Journal of Crohn's and Colitis (2011) 5, 577–584

available at www.sciencedirect.com

Environmental factors in inflammatory bowel disease: A case-control study based on a Danish inception cohort

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Received 29 December 2010; received in revised form 19 May 2011; accepted 26 May 2011

KEYWORDS
Crohn's disease;
Aetiology;
Environmental factors;
Inflammatory bowel disease;
Ulcerative colitis

Abstract

Background: The role of environmental factors in development of inflammatory bowel disease (IBD) remains uncertain. The aim of the present study was to assess a number of formerly suggested environmental factors in a case-control study of an unselected and recently diagnosed group of patients with IBD and a control group of orthopaedic patients.
Methods: A total of 123 patients diagnosed with Crohn's disease (CD) and 144 with ulcerative colitis (UC) in Copenhagen (2003–2004) were matched 1:1 on age and gender to 267 orthopaedic controls. Participants received a questionnaire with 87 questions concerning environmental factors prior to IBD/orthopaedic admission. Odds ratios (OR) were calculated by logistic regression.
Results: Being breastfed >6 months (OR, 0.50; 95% CI, 0.23–1.11) and undergoing tonsillectomy (OR, 0.49; 95% CI, 0.31–0.78) decreased the odds for IBD, whereas appendectomy decreased the odds for UC only (OR, 0.29; 95% CI, 0.12–0.71). Vaccination against pertussis (OR, 2.08; 95% CI, 1.07–4.03) and polio (OR, 2.38; 95% CI, 1.04–5.43) increased the odds for IBD, whereas measles infection increased the odds for UC (OR, 3.50; 95% CI, 1.15–10.6). Low consumption of fibres and high consumption of sugar were significantly associated with development of CD and UC. Smoking increased the risk for CD and protected against UC.
Conclusion: Among Danish patients with CD and UC belonging to an unselected cohort, disease occurrence was found to be associated both with well-known factors such as smoking and appendectomy, and with more debated factors including breastfeeding, tonsillectomy, childhood vaccinations, childhood infections, and dietary intake of fibres and sugar.

Abbreviations: CD, Crohn's disease; IBD, inflammatory bowel disease; UC, ulcerative colitis.

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doi:10.1016/j.crohns.2011.05.010

1. Introduction

Despite excessive research on the topic, the aetiology of inflammatory bowel diseases (IBD), Crohn's disease (CD) and ulcerative colitis (UC), remains uncertain. Genetics are known to play a role in development of especially CD,[1] however, the lack of complete penetrance of UC and CD among monozygotic twins and the limited familial occurrence of IBD (5–10%)[2–4] indicate that also environmental factors play a role in development of these disorders. This assumption is further supported by a pronounced increase in incidence of IBD during the last decades in Western countries and in countries with westernized lifestyle.[5–9] In Denmark, a Western country with one of the highest prevalence-rates of IBD, the incidence of CD has increased both in urban and rural areas from 4.1 to 10.7/100,000 during the last five decades, whereas the incidence of UC has increased from 8.1 to 17.0/100,000.[6,10–12]

A combination of various exposures may contribute to the development of IBD in genetically susceptible individuals.[7] Among suggested factors are diet, tonsillectomy, usage of oral contraceptives, breastfeeding, and vaccinations, but there is still uncertainty as to whether the observed associations are true, since studies are often affected by recall bias or other methodological problems.[7,13,14] Smoking and appendectomy are the only risk factors which are fairly consistently found to be associated with IBD.[14,15]

The aim of the present study was to assess a population-based inception cohort of patients diagnosed with IBD in Copenhagen, Denmark during the period 2003–2004 in order to perform a questionnaire-based case-control study of the influence of exposure to specific environmental factors on development of CD and UC. An age- and gender-matched group of orthopaedic patients served as controls.

