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Environmental factors associated with biological use and surgery in inflammatory bowel disease

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Abstract

Background and Aim: While major efforts were made studying the complex etiology of inflammatory bowel disease (IBD) including environmental factors, less is known about underlying causes leading to the heterogeneous and highly variable course of disease. As cigarette smoking cessation is the best-known environmental factor with beneficial effect in Crohn's disease (CD), more exposome factors are likely involved. Further insights into the role of the exposome in heterogeneity of disease might not only further knowledge of underlying pathways, but also allow for better risk stratification.
Methods: Seven hundred twenty-eight IBD patients completed the validated Groningen IBD Environmental Questionnaire, collecting exposome data for 93 exposome factors. Associations with disease course, that is, for need for surgery or biological therapy, were evaluated using univariate and multivariate-adjusted logistic regression modeling.
Results: No significant associations were seen after Bonferroni correction. However, 11 novel exposome factors were identified with $P < 0.05$. Two factors were associated with course of CD and ulcerative colitis (UC): beer (CD OR0.3/UC OR0.3) and cannabis (0.5/2.2). While in CD, carpet flooring (0.5) was associated with biological use, and four factors were associated with surgery: working shifts (1.8), appendectomy (2.4), frequent tooth brushing (2.8), and large household size (0.1). For UC, migrants more often required biologicals (10.2). Childhood underweight (3.4), amphetamine use (6.2), and cocaine use (4.8) were associated with surgery. Five factors were replicated.
Conclusions: We identified 16 environmental factors nominally associated with biological use and surgery in established IBD. These new insights form an important stepping stone to guide research on biological pathways involved, risk stratification, tailor-made interventions, and preventive strategies in IBD.

Ethical approval: This study was approved by the medical ethics committee of the University Medical Center Groningen, the Netherlands (no. 2017.138).

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Introduction

Inflammatory bowel disease (IBD) consists of Crohn's disease (CD) and ulcerative colitis (UC), both chronic and relapsing inflammatory diseases of the gastrointestinal tract.[1] While major efforts have been made studying the complex etiology of IBD with a role for the genome, microbiome, and exposome, as a measure of environmental exposures during one's lifetime, less is known about the underlying causes leading to the heterogeneous and highly variable course of disease.[2,3] Whereas mild immunomodulating therapy is effective in some patients, others progress to a more severe disease that requires biological therapy. Even, up to 80% of CD patients eventually need a surgical resection of affected bowel segments.[1] The increased intensity of treatment has led to a global decrease of IBD-related surgery and mortality. Yet along with the known importance of the exposome in disease etiology, this has generated significant interest into the potential effects of the exposome in disease course, its underlying biological pathways and eventually the possibility to modify the exposome to influence disease course.[4]

As in disease etiology, smoking is probably the best known exposome factor involved in disease course, with a divergent effect for CD and UC.[5] Among few available studies, a previous trial showed the potential of personalized lifestyle interventions, with a decrease of flares in CD patients aided to quit smoking.[6] Likewise, increased physical activity, not only associated with an improved quality of life but also a decreased risk of active disease.[7] However, as with disease etiology, it is likely that many more yet to be identified exposome factors are involved in disease course. Despite its potential desirable effects in management of IBD, modifiable exposome factors have not been systematically studied in the past.[4] Therefore, their potential application remains unknown.

In the current study, we aim to identify (modifiable) exposome factors involved in course of IBD, possibly leading to a better understanding of underlying mechanisms, risk stratification, and potential targets for implementation of personalized lifestyle interventions in IBD. The effect of a wide range of exposome factors was examined using a validated questionnaire in a large cohort of IBD patients.[8,9]

Materials and methods

Study population. We performed a case-only cross-sectional study embedded within the longitudinal 1000IBD cohort of the University Medical Center Groningen, a tertiary referral center in the Netherlands.[9] Patients enrolled in the 1000IBD cohort are prospectively followed while detailed information is collected concerning clinical characteristics as well as in-depth subphenotypes and molecular data, as described in detail elsewhere.[9] An overview of the process of inclusion of patients in this study is shown in Figure 1.[8]

Data collection

Exposome data. The web-based Groningen IBD Environmental Questionnaire (GIEQ) was used to obtain environmental data from all patients.[8] This questionnaire was previously validated by our group, and detailed information concerning the development of the GIEQ and its validation is published elsewhere.[8] Next, patients of the 1000IBD cohort were asked to enroll in the current study from 2016 to 2017, after which the data collection was finalized in March 2018. During this period, 728 patients completed the GIEQ. For patients without access to a computer, a

