. 2005). Despite the faster increase, the incidence of CD remained lower than UC during the whole study period. The
The predominance of UC over CD is comparable to the Finnish adult study (Jussila et al. 2011) and to some other countries for instance Iceland and Denmark (Agnarsson et al. 2013, Jakobsen et al. 2011).

Alternative explanations for the increase in pediatric IBD in Finland, however, need to be taken into consideration. Videoendoscopies were not in use in the earlier period (1987-1991) and thus the terminal ileum was less frequently assessed during the diagnostic procedure. Because of this and more systematic use of EGD towards the end of the study period, the sensitivity of diagnosis could have slightly increased. As this study revealed, most of the CD patients, however, presented with pancolitis. Thus, the influence of advanced diagnostics on the increasing incidence rates is likely to be minor. Additionally, a more active medical treatment could result in increased reimbursement decisions. Nevertheless, apart from few exceptions, every IBD patient needs medication during the course of the disease. For example, 83% of hospital cases had received systemic glucocorticoids and the proportion of the children receiving these as a primary therapy had remained similar through the study period. Further, merely 6% of the patients identified through the hospital databases had not received the reimbursement certificate. Thus, more frequent reimbursement decisions are unlikely to explain the increasing trend in the incidence.

6.3 Environmental factors related to incidence of IBD

Although genetic factors contribute undoubtedly to the etiology of IBD, those are unlikely behind the rising incidence rates. Therefore, it is probable that environmental factors play an important role in the increasing trend of the IBD incidence among children. In addition to IBD, the type 1 diabetes, also autoimmune disease, has been increasing particularly fast among Finnish children (Harjutsalo, Sjoberg & Tuomilehto 2008), although the increasing trend has reached a plateau after the year 2006 (Harjutsalo et al. 2013). This is also in concordance with the hypothesis suggesting environmental and lifestyle factors may trigger both of these diseases.

Higher incidence rate of pediatric IBD among Asian origin immigrants in Canada compared to children living in Asia suggests also a major role of the environmental factors in the etiology of IBD (Pinsk et al. 2007, Tsai et al. 2004, El Mouzan et al. 2014). The younger the age at the time of the immigration, the higher is the risk of pediatric IBD (Benchimol et al. 2015).
The etiology of IBD is multifactorial complicating the assessment of single environmental factors. Prospective cohort studies would be ideal to evaluate the role of the environmental determinants in the rising incidence rates (Molodecky et al. 2011a). Otherwise, the potential interactions between different environmental factors need to be taken into consideration. Differences in genetic susceptibility between populations may have an impact as well. Although Finnish population is generally of Caucasian origin with little immigration (Statistics Finland 2010), genetic variation between Eastern and Western Finland has been demonstrated (Lappalainen et al. 2006).

6.3.1 North-south gradient

In this study, no statistically significant differences in the incidence rates analyzed by latitude and longitude were observed. Nonetheless, the incidence rates were as a whole slightly higher in the north and west. Further, some pediatric IBD studies from the Northern hemisphere have reported a north-south gradient with higher incidence rates in the north (Karolewska-Bochenek et al. 2009, Kappelman et al. 2007, Armitage et al. 2004). In Finland, the gradient was demonstrated earlier for adult UC (Jussila et al. 2013). The gradient is reverse in the Southern hemisphere with the highest incidence figures in Australia and New Zealand (Molodecky et al. 2011b).

6.3.2 Vitamin D

The exposure to the sunlight and thus the plasma levels of D vitamin could possibly explain the north-south gradient seen in the IBD incidence (Bernstein 2012). Higher plasma levels of 25(OH)D show an association with a significant reduction in the risk of CD (Ananthakrishnan et al. 2012). Additionally, vitamin D can alter immune responses and intestinal barrier function as shown in mouse model studies (Meeker et al. 2016). In addition to IBD, low levels of vitamin D have been associated with other chronic diseases for instance with type 1 diabetes mellitus and multiple sclerosis (Grant 2006, Skaaby et al. 2015). An association between insufficient intake of vitamin D during the first year of life and an increased frequency of type 1 diabetes mellitus has been demonstrated in a Finnish study (Hypponen et al. 2001). Moreover, high plasma levels of vitamin
D have been shown to be causally associated with reduced risk of hypertension (Vimaleswaran et al. 2014).

In the northern parts of Finland, the duration of darkness is substantially longer during the winter (Finnish Meteorological Institute 2015). In the summer time, there are no significant differences in the length of daylight affecting D vitamin supply. In fact, the D vitamin levels among adults are slightly lower in the northern parts compared with the southern parts of Finland (Jussila et al. 2013).