2. Materials and methods

2.1. Patients

In total, 562 patients were diagnosed with IBD (CD, UC or indeterminate colitis) during 2003–2004 in Copenhagen County and City.[6] Among these, 488 were Caucasians with CD or UC, of whom 347 (71%) agreed to be genotyped.[16] All genotyped patients received a questionnaire (<3 months after diagnosis) concerning exposure to environmental factors before diagnosis of IBD. A total of 267 IBD patients (123 with CD and 144 with UC) answered the questionnaire. For the present study, these patients were matched on age +/−5 years (at IBD diagnosis), gender, ethnicity and geographic location with 267 orthopaedic patients (included consecutively when seen in the emergency room or hospitalized, based on the inclusion criteria that they should match a patient from the IBD cohort). All controls fulfilled the matching criteria, apart from a 95-year-old patient matched with an 86-year-old control and three other patients matched with controls six year younger or older of age. Controls were judged to be representative of the general population, since all Danes have access to free hospital care, and patients categorized as 'orthopedic' encompasses a broad spectrum, from young people with emergency room contacts for sports related injuries to old hospitalized patients with for example hip fractures. The prevalence of other autoimmune diseases in the control group was low according to the National Danish Discharge Registry. Among 40 common and rare autoimmune disorders assessed, 0.5% of controls had been diagnosed with Hashimoto's thyroiditis, 0.5% with Guillain-Barré syndrome, 0.5% with rheumatic fever, 1.6% with rheumatoid arthritis, 3.8% with asthma, and 3.8% with diabetes mellitus (type I or II) prior to the present study.

2.2. Questionnaire

Cases and controls were handed the same questionnaire, proposed by the International Organization of Inflammatory Bowel Disease (IOIBD) with 87 questions concerning environmental factors prior to development of IBD covering different topics considered to be putative risk factors for CD and/or UC.[13] For statistical analyses, questions were grouped into 1) markers of immunity and infections (breast feeding; appendectomy before age 20 and >1 year prior to diagnosis; tonsillectomy before age 20 and >1 year prior to diagnosis; childhood vaccinations against tuberculosis, pertussis, measles, rubella, diphtheria, tetanus, or polio; childhood infections including measles, pertussis, rubella, chickenpox, mumps, and scarlet fever; sanitary conditions before age 20 [access to running water at home]), 2) diet (daily, weekly or rarer consumption of fruit, vegetables, egg, bread, cereal, sugar, and coffee), 3) use of oral contraceptives, and 4) smoking habits at diagnosis (classified as non-smoker, ex-smoker, or active smoker [defined as a daily consumption of tobacco for at least 6 months]).

2.3. Ethical considerations

The study was performed according to the Helsinki Declaration, and was approved by the local ethics committees and the Danish Data Protection Agency. All patients gave their written consent.

2.4. Statistical analysis

Each environmental factor was first tested by univariate analysis assessing the ratio of matched case-control pairs concordant and discordant for the given factor. In subsequent analyses, adjustment for potential confounding variables was performed by conditional logistic regression analysis. Cases and controls were matched on age and gender, and the following available confounders were chosen a priori based on review of the literature (and mutually adjusted for in analyses): smoking status, appendectomy, tonsillectomy, usage of oral contraceptives, and consumption of fibre, sugar, coffee, and eggs. Results were presented as odds ratio (OR) with corresponding 95% confidence intervals (CI) for CD and UC separately, as well as for IBD combined. All analyses were performed with SAS software version 9.0 (SAS Institute, Cary, NC). A two-sided probability value of <0.05 was considered statistically significant.

3. Results

In Table 1, basic characteristics of cases ($n=267$) and controls ($n=267$) are presented. All individuals were Caucasians with a median age at study entrance of 37.5 years among IBD patients and of 39 years among controls.

Table 1 Basic characteristics for 267 unselected incident cases with inflammatory bowel disease and 267 orthopaedic controls.

