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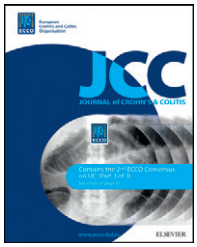

Environmental factors and risk of developing paediatric inflammatory bowel disease — A population based study 2007–2009☆

Christian Jakobsen [a,*], Anders Paerregaard [a], Pia Munkholm [b], Vibeke Wewer [a]

[a] Department of Paediatrics, Copenhagen University Hospital, Hvidovre, Denmark
[b] Department of Gastroenterology, Medical Section, Copenhagen University Hospital, Herlev, Denmark

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Abstract

Background and aims: To identify environmental risk factors for developing inflammatory bowel disease (IBD) in children <15 years of age.
Methods: IBD patients and randomly selected healthy controls from a well defined geographical area in Denmark were prospectively recruited in the period 1.1.2007–31.12.2009. Data regarding socioeconomic status, area of residence, living conditions, infections and diet were obtained by a questionnaire.
Results: A total of 118 IBD patients (59 Crohn's disease (CD), 56 ulcerative colitis (UC) and 3 IBD unclassified (IBDU)) and 477 healthy controls filled out the questionnaire. The response rates were 91% in patients and 45% in controls, respectively. Several risk factors for IBD were identified: IBD in first degree relatives (IBD: OR (odds ratio): 6.1 (95%CI: 2.5–15.0), CD (OR: 6.8 (2.3–20.2)) and UC (OR: 6.1 (2.3–16.0))); bedroom sharing (IBD: OR: 2.1 (1.0–4.3), CD (OR: 3.6 (1.3–9.4))); high sugar intake (IBD: OR: 2.5 (1.0–6.2), CD (OR: 2.9 (1.0–8.5))); prior admission to a hospital for gastrointestinal infections (IBD: 7.7 (3.1–19.1), CD (7.9 (2.5–24.9)) and UC (7.4 (2.5–21.6))); stressful events (IBD: 1.7 (1.0–2.9)). Protective factors were daily vs. less than daily vegetable consumption (CD: 0.3 (0.1–1.0), UC (0.3 (0.1–0.8))) and whole meal bread consumption (IBD: OR: 0.5 (0.3–0.9), CD (0.4 (0.2–0.9))). An increased risk of diagnosis of CD compared to UC was shown for patients living in more urban areas (OR: 1.3 (1.1–1.6)).

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* Corresponding author at: Hvidovre University Hospital, Kettegaard Alle 30, 2650 Hvidovre, Denmark. Tel.: +45 36322607; fax: +45 36323770.
E-mail addresses: Christian.jakobsen@hvh.regionh.dk (C. Jakobsen), anders.paerregaard@hvh.regionh.dk (A. Paerregaard), pia_munkholm@mail.dk (P. Munkholm), vibeke.wewer@hvh.regionh.dk (V. Wewer).

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Conclusion: We identified several risk and protective factors for developing IBD. Studies on the influence of environmental factors are important in our understanding of aetiology and phenotypes of paediatric IBD.

1. Introduction

The aetiology of inflammatory bowel disease (IBD) remains obscure. IBD is likely caused by a complex interplay between genetic and environmental factors. In the last decade great advances have been made with regards to the genetic contribution to IBD[1,2] in both adults and children with the disease. Some of the genes involved are related to the innate immune system (TLR, NOD2) others to homeostatic mechanism such as autophagy (IRGM, ATG16L1).[1,2] The increase in the incidence of IBD especially CD over the past 20–30 years cannot be explained by a change in genetic susceptibility alone but is likely to be related to environmental factors, including changes in lifestyle.[3] Many studies on environmental factors in IBD have been published, especially in adult patients.[4–13] Paediatric studies exist but are sparse,[14–19] especially in population based cohorts.[16]

Several environmental factors have been associated with IBD such as prior gastrointestinal infections,[9] active and passive smoking,[20] appendectomy and poor socioeconomic status.[21] Most of these studies include adult IBD patients. To our knowledge only one retrospective population based study investigating the impact of environmental factors on paediatric IBD has been published.[16] One advantage of our study design is that the patients are included a short time after diagnosis and thereby minimize the recall bias to questions regarding their life style and medical history before diagnosis.

In our opinion childhood is the ideal time for studying the impact of environmental factors as most parents are very attentive to their children's lifestyle and medical history.

In this population based study of children with IBD the aim was to identify environmental factors associated with the development of IBD using a questionnaire survey.

2. Material and methods

2.1. Study design

Our study was a population based case–control study including IBD patients diagnosed before 15 years of age. Patients were included over a three-year period (1.1.2007–31.12.2009) from a well defined geographical region in Denmark (Fig. 1). Healthy controls were randomly selected from the same geographical area during the period 1.1.2007–31.12.2007.

2.2. Patients

The study area covered Eastern Denmark, Funen and Aarhus (Fig. 1) including a total population of 668,056 children <15 years of age (January 2009), which comprised 62% of all children <15 years of age in Denmark.[22] The area was well defined as the Danish health care system dictated that all paediatric patients <15 years of age in a specific municipality should be referred to the local paediatric departments for diagnosis/treatment of IBD. All paediatric departments within the area participated in the study. Patients were prospectively included in the study as previously described.[23] Patients were diagnosed using the Copenhagen Diagnostic criteria.[24] To ensure that all paediatric patients were included, letters were sent twice during the three-year study period to all adult gastroenterology departments in the catchment area and 100% responded (17/17). None had diagnosed and/or treated IBD patients <15 years of age during the study period. In Denmark, treatment of paediatric IBD is conducted in hospital settings and is free for all inhabitants. Very few, if any, children are diagnosed by private practicing gastroenterologists.

2.3. Controls

All persons living in Denmark are registered by a unique 10-digit number in The Danish Central Person Registry. Controls <15 years of age were randomly selected from the Danish Central Person Registry from the same catchment area as the patients. Only controls without an ICD-10 diagnosis of DK500-519 in the National Patient Registry were selected.