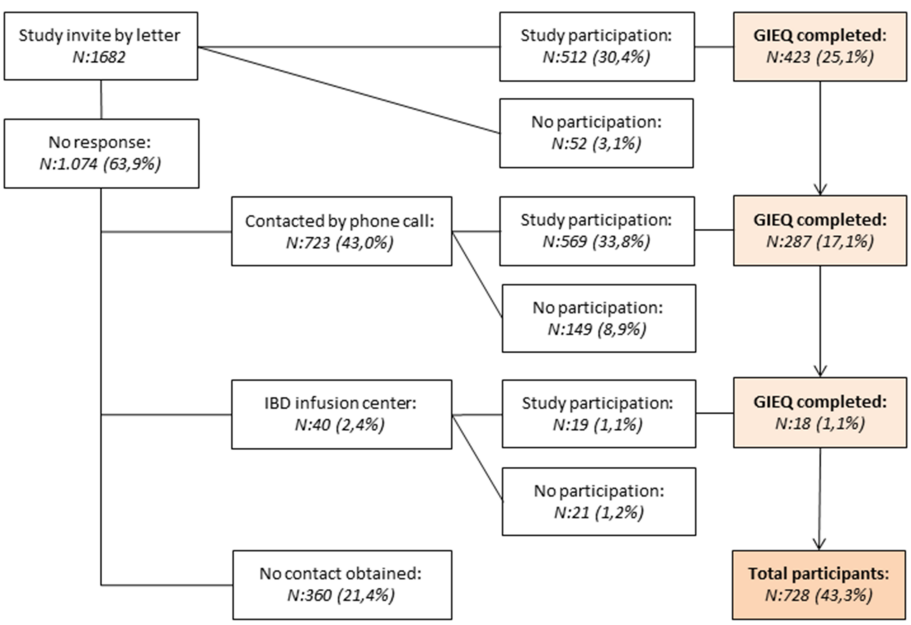

Figure 1 Overview of study inclusion strategies and participation. GIEQ, Groningen IBD Environmental Questionnaire; IBD, inflammatory bowel disease.

paper version of the GIEQ was made available (*n*: 82, 11.3%). Out of the 844 items within the GIEQ, 337 (39.7%) items, comprising of 93 different exposome factors during childhood, the present situation or independent of timing of disease development was suitable to examination of their potential role in course of IBD.

Clinical data. As part of the 1000IBD cohort, enrolled patients are prospectively followed by their treating IBD specialist at the outpatient IBD clinic of the University Medical Center Groningen where extensive information on disease diagnosis as well as disease course is collected. The primary outcome measures were determined to be the ever need for IBD-related surgery (consisting of abscess drainage, intestinal resection due to therapy resistance, fistula or stricture formation or developed malignant disease, and strictureplasty) and the ever need for biological therapy (consisting of infliximab, adalimumab, golimumab, ustekinumab, and vedolizumab).

Data analysis. First, to rule out potential selection-bias, baseline characteristics between participating and nonparticipating patients were compared using univariate statistical testing (Table S1). For categorical variables, χ^2-square tests were used. Continuous variables were compared between groups using either Mann–Whitney *U* tests or one-way ANOVA tests, based on variable distribution. To examine the role of personality, the data reduction method "principal component analysis" was run on the 64 personality-related questions, forming two personality traits to be studied in more detail: "neuroticism" and "conscientiousness." Based on the median, patients were stratified into a low or high score of each trait. With these components, 65.1% of total data variability was described, while all model assumptions were met (Table S2).[10]

Next, all environmental factors were evaluated for their association with either surgery or biological therapy using aforementioned univariate testing. In total, 52 factors reached a borderline *P* value of < 0.10 in univariate testing and were selected for multivariate testing (Fig. 2). Binary logistic regression (LR) modeling was used to estimate the odds ratio (OR) and 95% confidence