	Cases	Controls
Total	267	267
Crohn's disease	123	0
Ulcerative colitis	144	0
Gender		
Male	124	124
Female	143	143
Median age in yrs (range)		
All patients	37.5 (10–95)	39.0 (10–86)
Crohn's disease	35.5 (10–85)	34.0 (10–85)
Ulcerative colitis	38.5 (13–95)	40.5 (11–86)
Ethnicity		
Caucasian	267	267

3.1. Childhood immunity and infections

Univariate analyses of factors influencing immunity in childhood are presented in Table 2. Adjusted estimates are mentioned in the text only if differing from unadjusted estimates.

A trend towards a decreased risk of CD and UC in individuals who had been breastfed for more than six months during infancy was seen (combined OR, 0.50; 95% CI, 0.23–1.11), whereas no effect of 'ever breastfed' was observed (Table 2).

Tonsillectomy in childhood was reported in 20% of CD patients and 14% of UC patients as compared to 28% and 26% of matched controls, hence decreasing the odds for both UC and CD (Table 2) with a combined OR of 0.49 (95% CI, 0.31–0.78). Appendectomy before age 20 had no clear impact on development of CD (observed in 9% of patients vs. 11% of controls), but significantly reduced the odds for developing UC (4% in UC vs. 10% in controls) (Table 2).

Concerning childhood vaccinations, no effect of vaccination against diphtheria, measles, rubella, tetanus, or tuberculosis was observed, whereas vaccination against pertussis increased the risk of especially UC (Table 2, combined OR, 2.08; 95% CI, 1.07–4.03) as did vaccination against polio (Table 2, combined OR, 2.38; 95% CI, 1.04–5.43).

Regarding childhood infections, mumps and rubella did not influence later occurrence of CD or UC, whereas a tendency towards decreased odds of IBD in individuals reporting to have had pertussis (combined OR, 0.56; 96% CI, 0.27–1.20) or scarlatina (combined OR, 0.57; 95% CI, 0.31–1.03) was observed. Contrarily, measles infection (reported in 81% of UC patients vs. 68% of controls) significantly increased the odds for UC (Table 2). Occurrence of chicken pox before age 20 tended to increase the odds for both CD and UC (Table 2, combined OR, 1.53; 95% CI, 0.80–2.94).

No significant associations between sanitary conditions (as measured by access to running water at home during childhood) and development of CD or UC were observed (Table 2).

3.2. Diet

Analyses of diet, oral contraceptive use, and smoking are presented in Table 3. Daily consumption of fruits and vegetables (comparing daily vs. rarer intake of fruit and vegetables) significantly decreased the odds for both CD and UC, as did daily intake of whole meal bread (Table 3). Accordingly, when comparing high fibre intake (daily intake of three or more of the following categories: fruit, vegetables,

Table 2 Immunologic factors in childhood and subsequent risk of Crohn's disease and ulcerative colitis. A case-control study of 267 incident cases and 267 age- and gender-matched orthopaedic controls from Copenhagen County and City 2003–2004.