6.3.3 Population density

Current study demonstrated higher incidence of IBD in the areas with low than high density of child population. This finding is in contrast to most previous pediatric studies (El-Matary, Moroz & Bernstein 2014, Orel et al. 2009, Ponsonby et al. 2009). Higher incidence of IBD in the densely inhabited districts has been observed among adults as well (Soon et al. 2012). Nevertheless, Lapland, which is almost entirely sparsely inhabited, is the northern part of the Finland. This fact together with the effects of vitamin D levels could explain at least partially the higher incidence rates in the sparsely populated areas compared with densely populated seen in this study.

The highest incidence figures of IBD within Asia are found in urbanized districts in China (Ng et al. 2013). Hence, it appears that urbanization and increased income level in China together with westernized diet maybe behind increasing incidence of IBD (Gasparetto, Guariso 2013, Ng et al. 2014). Theoretically, the increased incidence rates in urban areas of Asia may result from better recognition of IBD along improved availability of health services. However, the association between the densely inhabited urban districts and high level of IBD incidence is demonstrated also in Western countries (El-Matary, Moroz & Bernstein 2014, Orel et al. 2009, Ponsonby et al. 2009), where strong differences in the availability of the health services are more infrequent. The standard of living is high in Finland compared to several other European countries with no substantial regional differences (Statistics Finland 2014b).

6.3.4 Drinking water

In this study, no significant associations between chemical concentrations of tap water and the incidence rates of pediatric IBD were found. However, the
incidence was a slightly higher in the districts with intermediate or high levels of iron in tap water compared with the low-level areas. In the adult study from Norway, higher concentration of iron in the drinking water was associated with increased risk of IBD (Aamodt et al. 2008a). The variability in the concentrations of the other chemical compounds was minor. The limitation of this study was the lack of individual-level exposure data on tap water including personal drinking habits, which may lead to miss-classification. These are substantive features in the analyses concerning the potential effect of tap water on diseases (Villanueva et al. 2014). In Finland, tap water is, however, the main source of drinking water. The consumption of bottled water per capita is one of the lowest among European countries (Unesda 2015).

In Finland, the usage of well water is infrequent and even 98% of the households are integrated to the water system (Statistics Finland 2014a). Therefore, well water consumption in rural districts is unlikely to account for our finding of higher incidence rates in sparsely inhabited areas. The association between well water drinking and higher risk of IBD is, however, reported among children and adults alike (Baron et al. 2005, Van Kruiningen et al. 2005). The quality and the chemical contaminants of well water vary from well to well depending on the regional quality of ground water, well features and environmental pollutants (National Institute for Health and Welfare 2014). As a limitation, the information on consumption and chemical content of well water was unavailable. Consequently, its effects on the incidence of IBD in Finland could not be evaluated.

There are only few studies, which have earlier analyzed the association between metal compounds in tap water and IBD. In murine models, administration of aluminum enhances intestinal inflammation (Pineton de Chambrun et al. 2014). Further, aluminum has been suggested to be a potential factor for induction of CD (Lerner 2012).

6.3.5 Gut microbiota and antibiotics

Frequent use of antibiotics is associated with an increased risk of pediatric CD according several studies (Ungaro et al. 2014, Virta et al. 2012). However, this association is not evident in UC (Ungaro et al. 2014). Antibiotics alter the intestinal microbiota and differences in gut flora between CD and UC groups have been reported (Thorkildsen et al. 2013). Hence, these medications may influence differently the development of CD and UC. Antibiotic consumption has decreased
among Finnish children between years 1987 and 1995 (Arinen et al. 1998). Therefore, antibiotics cannot account for the rising trend in IBD incidence in the current study.

In addition to antibiotics, contaminants of drinking water may impact intestinal flora. In this study, the effects of chemical agents in the tap water on the risk of CD and UC were not evaluated separately. Nevertheless, no major differences between these two groups were found in the other analyses (population density, closeness of the sea or paper mills), maybe due to the small number of cases in the subgroups reducing the statistical power. The environmental agents behind IBD need more research in the future with the emphasis on the differences in the etiology of CD and UC.

6.3.6 Paper industry and seaside

The closeness of sea or paper mills is possible sources of toxic compounds. Fish caught from the Baltic Sea contains elevated levels of harmful contaminants such as dioxins and mercury (Leino 2014). It is likely that people living near the seaside consume local fish and are exposed to these compounds. Local factories influence the nearby air pollution. These pollutants have been suggested to be potentially able to trigger gastrointestinal inflammation (Salim, Kaplan & Madsen 2014). Exposures to sulfur dioxide and nitrogen dioxide are associated with early-onset UC and CD, respectively (Kaplan et al. 2010). Additionally, the air emissions of pollutants have been shown to have an association with the rate of IBD hospitalizations (Ananthakrishnan et al. 2011).