2.4. Questionnaire

The questionnaire was developed in 1999 by the International Organization for the study of Inflammatory Bowel Diseases (IOIBD) and has been evaluated in a recently published gender and age matched case–control study in adult IBD patients[25] and used in previous studies.[26,27] The original questionnaire was slightly modified for use in paediatric patients. Before sending out the questionnaire to patients and controls a small pilot study including 16 families was conducted. The 16 families filled out the questionnaire and gave feedback regarding the formulation and clarity of the questions and according to the feedback proper changes were made. This final questionnaire, covering the period from birth to present date, was sent out to patients and controls.

134 questions were included, relating to seven different fields: 1. *Family history* (siblings, history of IBD, colon cancer, type-1 diabetes, celiac disease), 2. *Demographics* (ethnicity, socioeconomic status/social class), 3. *Living conditions* (sharing bedroom with others, number of rooms in house/apartment, household pets, daycare institution/nursery (age at start, number of children excluding own child), swimming (pool, sea, rivers), physical activities (<1 h daily, 1–2 h daily, >2 h daily), active and passive smoking, travelling more than >3 months), 4. *Perinatal period* (maternal diseases during pregnancy, gestational age at birth, birth weight and length of the child), 5. *Vaccinations and diseases* (childhood immunisation in Denmark includes: *Pneumococcus* disease, *Haemophilus*

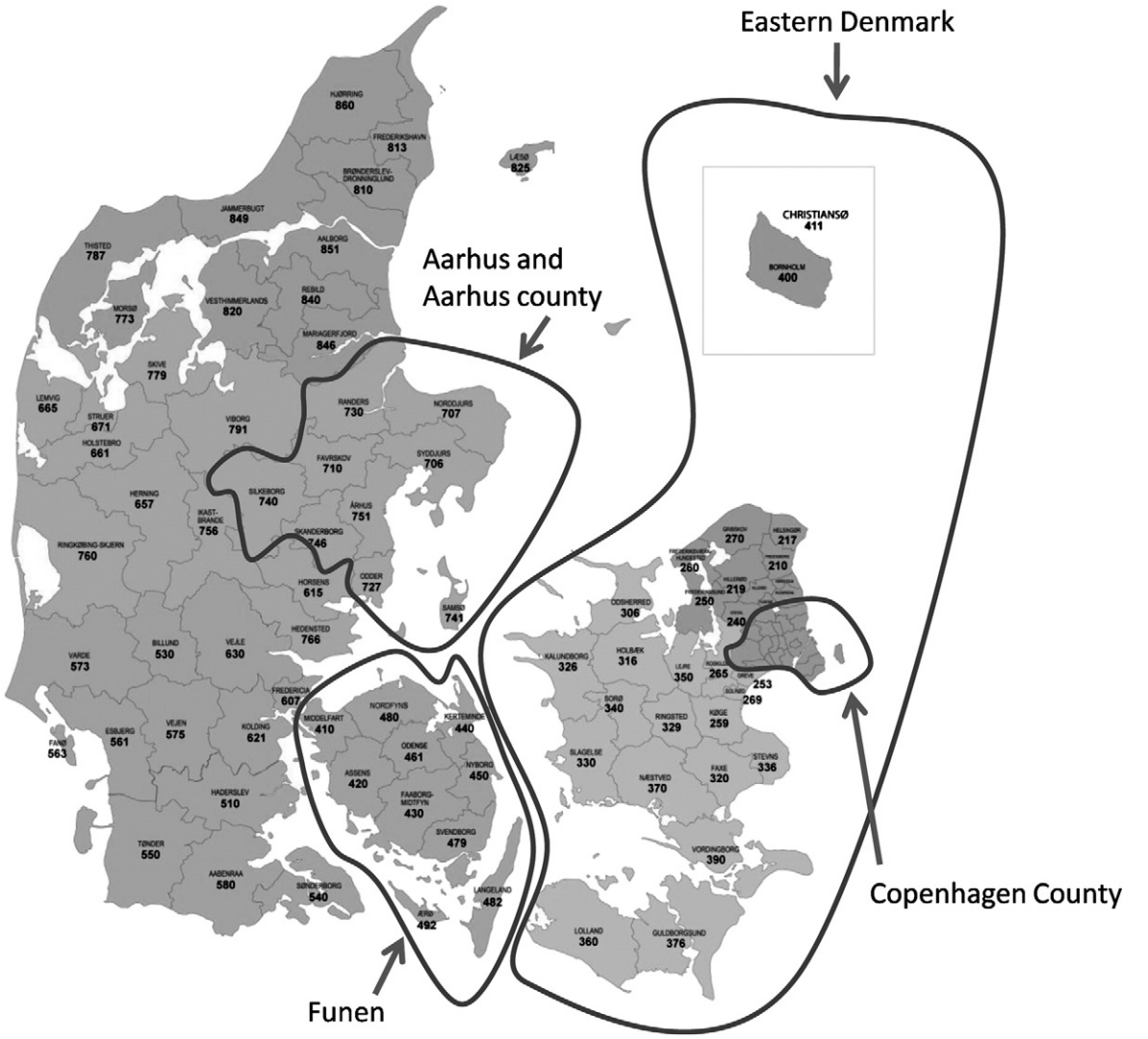

Figure 1 Map of the geographical area for the Danish population based paediatric IBD study in the period 1.1.2007–31.12.2009 covering Eastern Denmark, Funen, Aarhus and Aarhus County.

influenzae type b, measles, mumps, rubella, diphtheria, tetanus, pertussis and polio. Questions also included *Bacillus Calmette-Guerin* (BCG), hepatitis A/B and other vaccines. Diseases included asthma, asthmatic bronchitis, atopic eczema, other skin diseases, surgery (e.g. appendectomy, tonsillectomy), number of respiratory and gastrointestinal infections per year, number of hospital admissions for respiratory and gastrointestinal infections), 6 questions regarding diet were divided into two periods: the first year of life, and the last year before diagnosis (in patients) or before filling out the questionnaire (in controls) (breast feeding during infancy, frequency (daily or >1 per week, once per week or less) of consumption of bread (white, whole grain), vegetable, fruit, cereals, fast food, soft drinks, candy), and 7. *Stressful events* (death in family, divorce of parents, moving from one country to another).