	Crohn's disease		Ulcerative colitis		IBD	
	OR	95% CI	OR	95% CI	OR	95% CI
Breastfed - ever	1.80	0.60–5.38	0.70	0.27–1.84	1.07	0.52–2.16
Breastfed > 6 months	0.63	0.20–1.91	0.40	0.13–1.28	0.50	0.23–1.11
Tonsillectomy < age 20	0.63	0.33–1.19	0.39	0.19–0.76	0.49	0.31–0.78*
Appendectomy < age 20	1.22	0.66–2.28	0.29	0.12–0.71	0.72	0.44–1.17
Vaccination against diphtheria	0.83	0.25–2.73	1.83	0.68–4.96	1.33	0.63–2.82
Vaccination against pertussis	1.57	0.61–4.05	2.67	1.04–6.82	2.08	1.07–4.03*
Vaccination against measles	1.78	0.79–4.02	1.00	0.48–2.10	1.30	0.76–2.25
Vaccination against polio	1.75	0.51–5.98	3.00	0.97–9.30	2.38	1.04–5.43*
Vaccination against rubella	1.56	0.67–3.59	1.08	0.49–2.37	1.29	0.73–2.27
Vaccination against tetanus	1.50	0.25–8.98	1.67	0.40–6.97	1.60	0.52–4.89
Vaccination against tuberculosis	0.67	0.24–1.87	1.20	0.52–2.78	0.95	0.50–1.81
Mumps < age 20	0.93	0.44–1.98	1.09	0.48–2.47	1.00	0.57–1.74
Pertussis < age 20	0.67	0.24–1.87	0.44	0.14–1.44	0.56	0.27–1.20
Measles < age 20	1.13	0.57–2.21	3.50	1.15–10.6	1.60	0.92–2.80
Rubella < age 20	1.42	0.68–2.97	0.92	0.42–2.02	1.16	0.68–1.98
Scarlatina < age 20	0.53	0.24–1.19	0.62	0.26–1.49	0.57	0.31–1.03
Chicken pox < age 20	1.36	0.63–2.97	2.00	0.60–6.64	1.53	0.80–2.94
Running water	0.50	0.05–5.51	0.50	0.13–2.00	0.50	0.15–1.66

*Odds ratios excluding 1.0 ($p<0.05$).

Table 3 Diet, oral contraceptive use, and smoking and risk of Crohn's disease and ulcerative colitis. A case-control study of 267 incident cases and 267 age- and gender-matched orthopaedic controls from Copenhagen County and City 2003–2004.

	Crohn's disease		Ulcerative colitis	
	Odds ratio	95% CI	Odds ratio	95% CI
Fruit daily	0.39	0.22–0.70*	0.56	0.33–0.95*
Vegetables daily	0.41	0.24–0.71*	0.51	0.31–0.84*
Whole meal bread daily	0.26	0.15–0.48*	0.42	0.26–0.70*
Muesli daily	0.15	0.05–0.51*	0.50	0.24–1.03
High sugar intake**	3.50	1.73–7.07*	1.68	0.96–2.97
Eggs daily	1.80	0.60–5.37	0.86	0.40–1.85
Coffee (≥3 cups vs. less)	0.67	0.37–1.21	0.89	0.52–1.53
Oral contraceptive use	0.80	0.32–2.03	0.82	0.34–1.97
Smoking vs. never/ex-smoking	2.35	1.33–4.15*	0.43	0.26–0.91*
Ex-smoking vs. never smoking	0.63	0.31–1.29	0.94	0.51–1.74

*Odds ratios excluding 1.0 ($p<0.05$).
**Defined as at least two of the following: sugar in coffee, sugar in tea, daily intake of soft drinks, sugar on breakfast cereals, sugar on porridge.

whole meal bread, ≥4 pieces of bread, cornflakes, muesli) to low fibre intake (daily intake of less than three of the 6 categories), high intake of fibre was found to decrease the odds for developing both CD (OR, 0.28; 95% CI, 0.15–0.52) and UC (OR, 0.38; 95% CI, 0.21–0.68) and further analyses suggested a dose–response effect of fibre intake.

In contrast, a high intake of sugar (patient reporting at least two of the following: sugar in coffee, sugar in tea, daily intake of soft drinks, sugar on breakfast cereals, sugar on porridge) significantly increased the odds for both CD and UC, with the most pronounced effect on CD (Table 3). The result was somewhat confounded by intake of fibre (adjusted OR, 2.46; 95% CI, 1.15–5.27).

Consumption of eggs and coffee was not significantly associated with development of CD and UC (Table 3).

3.3. Oral contraceptives

A similar percentage of women with IBD and women in the control group (CD, 72% vs. 75%; UC, 70% vs. 73%) were former or current users of oral contraceptives and, hence, no associations could be observed (Table 3).

3.4. Smoking

The prevalence of smokers among CD patients was 43% vs. 25% in matched controls, whereas the prevalence in UC patients was 17% vs. 29% in controls. Accordingly, smoking was found to significantly increase the odds for developing CD and significantly reduce the odds for developing UC, whereas no significant effect of ex-smoking on the two diseases was observed (Table 3).