In the current study, the geographical variations of pediatric IBD incidence were not associated with the closeness of the paper mills or seaside. Nevertheless, the risk of IBD was increased near sea among boys especially in the group of farmers’ offsprings. The small number of the cases in the analysis and chance are presumably the explanatory factors behind this finding.
6.4 Disease characteristics and clinical picture

6.4.1 Medication

In general, the clinical picture of IBD is severe among children. This study demonstrated frequent need for systemic glucocorticoids and for surgery before the era of the biological agents. At 8 years after the diagnosis, most of the patients required regular medications. Over 80% of the patients had received glucocorticoids, the number being greater compared to previous studies in pediatric and adult-onset IBD (Tung et al. 2006, Faubion et al. 2001). However, this finding is in line with a recent Finnish study indicating that almost 75% of the pediatric IBD patients acquire systemic glucocorticoids during the first year after the diagnosis (Virta, Kolho 2012). Moreover, less than one third of patients with CD were using immunosuppressive medication at the end of the follow-up. The proportion is low compared to other studies (Adamiak et al. 2013, Vernier-Massouille et al. 2008). However, the proportion receiving immunosuppressive agents increased towards the end of the follow-up period in the present study. In a recent pediatric study from Greece, over half of the patients received thiopurines and 14% were using biological agents (Dimakou et al. 2015). It is likely that medical therapy of pediatric IBD with introduction of biological agents has progressed also in Finland after the current study was conducted.

6.4.2 Disease location

Half of the CD patients and nearly two thirds of the UC cases had pancolitis, congruent with previous pediatric studies (Levine 2009, Levine et al. 2013a). The proportion of CD patients with isolated ileal disease (20%) was substantially higher than in other studies (Van Limbergen et al. 2008).

6.4.3 Surgery

The majority of the operations had taken place during the few subsequent years after the diagnosis. This finding is in line with other studies (Newby et al. 2008, Vernier-Massouille et al. 2008). Only one out of five operations was performed after the age of 18 years, when including only patients older than 18 years at the
time of the survey. In total, almost quarter of the patients had been operated on by the age of 18 years. The proportion is consistent with other studies even if the variability between studies is substantial (Gupta et al. 2006, Abraham, Mehta & El-Serag 2012, Newby et al. 2008, Winter et al. 2015). The probability of abdominal surgery was similar between patients diagnosed in childhood and adolescence, while the frequency seemed to be lower in children diagnosed at the age of less than 6 years. This finding suggesting a milder disease course in early-onset IBD is in contrast to other studies (Aloi et al. 2014) and might be explained by the small number of patients in the youngest age group.

6.4.4 Disease reclassification

In more than one out of eight IBD cases, the initial diagnosis was reclassified during the disease course in the current study maybe indicating the diagnostic difficulty among pediatric patients especially in those with IBDU. This finding is in line with other studies (Stordal et al. 2004, Mamula et al. 2002). A high level of diagnostic reclassifications among patients with IBDU is also demonstrated in other studies (Newby et al. 2008, Abraham, Mehta & El-Serag 2012). Nevertheless, development and more extensive use of diagnostic methods may have influenced the degree of diagnostic reclassifications after this study was conducted. The diagnosis had been changed more often among the patients in the questionnaire survey compared to the patients followed through the hospital databases. This small distinction is probably explained by the longer follow-up time among patients who replied to the questionnaire.

6.4.5 Extraintestinal manifestations

In the present questionnaire study, 5.4% of the IBD patients had a joint disease which was the most common extraintestinal manifestation. Although the frequency was significantly higher compared to the control group, other studies have reported joint diseases even in 18-20% of the patients with pediatric-onset IBD (Dotson et al. 2010, Jose et al. 2009). The higher proportions can at least partly be explained by longer durations of the follow-up. In addition, PSC was also more common among patients than controls. The frequency of 2% is comparable to the other pediatric IBD studies (Dotson et al. 2010, Jose et al. 2009). Other possible extraintestinal manifestations were infrequently reported.
6.4.6 Growth retardation

Male patients with CD aged ≥18 years were shorter and weighed less in comparison with the controls and the UC patients in this study. The difference between IBD subtypes cannot be explained by systemic glucocorticoids because the use of these medications were equally common among CD and UC patients. These findings are consistent with previous surveys (Kugathasan et al. 2007, Vasseur et al. 2010, Abraham, Mehta & El-Serag 2012). Characteristics of inflammation are, however, divergent in CD and UC (North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition et al. 2007). Furthermore, inflammation is one of the main factors influencing growth retardation in pediatric CD (Cezard et al. 2002).