2.5. Urbanisation

Classification of a geographical area as urban or rural was done according to the classification from Statistics Denmark (http://www.dst.dk) by using degree of urbanisation. Degree of urbanisation is a number indicating the percentage of inhabitants, in a defined geographical region, living in an urban area. The definition of urban area is a town area with more than 200 inhabitants and a distance between houses of no more than 200 m.

2.6. Definition of social class

We used the social class definition proposed by the Danish National Centre for Social Research.[28] In this definition families are divided into five social classes: social class 1 includes top managers in big organisations (>50 employees), top level civil servants, jobs that require at least four years of university training. Social class 2 includes medium level managers (11–50 employees), medium level civil servants, primary school teachers, social workers. Social class 3 includes lower level white collar workers within administrative jobs (1–10 employees), jobs that require medium level of theoretical vocational training for specialised job functions. Social class 4 includes skilled manual workers i.e. jobs

that require years of practical training. Social class 5 includes unskilled and semi-skilled workers e.g. factory workers, lorry drivers. The social class assigned to each family was that of the highest social class of the parents.

2.7. Statistics

All data were doubled typed into a database (Microsoft Office Access 2007, Microsoft Corporation, USA) and any typing errors were corrected using the original questionnaires. Data normally distributed are shown as mean and standard deviation (SD), data not normally distributed are shown as median and inter quartile range (IQR). Univariate- and multivariate logistic regression analyses were used to identify variables associated with developing IBD. In the multivariate analysis gender, age, socioeconomic status, area of residence and ethnicity were included as these were considered confounding variables. Significance level was set at $p<0.05$. All statistical analyses were performed using SAS 9.2 (SAS institute, Cary, NC, USA).

2.8. Ethical considerations

The study was approved by the ethical committee in Region Hovedstaden (KF-01327756) and all subjects gave informed consent.

3. Results

3.1. Description of study population

Questionnaires were sent to 1267 controls, 17 letters were returned unopened because the family had moved. A total of 566 controls filled out and returned the questionnaire resulting in a response rate of 45.3% (566/1250). Of the 566 responding controls 21 were excluded because they had chronic diseases (n=7), were adopted or in foster care (n=5) or responded that they did not want to participate (n=9). Furthermore, controls below three years of age were excluded as all IBD patients were >3 years of age resulting in 477 controls included in the final analysis.

From 1.1.2007 to 31.12.2009 a total of 130 IBD patients were diagnosed (65 CD, 62 UC and 3 IBDU) and 118 patients (59 CD, 56 UC, 3 IBDU) filled out the questionnaire resulting in a response rate of 90.7%. Demographics of patients and controls are shown in Table 1. At the date of filling out the questionnaire controls were younger and generally belonged to a higher social class than the IBD patients. To accommodate for this potential confounding both variables were included in the multivariate analysis.

3.2. Environmental factors and IBD

Variables associated with IBD are shown in Table 2 (univariate analysis) and Table 3 (multivariate analysis). In the multivariate analysis several risk factors were associated with developing IBD. IBD in first degree relative not only was a strong risk factor (OR: 6.1 (95%CI: 2.5–15.0)) but also dietary factors such as high weekly intake of sugar in the form of soft drinks (2.5 (1.0–6.2)) were associated with an increased risk. Furthermore, not only hospital admission for gastrointestinal infections was a strong risk factor for developing IBD (7.7 (3.1–19.1)) but also bedroom sharing (2.1 (1.0–4.3)), atopic eczema (1.7 (1.0–2.9)) and parents' divorce (1.7 (1.0–2.9)) were associated with developing IBD. Being breastfed more than 3 months was associated with a decreased risk of IBD (0.5 (0.3–1.0)).

Table 1 Demographics of paediatric patients with inflammatory bowel disease and healthy controls from Denmark (1.1.2007–31.12.2009).

		Crohn's disease n=59	Ulcerative Colitis n=56	IBD-unclassified n=3	IBD total, n=118	Controls, n=477	p-value [a]
Gender, n (%):	Male	39 (66)	28 (48)	1 (32)	68 (56)	246 (50)	0.2
	Female	20 (33)	28 (48)	2 (67)	50 (41)	231 (48)	
Median age at diagnosis, yrs (range)		13.3 (2.9–14.9)	11.9 (3.1–14.9)	11.8 (10.8–13.7)	12.9 (2.9–14.9)	–	
Median age filling questionnaire, yrs (range)		13.7 (3.2–17.2)	12.4 (3.5–15.4)	12.1 (11.8–13.7)	13.4 (3.2–17.2)	10.2 (3.1–15.1)	0.004
Siblings, n (%):	None	5 (8)	2 (4)	0 (0)	7 (6)	24 (5)	0.1
	1	23 (38)	28 (48)	2 (67)	53 (44)	245 (49)	
	2	24 (40)	18 (31)	1 (32)	43 (35)	160 (33)	
	3	5 (9)	5 (9)	0 (0)	10 (9)	35 (7)	
	4 or more	2 (3)	3 (5)	0 (0)	5 (4)	13 (3)	
Social class [b], n (%)	Grp. 1	8 (14)	7 (13)	1 (32)	16 (14)	108 (23)	0.009
	Grp. 2	11 (19)	11 (20)	2 (67)	24 (20)	122 (25)	
	Grp. 3	17 (28)	20 (35)	0 (0)	37 (30)	134 (27)	
	Grp. 4	13 (22)	12 (21)	0 (0)	25 (21)	88 (18)	
	Grp. 5	6 (10)	4 (7)	0 (0)	10 (9)	14 (3)	
	NC [c]	4 (7)	2 (4)	0 (0)	6 (5)	11 (2)	

[a] Compares IBD total and controls.
[b] Social class is the coded for the whole family and reflects the family member with the highest social class.
[c] Non-classifiable (NC): The respondents were not classifiable into group 1–5 because of insufficient information in the answers.

Table 2 Univariate analysis of associations between environmental factors in childhood and inflammatory bowel disease in a population based cohort from Denmark 2007–2009.