4. Discussion

The present study of newly diagnosed IBD cases from an unselected Copenhagen incidence cohort and age- and gender-matched unaffected controls revealed that low consumption of dietary fibers and high consumption of sugar increased the risk for both UC and CD. Breastfeeding, on the other hand, appeared to have a protective effect on both diseases. Appendectomy during childhood significantly decreased the odds for developing UC, whereas tonsillectomy decreased the odds for both UC and CD. Vaccination against pertussis and polio increased the odds for developing IBD, whereas infection with pertussis or scarlatina seemed to decrease the odds. Measles infection significantly increased the odds for developing UC. No clear effect of sanitary conditions in childhood, oral contraceptive use in adulthood, or coffee intake was observed. As expected, smoking was positively associated with development of CD and negatively associated with development of UC.

Due to the steady increase in IBD in Western countries, it has been suggested that lifestyle factors such as consumption of diets low in fibre may play a role in development of CD and UC. In support of this hypothesis, we observed that a low intake of dietary fibres and a high consumption of sugar were associated with development of both CD and UC. This is in accordance with a study of Canadian children with recent onset of CD and matched controls from the same population, showing that higher intake of vegetables, fruits, fish and dietary fibre (assessed by a validated food-frequency questionnaire) significantly reduced the risk for developing CD.[17] Physiologically, fibres may influence intestinal physiology and pathology both directly and through metabolic products. The latter include short-chain fatty acids, which may provide energy to colonocytes, stimulate water and electrolyte absorption, increase colonic blood flow, and suppress inflammation through suppression of the nuclear factor (NF)-κB pathway.[18] Also, it has been observed that a high intake of dietary fibres is associated with lower levels of C-reactive protein (CRP) in adults from the general population.[19] In the Canadian study of children with CD, no association with intake of sucrose, fructose or other individual carbohydrates was observed,[17] whereas in a former Danish–Swedish co-twin control study, UC twins reported higher use of sugar prior to diagnosis than their healthy twin siblings.[13] Accordingly, a thorough literature review of intakes of sugars or sugar-containing foods and onset of Crohn's disease found that results have so far been

inconsistent and that most studies suffer from important methodological limitations, including lack of distinction between reporting of current and retrospective intakes.[20]

Still, it is likely that the difference in incidence of IBD in different geographic regions and the increased incidence in individuals migrating to Western countries may reflect impact of dietary habits on disease risk. Currently, in an ongoing web-based European IBD incidence study (www.epicom-ecco.eu), the reason for the East–West incidence gradient in IBD is being examined by using the questionnaire used in the present study.[21] The study may help to determine whether differences in incidences are due to increased awareness of disease and differences in diagnostic practices, or due to real differences in environmental factors, lifestyle and genetic susceptibility.[21,22] Changes in the lifestyle in Eastern Europe during the last two decades have resulted in a more westernized way of living. Westernized lifestyle meaning increased consumption of refined sugar, fatty acids, fast food, cereals and bread and reduced consumption of fruit, vegetables and fibers.[23] These and other aspects of westernization may be associated with IBD.[24,25] However, in addition to the present and ongoing study, there is a need for studies based on more detailed dietary questionnaires or use of novel biomarkers reflecting nutrient intake.

Among immunological factors in childhood, we observed a trend towards a decreased risk of IBD (especially UC) in individuals who had been breastfed for more than six months during infancy. In accordance, a meta-analysis from year 2004 found breastfeeding to be negatively associated with both CD and UC.[26] The meta-analysis was based on 17 reviewed studies, of which only five were graded to be of high quality. A recent case-control study from New Zealand confirmed a negative association between breastfeeding for more than 3 months and development of CD and UC.[27] However, recall bias is a concern in both the present and most former studies. Therefore, prospective large-scale and methodologically well-conducted studies are still needed, both to confirm the association between breastfeeding and IBD and to assure that breastfeeding is not a proxy measure for other factors operating in early life.