6.4.7 Long-term sequelae

In addition to extraintestinal manifestations and growth failure, the long-term sequelae of pediatric onset IBD are substantial. The patients with childhood onset IBD need often hospital care. Hospitalization rates vary in follow-up from 9 to 27 per 1000 person years (Abraham, Mehta & El-Serag 2012). More than one third of the CD patients confront complications including GI bleeding or malnutrition requiring hospital care during 7 years follow-up (Vernier-Massouille et al. 2008). In the present study, hospitalization rates were not evaluated. Nevertheless, extensive disease with frequent need for operations seen in this study may have resulted in high number of hospitalizations. The strength of the current questionnaire study was that most patients had already entered adulthood enabling to assess the long-term outcomes of pediatric onset IBD including the impact of the disease on HRQOL in early adulthood.

6.4.8 Quality of life

Self-assessed quality of life has been shown to be lower among children with IBD (Greenley et al. 2010, Marcus et al. 2009, De Boer et al. 2005), and similarly among children with other chronic diseases compared to controls (Mellion et al. 2014). In the present study, the scores of HRQOL were as a whole high. Nevertheless, the self-assessed overall quality of life among the patients was significantly lower compared to scores of their age-matched controls.
Additionally, physical functioning was reported as significantly lower by the patient group. This finding with lower physical functioning and similar emotional and social functioning is in line with other results (Rogler et al. 2013). Early recognition of the pediatric IBD patients with psychosocial problems is essential (Mackner, Crandall 2005). Operated patients reported somewhat lower scores in all dimensions of quality of life compared to other patients.

6.4.9 Fertility

In addition to quality of life, colectomy can decrease fertility among women (Heetun et al. 2007, van der Woude et al. 2014). In the present study, female patients aged >20 years had less frequently children compared to their controls. Whereas, the proportion of patients with children was, interestingly, higher among operated than in non-operated patients. Forming relationships and sexual activity have been shown to be similar between IBD patients and healthy controls (Timmer et al. 2007a). This suggest that the differences in relationship status cannot explain the finding. The results are, however, only suggestive due to the low median age (20 years) at the time of the questionnaire. Moreover, the current questionnaire included no questions about possible problems with fertility. In order to obtain reliable results about the effects of IBD on fertility, the questionnaire survey should be repeated later.

6.5 Future directions

The present study and data from other studies highlight the demand for further research especially on the role of environmental determinants in the etiology of pediatric IBD. These factors include water consumption, dietary factors and vaccinations. Use of individual-level rather than aggregate-level data is advisable in order to discover the true effects of these environmental factors. Prospective cohort studies would be ideal owing to the possibility of concurrent exposure assessment and inclusion of making direct measurements and obtaining samples. Nevertheless, their feasibility is severely limited by the low incidence of the disease. Therefore, large birth cohort studies with multiple end-points and exposures could possibly be utilized. Follow-up studies using both questionnaire and registry data are needed for the assessment of long-term patient outcomes in pediatric IBD. Multivariable analysis should be used to control for potential
confounding factors including sex, socioeconomic status and genetic background. Since the incidence of IBD has been on the increase in Finland still after this study (Jussila et al. 2012), active research is needed in children also in the future. Additionally, the influence of biological agents on the disease and patient outcomes warrants further investigations.
The increasing trend in pediatric IBD, in particular CD, has been widely recognized. The present nationwide study demonstrated that this increase has been evident also in Finland. The annual incidence of pediatric IBD increased threefold between the years 1987 and 2003. Moreover, the incidence of IBD among Finnish children is high in comparison with other reported pediatric incidences. Despite the more substantial increase, the incidence of CD remained lower than UC during the entire study period contrary to most other studies.

The role of environmental factors in the worldwide increase of IBD has been under active research. This study demonstrated higher incidence rates in the districts with sparse than dense pediatric population. Other environmental determinants (agricultural industry, paper mills or sea shore close to the place of residence, north-south gradient and chemical concentrations of tap water) included in the analysis were not significantly associated with the spatial variations of the incidence rates.

The disease course was found aggressive among children. More than 20% of the patients underwent surgery before the age of 18 years and 83% had received systemic glucocorticoids. In addition, quality of life in patients with pediatric onset IBD was lower compared to their peers. These findings emphasize the importance to identify the risk factors of pediatric IBD and to find preventive strategies for children at increased risk. Additionally, the development of targeted new therapies modified by disease type play a key role in the future.
8 Acknowledgements

This dissertation was conducted at the School of Health Sciences, University of Tampere during the years 2006-2016.