Variables		Odds ratio (95%CI) [a]	p-value
IBD in first degree relatives	Yes	7.4 (3.4–16.3)	<0.001
	No	Ref.	
Breastfeeding (months)	>3	0.5 (0.3–0.9)	0.02
	≤3	Ref.	
Vegetable consumption	Daily or >once weekly	0.4 (0.2–0.8)	0.009
	1 time weekly or less	Ref.	
Wholemeal bread consumption	Daily or >once weekly	0.5 (0.3–0.7)	0.001
	1 time weekly or less	Ref.	
Oatmeal consumption	Daily or >once weekly	0.5 (0.3–0.8)	0.001
	1 time weekly or less	Ref.	
Candy consumption	Daily or >once weekly	1.6 (1.1–2.6)	0.002
	1 time weekly or less	Ref.	
Soft drink consumption	≥4 times/week	4.8 (2.1–11.0)	0.0002
	≤3 times/week	Ref.	
Daily physical activity at present (hours)	>2	0.2 (0.1–0.5)	<0.0001
	1–2	0.4 (0.2–0.6)	
	<1	Ref.	
Currently or ever exposed to passive smoking	Yes	1.5 (1.0–2.3)	0.04
	No	Ref.	
Admitted to hospital for gastrointestinal infection	Yes	8.9 (4.0–20.0)	<0.0001
	No	Ref.	
Surgical removal of adenoids	Yes	1.8 (1.0–3.1)	0.05
	No	Ref.	
Has had any surgical procedure	Yes	1.6 (1.0–2.4)	0.04
	No	Ref.	
Sharing a bedroom with others	Yes	1.0 (0.5–1.8)	0.9
	No	Ref.	
Parents are divorced	Yes	2.4 (1.5–3.7)	<0.0001
	No	Ref.	

[a] Odds ratio models the risk of having IBD vs. controls.

3.3. Environmental factors and Crohn's disease

Variables associated with CD are shown in Table 4 (univariate analysis) and Table 5 (multivariate analysis). In the multivariate analysis we found several factors associated with developing CD. A strong risk factor was not only IBD in first degree relatives (6.8 (2.3–20.2)), but also white bread consumption (4.9 (1.0–23.4)), hospital admission for gastrointestinal infections (7.9 (2.5–24.9)) and bedroom sharing (3.6 (1.3–9.4)) were associated with developing CD. Dietary factors such as consumption of vegetables more than once weekly (0.3 (0.1–1.0)) and consumption of wholemeal bread more than once weekly (0.4 (0.2–0.9)) were associated with a protective effect on developing CD. Furthermore, CD patients were less physically active after diagnosis compared to healthy controls (p = 0.0003).

3.4. Environmental factors and ulcerative colitis

Variables associated with UC are shown in Tables 6 (univariate analysis) and 7 (multivariate analysis). In the multivariate analysis IBD in first degree relatives (5.2 (1.6–16.6)), frequent gastrointestinal infections (4.1 (1.5–11.2)), hospital admission for gastrointestinal infections (7.4 (2.5–21.6)) and more than three hospital admissions for upper respiratory infections (6.2 (1.3–29.4)) were associated with developing UC. In UC the only protective factors were more than weekly consumption of vegetables (0.3 (0.1–0.8)) and being breastfed for more than 3 months (0.5 (0.2–1–0)).

3.5. Urbanisation and inflammatory bowel disease

No association between degree of urbanisation and risk of developing IBD was found (p = 0.8). However, we found that for every 5% increase in degree of urbanisation (i.e. the percentage of inhabitants living in a urban setting in the catchment area) the odds of having CD compared to UC was 34% higher (OR 1.3 (1.1–1.6)).

4. Discussion

In our case control study of paediatric IBD patients several environmental factors were found to be associated with developing IBD. One of the strongest associations was not only IBD in first degree relatives but also dietary factors, infections, sharing a bedroom and stressful events were associated with developing IBD in our cohort. We also found an association between an urban living environment and being diagnosed with CD compared to UC.

Our study has several strengths as it is population based and patients were included shortly after diagnosis. However, there

Table 3 Multivariate analysis [a] of associations between environmental factors in childhood and inflammatory bowel disease in a population based cohort from Denmark 2007–2009.

Variables		Odds ratio (95%CI) [b]	p-value
IBD in first degree relatives	Yes	6.1 (2.5;15.0)	00003
	No	Ref.	
Breastfeeding (months)	>3	0.5 (0.3–1.0)	0.058
	≤3	Ref.	
Vegetable consumption	Daily or >once weekly	0.3 (0.1–0.7)	0.009
	1 time weekly or less	Ref.	
Wholemeal bread consumption	Daily or >once weekly	0.5 (0.3–0.9)	0.02
	1 time weekly or less	Ref.	
Candy consumption	Daily or >once weekly	1.5 (1.0–2.4)	0.07
	1 time weekly or less	Ref.	
Soft drink consumption	≥4 times/week	2.5 (1.0–6.2)	0.05
	≤3 times/week	Ref.	
Daily physical activity at present (hours)	>2	0.3 (0.1–0.6)	0.0004
	1–2	0.4 (0.3–0.8)	
	<1	Ref.	
Admitted to hospital for gastrointestinal infection	Yes	7.7 (3.1–19.1)	<0.0001
	No	Ref.	
Sharing a bedroom with others	Yes	2.1 (1.0–4.3)	0.04
	No	Ref.	
Parents are divorced	Yes	1.7 (1.0–2.9)	0.04
	No	Ref.	

[a] In the multivariate analysis age, gender, ethnicity, area of residence and socioeconomic status were included in the model.
[b] Odds ratio models the risk of having IBD vs. controls.

are also several limitations. The questionnaire, although previously used, has not been validated. Furthermore the response rate among the controls was just below 50% which could result in bias because typically more families from higher socioeconomic backgrounds and maybe with a healthier lifestyle returned the questionnaire. We tried to adjust for this bias by including socioeconomic status in the multivariate analysis, as it was considered a marker of a healthier lifestyle. Recall bias was also a limitation in this study; but minimized by including patients shortly after diagnosis. In our questionnaire regarding diet, the questions where directed to the period one year before diagnosis in order to exclude dietary changes related to disease activity.