Tonsillectomy was negatively associated with development of both UC and CD in the present study, hence questioning the results of former studies (many of limited size) suggesting that tonsillectomy increases the risk of CD[28] or has no effect on development of CD or UC.[29–31] Tonsillectomy and appendectomy are sometimes considered a combined risk factor (MALTectomy) under the assumption of shared biological effects, but this may not be an optimal handling of these variables in relation to IBD. In the present study, estimates for appendectomy did not follow those for tonsillectomy, since appendectomy was positively associated with CD and negatively with UC. Importantly, only appendectomies occurring before the age of 20 years and at least 1 year prior to diagnosis of CD and UC were assessed. Our results are to some extent in accordance with former literature, although prior observations have not been entirely consistent.[14] In addition to a number of case-control studies of varying quality, two national cohort studies have found a significantly lower occurrence of UC in people who had had their appendix removed, especially if surgery occurred before the age of 20.[32,33] Regarding CD, a recent meta-analysis of observational studies found a positive association with appendectomy, but this declined to baseline levels 5 yrs or more after appendectomy, hence underlining the diagnostic problems potentially explaining the first estimate.[34] Further, the prevalence of CD occurring after appendectomy with histological findings of epithelioid granulomas has been shown to be very low.[35]

It has been debated whether absence of infections or, on the contrary, a high frequency of (in particular gastrointestinal) infections during early childhood impose a risk on development of IBD.[7,36,37]

Other childhood diseases have received less attention. In the present study, we found that occurrence of pertussis and scarlatina seemed to decrease the odds for developing IBD, whereas measles infection significantly increased the odds for developing UC. Vaccination against pertussis and polio increased the odds for both CD and UC. Although results on childhood infections and vaccinations may suffer from recall bias, these findings are interesting in light of the hypothesized importance of early immunological alterations in development of IBD and the knowledge of a range of other non-specific effects of various vaccinations. There is, however, a lack of literature on childhood diseases and non-specific effects of vaccinations in relation to IBD. Focus has primarily been on the putative etiological role of paromyxoviral infection, and measles epidemics have been related to occurrence of CD[38] but overall there is no clear evidence that wild-type measles is a risk factor for CD.[39] The role of measles vaccination has also been debated[7] and in contrast to studies suggesting an increased risk of IBD following measles vaccination, a population-based study from the US showed that measles vaccination after the age of 18 months actually protected against IBD,[40] what is interesting considering our finding of an increased risk of UC following measles infection. Still, there is a need for further studies on this subject.

In our study we did not observe an association between sanitary conditions during childhood, definite by access to running water at home, and the development of IBD. A recent study from France showed a correlation between CD incidence and the proportion of houses equipped with individual toilets.[41] The determination of the effect of early sanitary conditions in the present study may have been limited by the assessment of a relatively young Danish population, since the majority of Danish citizens are expected to have lived under fairly equal circumstances.

Among environmental factors operating later in life, oral contraceptive use and smoking were assessed. A number of cohort and case-control studies have demonstrated an association between oral contraceptive use and development of especially CD, hypothetically explained by multifocal microvascular gastrointestinal infarctions.[7] Accordingly, a recent meta-analysis summarizing result of 14 studies of a total of 75,815 patients (36,797 exposed and 39,018 non-exposed women) found an increased risk for CD among current users which remained significant after adjustment for smoking and increased with length of exposure.[42] The RR for UC among current users was also significantly increased both before and after adjustment for smoking. Former use of oral contraceptives did, on the other hand, not associate significantly with development of CD or UC.[42] In the present study, the prevalence of current or former users of oral contraceptives was high in both cases and controls and no harmful effect could be observed.