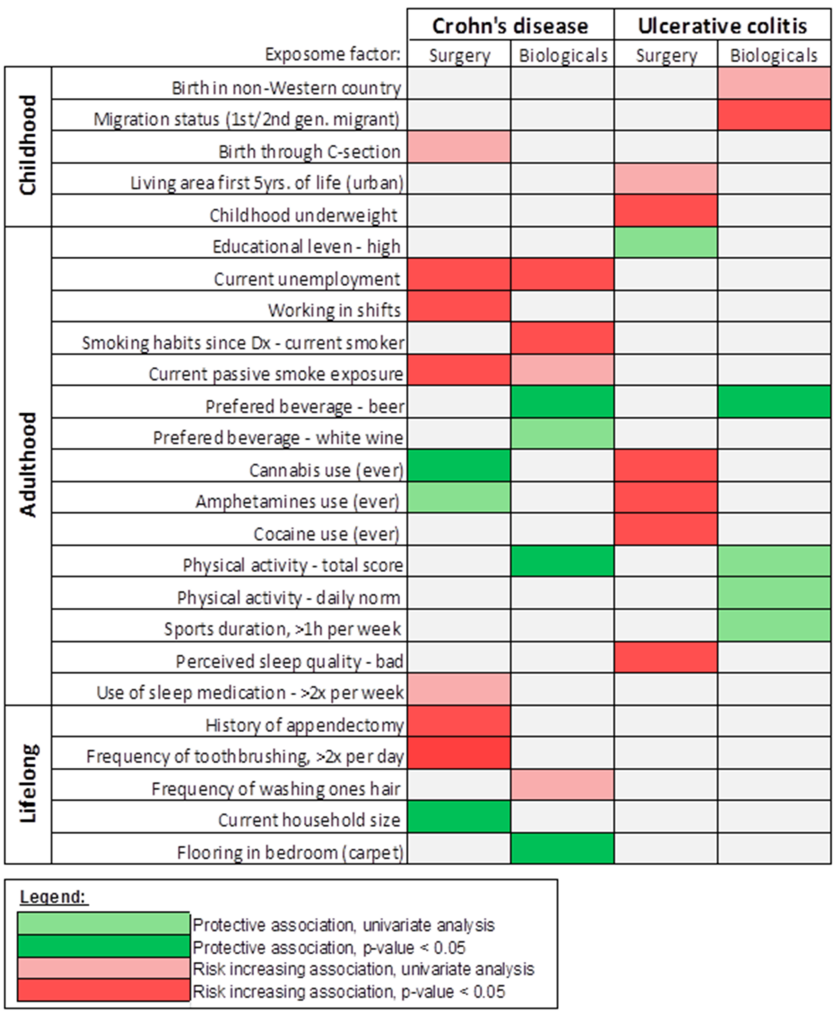

Figure 2 Heat map of nominally significant exposome factors.

Table 1 Baseline characteristics of IBD patients

Characteristic		IBD† *N*: 728	CD *N*: 349	UC *N*: 347
Age	Median (IQR)	50 (37–61)	48 (36–60)	51 (38–62)
Gender, female	*n* (%)	443 (60.9)	238 (68.2)	188 (54.2)
Disease duration	Median (IQR)	14 (8–21)	14 (8–22)	13 (8–21)
History of smoking				
Never smoked	*n* (%)	364 (50.0)	151 (43.3)	204 (58.8)
Former smoker	*n* (%)	261 (35.9)	121 (34.7)	118 (34.0)
Active smoker	*n* (%)	103 (14.1)	77 (22.1)	25 (7.2)
Need for surgery	*n* (%)	261 (35.9)	187 (54.0)	61 (17.7)
Need for biologicals	*n* (%)	256 (35.4)	184 (52.7)	75 (21.6)

CD, Crohn's disease; IBD, inflammatory bowel disease; IQR, interquartile range; *n*, number; UC, ulcerative colitis.
†Describing the full patient cohort, including 32 patients with IBD-unclassified.

interval (95%CI) for each independent exposure, while adjusting for the possible confounding effects of gender, age (in years), disease duration (in years), and smoking status (never/former/current), using the "Enter" method. A P value of < 0.05 was considered nominally significant. The Bonferroni method, based on the multivariate testing of 52 factors, was used to determine a statistical significance threshold, correcting for multiple testing, of a P value $< 9.62 \times 10^{-4}$. Statistical analyses were performed using SPSS statistical software Version 23 (SPSS Inc., Chicago, Illinois, USA).

Ethical consideration. The protocol of described study is in line with the ethical guidelines of the 1975 Declaration of Helsinki as reflected in approval by the medical ethical review board of the University Medical Center Groningen, the Netherlands (approval no.: 2017.138, date of approval 19-9-2017) for whom a returned questionnaire was considered as an informed consent.