I would like to express my sincere gratitude to my supervisors, Professor Anssi Auvinen and Docent Kaija-Leena Kolho. Professor Auvinen and Docent Kolho have always been very motivational and supportive of my research work. I am very grateful for the effort Professor Auvinen has invested in me. Docent Kolho has revised texts and proposed ideas endlessly during these years. I am sincerely grateful to her.

I would like to deeply thank Docent Merja Ashorn, who is also a member of my follow-up group, and PhD Sari Iltanen. They guided me at my first steps as a researcher and introduced this epidemiological project to me.

I would like to thank statistician Heini Huhtala for her statistical assistance. Thanks are also owed to my co-authors Kari Pasanen, MSc, Raimo Jauhola, M.D. and Pekka Jauhonen, M.D. for their co-operation. I wish to thank also Professor Suvi Virtanen, a member of my follow-up group.

I sincerely thank Docent Pekka Arikoski and Professor Marjo-Riitta Järvelin for reviewing this dissertation and constructive criticism on it.

This work was supported by grants from Finnish Pediatric Research Foundation and The Finnish Medical Society Duodecim.

Finally, I want to thank my husband Tuomas for his support and especially for being a loving father for our lovely children; Oosa and Antto.

Tampere, April 2016

Pieta Lehtinen


Henderson P, Anderson NH, Wilson DC. The Diagnostic Accuracy of Fecal Calprotectin During the Investigation of Suspected Pediatric Inflammatory Bowel Disease: A Systematic Review and Meta-Analysis. Am.J.Gastroenterol. 2013;.


Leino, O. 2014, Fish Consumption: human health effects and decision making., University of Eastern Finland.


Reed-Knight B, Lobato D, Hagen S, et al. Depressive Symptoms in Youth with Inflammatory Bowel Disease Compared with a Community Sample. Inflamm.Bowel Dis. 2014; .


Appendix 1

The questionnaire on the current health status, disease history and health-related quality of life

The patient form
HELSEINGIN JA UUDENMAAN
SAIRAANHOITOPIIRI
HYKS Lasten ja nuorten sairaala

Nro

Lasten tulehdukselliset suolistosairaudet
varhaisvaiheita ja pitkääikaisennustetta selvittävä tutkimus
Kysely potilaille

Vastaa/Vastatkaa näin:

Mikäli kysely on tullut postitettuna alaikäiselle lapselle tai nuorelle, pyydämme vanhempia vastaamaan kyselyyn joko yhdessä lapsen kanssa tai antamaan nuoren vastata itsenäisesti soveltuvin osin.
Vastauspäivämäärä__________________

Sukunimi ___________________________
Etunimet __________________________

Syntymäaika ________    ________    ________
Päivä     Kuukausi     Vuosi

Syntymäkotikunta _________________

Tämänhetkinen Paino___________ Pituus_________

1.Syntyikö tulehdukselliseen suolistosairauteen sairastunut täysiaikaisena?
   1 Täysiaikaisena (37-42 raskausviikolla)
   2 Ennenaikaisena (<37 raskausviikolla)
   3 Yliaikaisena (42 raskausviikon jälkeen)
   4 En osaa sanoa

2.Oliko tulehdukselliseen suolistosairauteen sairastuneen raskausaika normaali?
   0 Ei
   Millä tavoin?____________________________________________________
   1 Kyllä

3. Syntymämitat: Pituus ________________cm    Paino______________g
4. Onko tulehdukselliseen suolistosairauteen sairastuneella sisaruksia?

0 Ei

1 Kyllä (sama isä ja äiti)
   sisarusten syntymävuodet______________________

2 Kyllä (eri isä tai eri äiti)
   sisarusten syntymävuodet______________________

3 Kyllä (eri isä ja eri äiti)
   sisarusten syntymävuodet______________________

5. Onko tulehdukselliseen suolistosairauteen sairastuneella ollut kahden ensimmäisen elinvuoden aikana lääkärin toteama ruoka-aineallergia?