Our finding of an association between IBD in first degree relatives and developing IBD, CD and UC has been shown in previous adult[29] and paediatric IBD cohorts.[14,16]

In contrast to the literature dealing with adult IBD[6,26,30–33] very few paediatric studies have been published regarding the association between diet and developing IBD.[16,34,35] We found that the sugar intake in the form soft drinks and candy consumption was higher in IBD and CD patients than in the controls. Baron et al.[16] found no association between dietary factors and IBD, CD or UC in their population based cohort of 222 paediatric IBD patients. The higher sugar intake in IBD patients compared to controls has been shown in another paediatric study by Reif et al. which included patients until 20 years of age.[35] In this study of 87 patients two control groups were included; one comprised of out-patient clinic controls and one included healthy population controls. The higher sugar intake was significant when comparing IBD and out-patient controls (OR 3.2 (1.06–9.61)) but not when using healthy population controls (OR 1.27 (0.42–3.85)). However, in the same study consumption of soft drinks was associated with an increased risk of IBD (OR 3.99 (1.33–11.9)). In adult studies[36,37] however, an association between sugar intake and risk of CD has been demonstrated[25,38] but other studies suggest that the increased sugar consumption is due to an alteration of the diet of CD patients after diagnosis.[31,39] We found that the intake of wholemeal bread (dietary fibre) was lower in IBD and CD patients compared to controls. This is in accordance with the studies by Amre et al.[34] (CD: OR 0.12 (0.04–0.37)) and Reif et al.[35] (IBD: OR 0.43 (0.12–1.48), CD: OR 0.40 (0.21–1.65)). However the differences were not significant in the latter study. In an adult study from Copenhagen County[25] daily intake of wholemeal bread was lower among CD and UC patients compared to hospital controls. Other adult studies have not shown a significant association between dietary fibre intake and IBD, CD or UC.[30,33] In our study the intake of vegetables was significantly lower among CD and UC patients compared to controls. Other paediatric studies[16,34,35] have not found a significant association between vegetable consumption and developing CD or UC. In adult patients, one study[25] showed a significantly lower intake of vegetables in CD and UC patients which is in contrast to another study from Japan where no significant association was found.[33]

Not surprisingly, we found that IBD patients were less physically active than healthy controls after diagnosis. No difference was shown in physical activity one year before diagnosis when comparing patients and controls. In contrast a previous study has showed a negative correlation between regular physical activity and risk of developing CD.[40]

In our cohort we found that previous admission to hospital for gastrointestinal infections was associated with developing IBD, CD and UC which is in accordance with other studies.[9,26] However, our finding could be due to recall bias. Another

Table 4 Univariate analysis of associations between environmental factors in childhood and Crohn's disease in a population based cohort from Denmark 2007–2009.

Variables		Odds ratio (95%CI) [a]	p-value
IBD in first degree relatives	Yes	9.0 (3.6–22.3)	<0.0001
	No	Ref.	
Vegetable consumption	Daily or >once weekly	0.4 (0.1–0.8)	0.043
	1 time weekly or less	Ref.	
Wholemeal bread consumption	Daily or >once weekly	0.4 (0.2–0.7)	0.001
	1 time weekly or less	Ref.	
White bread consumption	Daily or >once weekly	4.5 (1.1–19.0)	0.04
	1 time weekly or less	Ref.	
Cereals cornflakes type	Daily or >once weekly	2.0 (1.1–3.4)	0.02
	1 time weekly or less	Ref.	
Oatmeal consumption	Daily or >once weekly	0.4 (0.2–0.8)	0.005
	1 time weekly or less	Ref.	
Candy consumption	Daily or >once weekly	1.8 (1.0–3.2)	0.04
	1 time weekly or less	Ref.	
Soft drink consumption	≥4 times/week	6.6 (2.6–17.0)	<0.0001
	≤3 times/week	Ref.	
Daily physical activity at present (hours)	>2	0.1 (0.04–0.2)	<0.0001
	1–2	0.3 (0.1–0.5)	
	<1	Ref.	
Admitted to hospital for gastrointestinal infection	Yes	8.8 (3.4–22–9)	<0.0001
	No	Ref.	
Sharing a bedroom with others	Yes	1.3 (0.6–2.6)	0.5
	No	Ref.	
Surgical removal of adenoids	Yes	2.5 (1.3–4.9)	0.009
	No	Ref.	
Has had any surgical procedure	Yes	1.9 (1.1–3.4)	0.02
	No	Ref.	
Parents are divorced	Yes	2.5 (1.4–4.6)	0.001
	No	Ref.	

[a] Odds ratio models the risk of having IBD vs. controls.

Table 5 Multivariate analysis [a] of associations between environmental factors in childhood and Crohn's disease in a population based cohort from Denmark 2007–2009.

Variables		Odds ratio (95%CI) [b]	p-value
IBD in first degree relatives	Yes	6.8 (2.3–20.2)	0.002
	No	Ref.	
Vegetable consumption	Daily or >once weekly	0.3 (0.1–1.0)	0.05
	1 time weekly or less	Ref.	
Wholemeal bread consumption	Daily or >once weekly	0.4 (0.2–0.9)	0.02
	1 time weekly or less	Ref.	
White bread consumption	Daily or >once weekly	4.9 (1.0–23.4)	0.05
	1 time weekly or less	Ref.	
Soft drink consumption	≥4 times/week	2.9 (1.0–8.5)	<0.0001
	≤3 times/week	Ref.	
Daily physical activity at present (hours)	>2	0.2 (0.07–0.5)	0.0003
	1–2	0.3 (0.2–0.6)	
	<1	Ref.	
Admitted to hospital for gastrointestinal infection	Yes	7.9 (2.5–24.9)	0.0004
	No	Ref.	
Sharing a bedroom with others	Yes	3.6 (1.3–9.4)	0.01
	No		

[a] In the multivariate analysis age, gender, ethnicity, area of residence and socioeconomic status were included in the model.
[b] Odds ratio models the risk of having IBD vs. controls.

Table 6 Univariate analysis of associations between environmental factors in childhood and ulcerative colitis in a population based cohort from Denmark 2007–2009.