Lastly, smoking was found to be negatively associated with development of UC and positively associated with development of CD, hence confirming earlier finding and thereby the validity of the present study. Already in 1982, smoking was shown to protect against development of UC and this finding has been replicated in a number of studies since then, also showing an association between ex-smoking and development of UC.[13,15,16,27] In contrast, smoking has been shown to increase the risk of both development and relapse of CD, severity of disease, and need for surgery.[15,43]

The primary strength of the present study was the assessment of a recently collected unselected population-based cohort of IBD patients from Copenhagen, representing the whole spectrum of CD and UC patients. The collection of questionnaire data immediately after diagnosis of IBD reduced the risk for recall bias in answers to questions regarding habits prior to diagnosis, and time from onset to diagnosis of IBD was fairly short in the present cohort (approximately 6 months).[6]

However, there are also a number of potential limitations to be considered. First, the one-to-one match of cases and controls may to some extent have limited the power to detect associations and the orthopaedic controls may not be entirely comparable to the general population. However, by including both young and older orthopaedic patients, who may be hospitalized for very different reasons, we do not believe that the control group as a whole has been included conditioned on a certain exposure variable and hence selection bias should be minimal. Also, the prevalence of other autoimmune diseases in the control population was indeed low. One may hypothesize that a fraction of the orthopaedic controls was actually hospitalized for extra-intestinal manifestations of undiagnosed IBD, but considering the overall prevalence of IBD in the Danish population, we consider this fairly unlikely. Further, none of the controls was diagnosed with IBD during the following three calendar years. Second, it may be questioned whether it is appropriate to present combined results for IBD, recognizing that CD and UC are different disease entities with suggested differences in aetiology. However, many features of the diseases are similar and, therefore, in order to gain power, we chose to present combined estimates for IBD in addition to separate estimates for CD and UC, but only when the separate estimates pointed in the same direction. Third, the testing of a relatively large number of environmental factors may in some cases have resulted in falsely rejection of the null hypothesis and new hypothesis arising from the present study should be confirmed in future studies. Fourth, questions regarding early lifetime factors, such as breast feeding, vaccinations and childhood infections, may have been affected by recall bias and results on these factors should therefore be interpreted with caution. On the other hand, such factors are of less risk than for example dietary factors to be influenced by differential misclassification, as answers are not likely to depend on disease status. It would of course be ideal to assess the role of environmental factors in development of IBD in prospective studies with reliable measurements of all factors of interest from early childhood and onwards, but due to the relatively rare occurrence of both CD and UC as well as onset of disease occurring up to decades after childhood, this seems fairly unrealistic. Lastly, we acknowledge that the IOIBD environmental factor questionnaire was adapted from a former Danish–Swedish twin study for which it had been developed as a questionnaire of non-open-end questions by the IOIBD group. The questionnaire was in relation to the twin study translated from English into Danish and Swedish by persons fluent in Danish, Swedish and English. Hence, a formal validation or forward/backward translation was not carried out.

In conclusion, the present study of an unselected and newly diagnosed IBD cohort and matched controls both confirms and adds to earlier findings concerning the aetiology of IBD. Our findings of a role of breastfeeding, tonsillectomy, appendectomy, vaccinations, childhood diseases, and diet in development of IBD all fit well with the hypothesis that immunological alterations early in life as well as a Western lifestyle may play a key role in development of these disorders. Although some results (especially regarding early lifetime factors) should be interpreted with caution due to risk of recall bias, the novel findings of the present study require further investigation through carefully designed studies.

Authors' contribution

The study was conceived and designed by I.V., T.J., and P.M. T.S.H., I.V., M.F.N. and M.E. collected the data. T.S.H. entered all data. M.G. performed the statistical analysis. Results were interpreted by T.S.H., M.G., T.J., and P.M. T.S.H. and T.J. drafted the manuscript, which was revised by co-authors. All authors approved the final version of the manuscript.

Conflicts of interest

The authors of the present paper declare to have no financial conflicts of interest in relation to the manuscript.

Acknowledgement

We thank Dr. Nete Munk Nielsen for her helpfulness in relation to the use of the National Danish Discharge Registry.

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