0 Ei → Siirry kysymykseen 8

1 Kyllä

6. Oliko ruoka-aineallergia 2 ensimmäisen elinvuoden aikana

   1 Lehmänmaitoallergia: Kyllä Ei
   2 Vilja-allergia Kyllä Ei
   3 Jokin muu ruoka-aineallergia, mikä?__________________________

7. Mikä oli ruoka-aineallergian oire?

   1 Ihottuma Kyllä Ei
   2 Pulauttelu Kyllä Ei
   3 Ripuli Kyllä Ei
   4 Vatsakipu Kyllä Ei
   5 Muu__________________________
8. Onko tulehdukselliseen suolistosairauuteen sairastuneella yli 2-vuoden iässä allergiasteinin todettu allergia

0 Ei
1 Kyllä
2 Ihotestein (Prick-testit) kyllä ei
   mikä allergia?_______________________
3 Verikokein kyllä ei
   mikä allergia?_______________________
4 Altistuskokein kyllä ei
   mikä allergia?_______________________

9. Mikä oli tulehdukselliseen suolistosairauuteen sairastuneen suolistosauren diagnostin taudin toteamisvaiheessa

1 Crohnin tauti
2 Haavainen paksusuolentulehdus (colitis ulcerosa)
3 Tarkkaa tautimääritystä ei tehty
4 Jokin muu. Mikä_______________________

10. Mikä tulehdukselliseen suolistosairauuteen sairastuneen diagnostin on tällä hetkellä?

1 Crohnin tauti
2 Haavainen paksusuolentulehdus (colitis ulcerosa)
3 Tarkkaa tautimääritystä ei ole tehty
4 Suolistosairaus on arvioitu parantuneeksi.
   Mikä oli taudin diagnosti aikanaan_______________________
11. Milloin tulehdukselliseen suolistosairaukseen sairastuneen oireet alkoivat?

Vuosi___________________

Vuodenaika

1 Kevät
2 Kesä
3 Syksy
4 Talvi

12. Missä asuitte tulehduksellisen suolistosairauden oireiden alkaessa?

Paikkakunta______________________________________________

Postinumero:___________________

13. Kuinka kauan arvionne mukaan kesti oireiden alusta siihen ennen kuin tulehdukselliseen suolistosairaukseen sairastuneen tauti todettiin tähystystutkimuksella? ____________kuukautta

14. Onko tulehdukselliseen suolistosairaukseen sairastuneella tällä hetkellä säännöllistä lääkitystä tulehduksellisen suolistosairauden hoitoon?

0 Ei
1Kyllä,

mikä/mitkä lääkkeet_____________________________________________

2 Säännöllistä lääkitystä ei ole koskaan käytetty
3 Säännöllinen lääkitys on lopetettu vuonna___________
15. Onko tulehdukselliseen suolistosairauuteen sairastunut saanut kortisonitabletteja (Prednisolon, Prednison, Entocort) tämän suolistosairauden hoitoon taudin toteamisvaiheessa (0-1kk diagnoosin teosta)?

0 Ei
1 Kyllä Arviolta kuinka monta kuukautta ________________

16. Onko tulehdukselliseen suolistosairauuteen sairastunut saanut kortisonitabletteja (Prednisolon, Prednison, Entocort) tämän suolistosairauden hoitoon taudin toteamisvaiheen jälkeen lukuun ottamatta mahdollista toteamisvaiheessa aloitettua hoitoa?

0 Ei
1 Kyllä Arviolta kuinka monta kuukautta ________________
Arviolta kuinka monta eri kuuria__________________

17. Onko tulehdukselliseen suolistosairauuteen sairastuneelle tehty leikkausta suolistosairauden takia

0 Ei
1 Kyllä, mikä leikkaus (koko paksusuolen poisto, osittainen suolenpoisto):___________________________________________________
leikkausajankohta ja vuosi:________________________
18. Mieti, kuinka tulehduskseelliseen suolistosairauteen sairastunut on voinut viimeisen
viikon aikana ja ympyröi sopivin vaihtoehto

1. fyysinen vointi (ruumiilline terveys) on ollut

<table>
<thead>
<tr>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erittäin</td>
<td>Huono</td>
<td>Melko</td>
<td>Kohtalainen</td>
<td>Melko</td>
<td>Hyvä</td>
<td>Erittäin</td>
</tr>
<tr>
<td>huono</td>
<td>huono</td>
<td>hyvä</td>
<td>hyvä</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2. mieliala on ollut

<table>
<thead>
<tr>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erittäin</td>
<td>Huono</td>
<td>Melko</td>
<td>Kohtalainen</td>
<td>Melko</td>
<td>Hyvä</td>
<td>Erittäin</td>
</tr>
<tr>
<td>huono</td>
<td>huono</td>
<td>hyvä</td>
<td>hyvä</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

3. millaista kanssakäyminen muiden ihmisten kanssa on ollut viimeisen viikon aikana

<table>
<thead>
<tr>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erittäin</td>
<td>Huono</td>
<td>Melko</td>
<td>Kohtalainen</td>
<td>Melko</td>
<td>Hyvä</td>
<td>Erittäin</td>
</tr>
<tr>
<td>huono</td>
<td>huono</td>
<td>hyvä</td>
<td>hyvä</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

4. kuinka hyvä elämänlaatu (hyvinvointi ja toimintakyky) on kaiken kaikkiaan ollut?