Variables		Odds ratio (95%CI) [a]	p-value
IBD in first degree relatives	Yes	6.3 (2.3–17.1)	0.0003
	No	Ref.	
Breastfeeding (months)	>3	0.4 (0.2–0.9)	0.02
	≤3	Ref.	
Vegetable consumption	Daily or >once weekly	0.3 (0.1–0.9)	0.03
	1 time weekly or less	Ref.	
Soft drink consumption	≥4 times/week	3.3 (1.0–10.1)	0.05
	≤3 times/week	Ref.	
Daily physical activity at present (hours)	>2	0.2 (0.1–0.5)	0.003
	1–2	0.5 (0.3–1.0)	
	<1	Ref.	
Total number of hospital admissions for upper respiratory infections	≤3	6.7 (1.8–24.6)	0.004
	≥4	Ref.	
Admitted to hospital for gastrointestinal infection	Yes	9.7 (3.7–25.7)	<0.0001
	No	Ref.	
Parents are divorced	Yes	2.2 (1.2–4.1)	0.01
	No	Ref.	

[a] Odds ratio models the risk of having IBD vs. controls.

explanation could be an incorrect diagnosis of gastrointestinal infection as the symptoms could be due to the debut of IBD. We found that patients with UC had more admissions to the hospital for upper respiratory infections compared to healthy controls. Other studies have shown similar results. Gilat et al.[41] showed that recurrent respiratory infections and hospitalization for respiratory infections were more common in UC and CD patients below 20 years of age compared to healthy controls. Wurzelmann et al.[42] found that adult CD patients had a higher frequency of childhood infections especially pharyngitis compared to healthy controls. In a recent paediatric study by Amre et al.[14] no association between physician diagnosed childhood disease and CD was found.

In connection with an increased frequency of childhood infections we found that sharing a bedroom was associated with developing IBD and CD. This has also been shown for UC patients in another population based study by Baron et al.[16] Other studies have failed to show this association for UC as well as CD.[4] The possible association between bedroom sharing and CD could relate to an increased risk of infections due to crowded living conditions.

We found that the frequency of parental divorce (before diagnosis of IBD in their child) was higher in IBD patients than healthy controls. This is a stressful event for a child and psychological stress could induce a hormonal response that triggers the immune system in a susceptible individual. A recently published review has focused on this issue.[43] The physiological response to stress involves two systems that normally work in parallel namely the hypothalamic–pituitary–adrenal (HPA) axis and sympathetic–adrenal–medullary (SAM) system. Activation of the HPA axis results in an increased level of cortisol which has an inhibitory role on inflammation by suppressing proinflammatory cytokines. Studies on rheumatoid arthritis[44,45] and one study in paediatric IBD (abstract)[46] have shown that the HPA axis is hyporesponsive which could facilitate or maintain inflammation.

To our knowledge no paediatric study has been published on stressful events and risk of developing IBD. Only three adult studies have been published and all failed to show an association between psychological stress and risk of developing IBD.[47–49] Several studies have been published on psychological stress and risk of relapse and although the

Table 7 Multivariate analysis [a] of associations between environmental factors in childhood and ulcerative colitis in a population based cohort from Denmark 2007–2009.

Variables		Odds ratio (95%CI) [b]	p-value
IBD in first degree relatives	Yes	6.1 (2.3–16.0)	0.0003
	No	Ref.	
Breastfeeding (months)	>3	0.5 (0.2–1.0)	0.06
	≤3	Ref.	
Vegetable consumption	Daily or >once weekly	0.3 (0.1–0.8)	0.02
	1 time weekly or less	Ref.	
Total number of hospital admissions for upper respiratory infections	>3	6.1 (1.3–28.2)	0.02
	≤3	Ref.	
Admitted to hospital for gastrointestinal infection	Yes	7.4 (2.5–21.6)	0.0003
	No	Ref.	

[a] In the multivariate analysis age, gender, ethnicity, area of residence and socioeconomic status were included in the model.
[b] Odds ratio models the risk of having IBD vs. controls.

results are conflicting, it seems that psychological stress could be a risk factor for relapse.[50–53]

In our cohort we found an association between living in an urban area and a diagnosis of CD compared to UC. Several studies have been published in this area with conflicting results.[6,42,54] A study from Northern France found that the relative risk of developing CD was higher in rural and periurban cantons of Pas-de-Calais, Somme and Nord department but not in Seine-Maritime.[55] Very few paediatric studies dealing with this issue have been published. In a study from Wisconsin no difference in incidences was found between densely and sparsely populated areas.[56] The differences between the results of our study and the study from Wisconsin could be due to methodological differences (for instance differences in definition of urban) and could also reflect genuine differences between countries due to different environmental factors such as diet and living conditions.

In conclusion, we found not only several well known risk factors associated with IBD but also factors that could be new etiological clues such as stress related events, which are highly prevalent in both adults and in children in modern-day families. More studies on stress induced hormonal influence on gastrointestinal inflammation are needed.

Conflict of interest

All authors have made substantial contributions to the conception, design, acquisition- and analysis of data and in drafting and approving the submitted manuscript.

Our manuscript, including related data, figures and tables has not been previously published and is not under consideration elsewhere.

Financial conflicts:

Vibeke Wewer is on the advisory board at MSD, Pia Munkholm is on the advisory board at MSD, Ferring, Tillots and Swedish Orphan. Anders Paerregaard and Christian Jakobsen have no financial conflicts.

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References

1. Barrett JC, Hansoul S, Nicolae DL, Cho JH, Duerr RH, Rioux JD, et al. Genome-wide association defines more than 30 distinct susceptibility loci for Crohn's disease. *Nat Genet* 2008;**40**:955–62.
2. Imielinski M, Baldassano RN, Griffiths A, Russell RK, Annese V, Dubinsky M, et al. Common variants at five new loci associated with early-onset inflammatory bowel disease. *Nat Genet* 2009;**41**:1335–40.
3. Benchimol EI, Fortinsky KJ, Gozdyra P, Van den Heuvel M, Van LJ, Griffiths AM. Epidemiology of pediatric inflammatory bowel disease: A systematic review of international trends. *Inflamm Bowel Dis* 2010;**17**:423–39.
4. Duggan AE, Usmani I, Neal KR, Logan RF. Appendicectomy, childhood hygiene, Helicobacter pylori status, and risk of inflammatory bowel disease: a case control study. *Gut* 1998;**43**:494–8.
5. Feeney MA, Murphy F, Clegg AJ, Trebble TM, Sharer NM, Snook JA. A case-control study of childhood environmental risk factors for the development of inflammatory bowel disease. *Eur J Gastroenterol Hepatol* 2002;**14**:529–34.
6. Gearry RB, Richardson AK, Frampton CM, Dodgshun AJ, Barclay ML. Population-based cases control study of inflammatory bowel disease risk factors. *J Gastroenterol Hepatol* 2010;**25**:325–33.
7. Green C, Elliott L, Beaudoin C, Bernstein CN. A population-based ecologic study of inflammatory bowel disease: searching for etiologic clues. *Am J Epidemiol* 2006;**164**:615–23.
8. Lopez-Serrano P. Perez-Calle JL, Perez-Fernandez MT, Fernandez-Font JM, Boixeda de MD. *Fernandez-Rodriguez CM: Environmental risk factors in inflammatory bowel diseases. Investigating the hygiene hypothesis: a Spanish case-control study. Scand J Gastroenterol* 2010;**45**:1464–71.
9. Porter CK, Tribble DR, Aliaga PA, Halvorson HA, Riddle MS. Infectious gastroenteritis and risk of developing inflammatory bowel disease. *Gastroenterology* 2008;**135**:781–6.
10. Russel MG, Engels LG, Muris JW, Limonard CB, Volovics A, Brummer RJ, et al. Modern life' in the epidemiology of inflammatory bowel disease: a case-control study with special emphasis on nutritional factors. *Eur J Gastroenterol Hepatol* 1998;**10**:243–9.
11. Sicilia B, Lopez MC, Arribas F, Lopez ZJ, Sierra E, Gomollon F. Environmental risk factors and Crohn's disease: a population-based, case-control study in Spain. *Dig Liver Dis* 2001;**33**:762–7.
12. Sonntag B, Stolze B, Heinecke A, Luegering A, Heidemann J, Lebiedz P, et al. Preterm birth but not mode of delivery is associated with an increased risk of developing inflammatory bowel disease later in life. *Inflamm Bowel Dis* 2007;**13**:1385–90.
13. Van Kruiningen HJ, Joossens M, Vermeire S, Joossens S, Debeugny S, Gower-Rousseau C, et al. Environmental factors in familial Crohn's disease in Belgium. *Inflamm Bowel Dis* 2005;**11**:360–5.
14. Amre DK, Lambrette P, Law L, Krupoves A, Chotard V, Costea F, et al. Investigating the hygiene hypothesis as a risk factor in pediatric onset Crohn's disease: a case-control study. *Am J Gastroenterol* 2006;**101**:1005–11.
15. Aspberg S, Dahlquist G, Kahan T, Kallen B. Fetal and perinatal risk factors for inflammatory bowel disease. *Acta Paediatr* 2006;**95**:1001–4.
16. Baron S, Turck D, Leplat C, Merle V, Gower-Rousseau C, Marti R, et al. Environmental risk factors in paediatric inflammatory bowel diseases: a population based case control study. *Gut* 2005;**54**:357–63.
17. Klement E, Lysy J, Hoshen M, Avitan M, Goldin E, Israeli E. Childhood hygiene is associated with the risk for inflammatory bowel disease: a population-based study. *Am J Gastroenterol* 2008;**103**:1775–82.
18. Lashner BA, Shaheen NJ, Hanauer SB, Kirschner BS. Passive smoking is associated with an increased risk of developing inflammatory bowel disease in children. *Am J Gastroenterol* 1993;**88**:356–9.
19. Ponsonby AL, Catto-Smith AG, Pezic A, Dupuis S, Halliday J, Cameron D, et al. Association between early-life factors and risk of child-onset Crohn's disease among Victorian children born 1983–1998: a birth cohort study. *Inflamm Bowel Dis* 2009;**15**:858–66.