<table>
<thead>
<tr>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erittäin</td>
<td>Huono</td>
<td>Melko</td>
<td>Kohtalainen</td>
<td>Melko</td>
<td>Hyvä</td>
<td>Erittäin</td>
</tr>
<tr>
<td>huono</td>
<td>huono</td>
<td>hyvä</td>
<td>hyvä</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
19. Onko tulehdukselleen suolistosairauteen sairastuneella todettu jokin seuraavista pitkäaikaisista sairauksista

1 Astma   Kyllä   Ei
   Milloin todettu (vuosi)?

2 Niveltulehdus   Kyllä   Ei
   Mikä?  
   Milloin todettu (vuosi)?

3 Kilpirauhassairaus   Kyllä   Ei
   Mikä?  
   Milloin todettu (vuosi)?

4 Sydänsairaus   Kyllä   Ei
   Mikä?  
   Milloin todettu (vuosi)?

5 Munuaissairaus   Kyllä   Ei
   Mikä?  
   Milloin todettu (vuosi)?

6 Maksasairaus   Kyllä   Ei
   Mikä?  
   Milloin todettu (vuosi)?

7 Sappiteiden sairaus   Kyllä   Ei
   Mikä?  
   Milloin todettu (vuosi)?

8 Jokin muu, mikä  
   Milloin todettu (vuosi)?


20. Onko perheessänne joku/muita, joilla tulehduksellinen suolistosairaus (Crohnin tauti tai haavainen paksunsuolen tulehdus colitis ulcerosa) on varmennettu lääkärintutkimuksin

0 Ei
1 Kyllä
   Kenellä? (sukulaisuussuhde)_____________________

21. Onko lähisuvussanne oman perheenne ulkopuolella joku/muita, joilla on tulehduksellinen suolistosairaus (Crohnin tauti tai haavainen paksunsuolen tulehdus colitis ulcerosa)

0 Ei
1 Kyllä, lääkärintutkimuksen varmennettu
   Kenellä? (sukulaisuussuhde)_____________________

Kysymykset aikuisille potilaille, joilla on lapsena/nuorena todettu tulehduksellinen suolistosairaus

22. Onko sinulla lapsia

0 Ei
1 Kyllä, lasten syntymävuodet_____________

23. Jos vastasit edelliseen kysymykseen kyllä, onko lapsellasi pitkäaikainen suolistosairaus

1 Ei ole pitkäaikaista suolistosairautta
2 On pitkäaikainen suolistosairaus
   Mikä sairaus_________________________
   Toteamisikä______
Kiitämme teitä antamastanne avusta!

Lisätietoja:______________________________
Appendix 2

The questionnaire on the current health status, disease history and health-related quality of life

The form for the controls
Lasten tulehdukselliset suolistosairaudet
varhaisvaiheita ja pitkääikaisennustetta selvittävä tutkimus

Kysely terveille verrokeille

Vastaa/Vastatkaa näin:


Mikäli kysely on tullut postitettuna alaikäiselle lapselle tai nuorelle, pyydämme vanhempia vastaamaan kyselyyn joko yhdessä lapsen kanssa tai antamaan nuoren vastata itsenäisesti soveltuvin osin.
Vastauspäivämäärä________

Sukunimi_____________________  Etunimet__________________________

Syntymäaika ________ ________ ________
   Päivä     Kuukausi     Vuosi

Syntymäkotikunta __________________________

Tämänhetkinen     Paino___________ Pituus___________

1. Syntyikö kyselyn saanut täysiaikaisena?
   1  Täysiaikaisena (37-42 raskausviikolla)
   2  Ennenaikaisena (<37 raskausviikolla)
   3  Yliaikaisena (42 raskausviikon jälkeen)
   4  En osaa sanoa

2. Oliko kyselyn saaneen raskausaika normaali?
   0  Ei
   Millä tavoin?____________________________________________________
   1  Kyllä

3. Syntymämitat: Pituus________________cm     Paino_______________g
4. Onko kyselyn saaneella sisaruksia?
   0 Ei
   1 Kyllä (sama isä ja äiti)
       sisarusten syntymävuodet______________________
   2 Kyllä (eri isä tai eri äiti)
       sisarusten syntymävuodet______________________
   3 Kyllä (eri isä ja eri äiti)
       sisarusten syntymävuodet______________________

5. Onko kyselyn saaneella ollut kahden ensimmäisen elinvuoden aikana lääkärin 
toteama ruoka-aineallergia?
   0 Ei → Siirry kysymykseen 8
   1 Kyllä