20. Calkins BM. A meta-analysis of the role of smoking in inflammatory bowel disease. *Dig Dis Sci* 1989;**34**:1841–54.
21. Danese S, Sans M, Fiocchi C. Inflammatory bowel disease: the role of environmental factors. *Autoimmun Rev* 2004;**3**:394–400.
22. http://www.statistikbanken.dk: 2009.
23. Jakobsen C, Paerregaard A, Munkholm P, Faerk J, Lange A, Andersen J, et al. Pediatric inflammatory bowel disease: Increasing incidence, decreasing surgery rate, and compromised nutritional status: A prospective population-based cohort study 2007–2009. *Inflamm Bowel Dis* 2011;**17**:2541–50.
24. Vind I, Riis L, Jess T, Knudsen E, Pedersen N, Elkjaer M, et al. Increasing incidences of inflammatory bowel disease and decreasing surgery rates in Copenhagen City and County, 2003–2005: a population-based study from the Danish Crohn colitis database. *Am J Gastroenterol* 2006;**101**:1274–82.
25. Hansen TS, Jess T, Vind I, Elkjaer M, Nielsen MF, Gamborg M, et al. Environmental factors in inflammatory bowel disease: A case-control study based on a Danish inception cohort. *Journal of Crohns and Colitis* 2011;**5**:577–84.
26. Halfvarson J, Jess T, Magnuson A, Montgomery SM, Orholm M, Tysk C, et al. Environmental factors in inflammatory bowel disease: a co-twin control study of a Swedish-Danish twin population. *Inflamm Bowel Dis* 2006;**12**:925–33.
27. Vind I, Riis L, Jespersgaard C, Jess T, Knudsen E, Pedersen N, et al. Genetic and environmental factors as predictors of disease severity and extent at time of diagnosis in an inception cohort of inflammatory bowel disease, Copenhagen County and City 2003–2005. *Journal of crohn's and colitis* 2008;**2**:162–9.
28. Kamper-Jorgensen F, Enevoldsen B, Michelsen N. Friis-Hasche E (Social classifications. 1. Review, concepts and criteria of choice). *Ugeskr Laeger* 1980;**142**:472–7.
29. Brant SR, Wang MH, Rawsthorne P, Sargent M, Datta LW, Nouvet F, et al. A population-based case-control study of CARD15 and other risk factors in Crohn's disease and ulcerative colitis. *Am J Gastroenterol* 2007;**102**:313–23.
30. Geerling BJ, Dagnelie PC, Badart-Smook A, Russel MG, Stockbrugger RW, Brummer RJ. Diet as a risk factor for the development of ulcerative colitis. *Am J Gastroenterol* 2000;**95**:1008–13.
31. Jarnerot G, Jarnmark I, Nilsson K. Consumption of refined sugar by patients with Crohn's disease, ulcerative colitis, or irritable bowel syndrome. *Scand J Gastroenterol* 1983;**18**:999–1002.
32. Persson PG, Ahlbom A, Hellers G. Diet and inflammatory bowel disease: a case-control study. *Epidemiology* 1992;**3**:47–52.
33. Sakamoto N, Kono S, Wakai K, Fukuda Y, Satomi M, Shimoyama T, et al. Dietary risk factors for inflammatory bowel disease: a multicenter case-control study in Japan. *Inflamm Bowel Dis* 2005;**11**:154–63.
34. Amre DK, D'Souza S, Morgan K, Seidman G, Lambrette P, Grimard G, et al. Imbalances in dietary consumption of fatty acids, vegetables, and fruits are associated with risk for Crohn's disease in children. *Am J Gastroenterol* 2007;**102**:2016–25.
35. Reif S, Klein I, Lubin F, Farbstein M, Hallak A, Gilat T. Pre-illness dietary factors in inflammatory bowel disease. *Gut* 1997;**40**:754–60.
36. Mayberry JF, Rhodes J, Newcombe RG. Increased sugar consumption in Crohn's disease. *Digestion* 1980;**20**:323–6.
37. Andersen V, Olsen A, Carbonnel F, Tjoenneland A, Vogel U. *Diet and risk of inflammatory bowel disease Dig Liver Dis* 2012;**44**:185–94.
38. Tragnone A, Valpiani D, Miglio F, Elmi G, Bazzocchi G, Pipitone E, et al. Dietary habits as risk factors for inflammatory bowel disease. *Eur J Gastroenterol Hepatol* 1995;**7**:47–51.
39. Riordan AM, Ruxton CH, Hunter JO. A review of associations between Crohn's disease and consumption of sugars. *Eur J Clin Nutr* 1998;**52**:229–38.
40. Persson PG, Leijonmarck CE, Bernell O, Hellers G, Ahlbom A. Risk indicators for inflammatory bowel disease. *Int J Epidemiol* 1993;**22**:268–72.
41. Gilat T, Hacohen D, Lilos P. Langman MJ: Childhood factors in ulcerative colitis and Crohn's disease. *An international cooperative study. Scand J Gastroenterol* 1987;**22**:1009–24.
42. Wurzelmann JI, Lyles CM, Sandler RS. Childhood infections and the risk of inflammatory bowel disease. *Dig Dis Sci* 1994;**39**:555–60.
43. Mackner LM, Clough-Paabo E, Pajer K, Lourie A, Crandall WV. Psychoneuroimmunologic factors in inflammatory bowel disease. *Inflamm Bowel Dis* 2011;**17**:849–57.
44. Dekkers JC, Geenen R, Godaert GL, Glaudemans KA, Lafeber FP, van Doornen LJ, et al. Experimentally challenged reactivity of the hypothalamic pituitary adrenal axis in patients with recently diagnosed rheumatoid arthritis. *J Rheumatol* 2001;**28**:1496–504.
45. Calcagni E, Elenkov I. Stress system activity, innate and T helper cytokines, and susceptibility to immune-related diseases. *Ann N Y Acad Sci* 2006;**1069**:62–76.
46. Mackner L, Pajer K, Glaser R, Crandall W: Relationships between depression, cytokines and cortisol in pediatric inflammatory bowel disease; 2010, p s303.
47. Lerebours E, Gower-Rousseau C, Merle V, Brazier F, Debeugny S, Marti R, et al. Stressful life events as a risk factor for inflammatory bowel disease onset: A population-based case-control study. *Am J Gastroenterol* 2007;**102**:122–31.
48. Li J, Norgard B, Precht DH, Olsen J. Psychological stress and inflammatory bowel disease: a follow-up study in parents who lost a child in Denmark. *Am J Gastroenterol* 2004;**99**:1129–33.
49. Mendeloff AI, Monk M, Siegel CI, Lilienfeld A. Illness experience and life stresses in patients with irritable colon and with ulcerative colitis An epidemiologic study of ulcerative colitis and regional enteritis in Baltimore, 1960–1964. *N Engl J Med* 1970;**282**:14–7.
50. Bitton A, Sewitch MJ, Peppercorn MA. deB Edwardes MD, Shah S, Ransil B et al: Psychosocial determinants of relapse in ulcerative colitis: a longitudinal study. *Am J Gastroenterol* 2003;**98**:2203–8.
51. Bitton A, Dobkin PL, Edwardes MD, Sewitch MJ, Meddings JB, Rawal S, et al. Predicting relapse in Crohn's disease: a biopsychosocial model. *Gut* 2008;**57**:1386–92.
52. Levenstein S, Prantera C, Varvo V, Scribano ML, Andreoli A, Luzi C, et al. Stress and exacerbation in ulcerative colitis: a prospective study of patients enrolled in remission. *Am J Gastroenterol* 2000;**95**:1213–20.
53. Vidal A, Gomez-Gil E, Sans M, Portella MJ, Salamero M, Pique JM, et al. Life events and inflammatory bowel disease relapse: a prospective study of patients enrolled in remission. *Am J Gastroenterol* 2006;**101**:775–81.
54. Aamodt G, Bukholm G, Jahnsen J, Moum B, Vatn MH. The association between water supply and inflammatory bowel disease based on a 1990–1993 cohort study in southeastern Norway. *Am J Epidemiol* 2008;**168**:1065–72.
55. Declercq C, Gower-Rousseau C, Vernier-Massouille G, Salleron J, Balde M, Poirier G, et al. Mapping of inflammatory bowel disease in northern France: Spatial variations and relation to affluence. *Inflamm Bowel Dis* 2010;**16**:807–12.
56. Kugathasan S, Judd RH, Hoffmann RG, Heikenen J, Telega G, Khan F, et al. Epidemiologic and clinical characteristics of children with newly diagnosed inflammatory bowel disease in Wisconsin: a statewide population-based study. *J Pediatr* 2003;**143**:525–31.