6. Oliko ruoka-aineallergia 2 ensimmäisen elinvuoden aikana
   1 Lehmänmaitoallergia:     kyllä  ei
   2 Vilja-allergia     kyllä  ei
   3 Jokin muu ruoka-aineallergia, mikä?______________________

7. Mikä oli ruoka-aineallergian oire?
   1 Ihottuma     kyllä  ei
   2 Pulauttelu     kyllä  ei
   3 Ripuli     kyllä  ei
   4 Vatsakipu     kyllä  ei
   5 Muu________________
8. Onko kyselyn saaneella yli 2-vuoden iässä allergiatestein todettu allergia

0 Ei
1 Kyllä

2 Ihotestein (Prick-testit) kyllä ei
   Mikä allergia?__________________________

3 Verikokein kyllä ei
   Mikä allergia?__________________________

4 Altistuskokein kyllä ei
   Mikä allergia?__________________________

9. Onko kyselyn saaneella tällä hetkellä säännöllistä lääkitystä?

0 Ei
1 Kyllä, mikä/mitkä lääkkeet_______________________________

10. Onko kyselyn saaneella tehty vatsalanalueen leikkausta?

0 Ei
1 Kyllä, mikä leikkaus:_________________________
   leikkausajankohta ja vuosi:___________________
11. Mieti, kuinka kyselyn saanut on voinut viimeisen viikon aikana ja ympyröi sopivin vaihtoehto

1. fyysinen vointi (ruumiillinen terveys) on ollut

<table>
<thead>
<tr>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erittäin huono</td>
<td>Melko kohtalainen</td>
<td>Melko hyvä</td>
<td>Erittäin hyvä</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2. mieliala on ollut

<table>
<thead>
<tr>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erittäin huono</td>
<td>Melko kohtalainen</td>
<td>Melko hyvä</td>
<td>Erittäin hyvä</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

3. millaista kanssakäyminen muiden ihmisten kanssa on ollut viimeisen viikon aikana

<table>
<thead>
<tr>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erittäin huono</td>
<td>Melko kohtalainen</td>
<td>Melko hyvä</td>
<td>Erittäin hyvä</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

4. kuinka hyvä elämänlaatu (hyvinvointi ja toimintakyky) on kaiken kaikkiaan ollut?

<table>
<thead>
<tr>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erittäin huono</td>
<td>Melko kohtalainen</td>
<td>Melko hyvä</td>
<td>Erittäin hyvä</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
12. Onko kyselyn saaneella todettu jokin seuraavista pitkäaikaisista sairauksista

1 Astma       Kyllä       Ei
   Milloin todettu (vuosi)? _______

2 Niveltulehdus    Kyllä       Ei
   Mikä? _______________________
   Milloin todettu (vuosi)? _______

3 Kilpirauhassairaus     Kyllä       Ei
   Mikä? _______________________
   Milloin todettu (vuosi)? _______

4 Sydänsairaus     Kyllä       Ei
   Mikä? _______________________
   Milloin todettu (vuosi)? _______

5 Munuaissairaus     Kyllä       Ei
   Mikä? _______________________
   Milloin todettu (vuosi)? _______

6 Maksasairaus     Kyllä       Ei
   Mikä? _______________________
   Milloin todettu (vuosi)? _______

7 Sappiteiden sairaus     Kyllä       Ei
   Mikä? _______________________
   Milloin todettu (vuosi)? _______

8 Jokin muu, mikä_________________
   Milloin todettu (vuosi)? _________
13. Onko perheessänne joku/ joitain, joilla tulehduksellinen suolistosairaus (Crohnin tauti tai haavainen paksunsuolen tulehdus colitis ulcerosa) on varmennettu lääkärintutkimuksin

0 Ei
1 Kyllä

Kenellä? (sukulaisuuussuhde)_____________________

14. Onko lähisuvussanne oman perheenne ulkopuolella joku/ joitain, joilla on lääkärintutkimuksin varmennettu tulehduksellinen suolistosairaus (Crohnin tauti tai haavainen paksunsuolen tulehdus colitis ulcerosa)

0 Ei
1 Kyllä

Kenellä? (sukulaisuuussuhde)_____________________

Kysely aikuisille verrokkitutkimukseen valituille

15. Onko kyselyn saaneella lapsia

0 Ei
1 Kyllä, lasten syntymävuodet______________

16. Lapsellani (kyselyn saaneen lapsella)

0 Ei lapsia
1 Ei ole pitkääikaista suolistosairautta
2 On pitkääikainen suolistosairaus

Mikä sairaus ______________________
Toteamisikä____
Kiitämme teitä antamastanne avusta!

Lisätietoja:________________________________________________________