Results

In total, 1682 patients were invited to participate, of whom 728 completed the GIEQ (completion rate 40.1%, Fig. 1). Compared with nonparticipating patients, participants were more often female and of Western origin (Table S1). Also, participants were shown to need IBD-related surgery more often than non-participants (36.0% *vs* 29.7%). Baseline characteristics of all participants are shown in Table 1. Overall, 261 (35.9%) patients required surgery while 256 (35.4%) patients required biological therapy during their disease course, with the highest rate of need for surgery (*N*:187, 54.0%) or biological therapy (*N*:184, 52.7%) seen in CD patients. Ninety-three exposome factors were examined in relation to biological use or surgery in CD as well as UC. All nominal significant factors are shown in Figure 3 and discussed below. Nonassociated factors with P values > 0.05 are

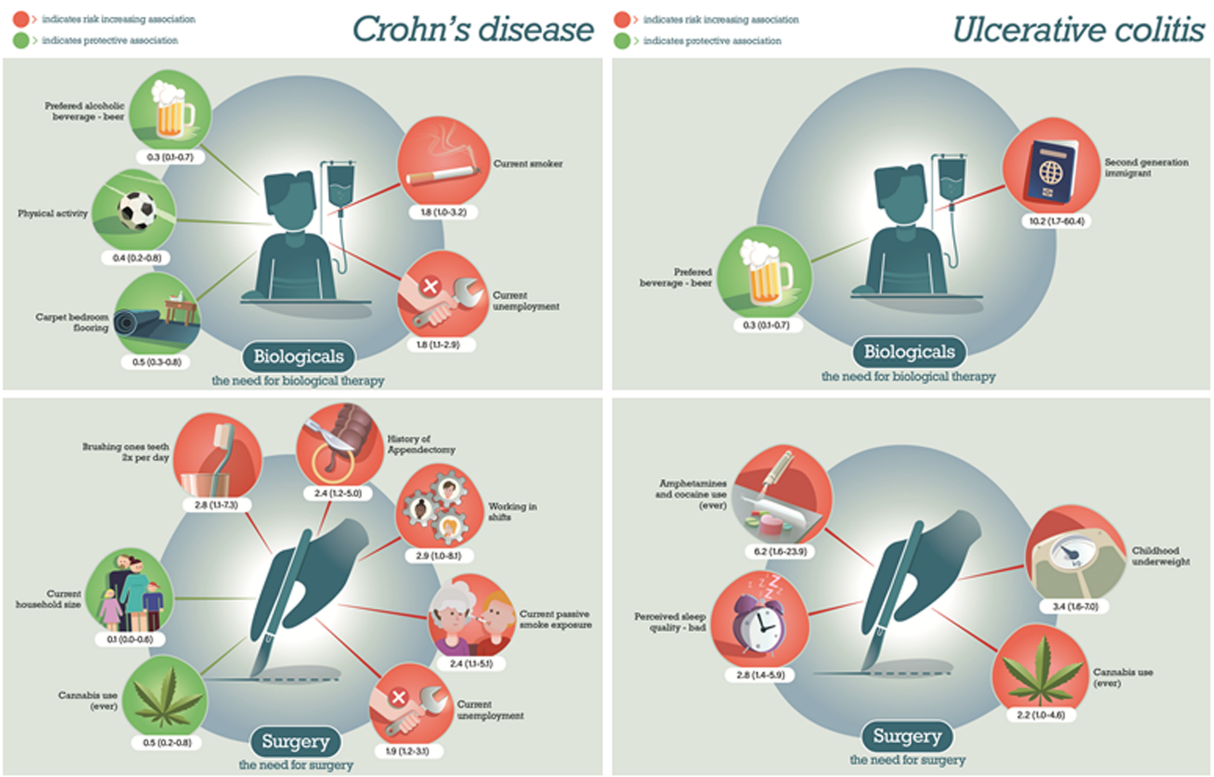

Figure 3 Overview of all exposome factors associated with need for biologicals or surgery in Crohn's disease and ulcerative colitis. *All P values < 0.05.

shown in Table S3. After Bonferroni correction for multiple testing, none of the associated exposome factors remained statistically significant for their association with course of IBD (Fig. 2).

Childhood exposures. In total, 21 childhood-related exposures were examined. While no associations were seen with course of CD, several exposures showed a nominally significant association to biological use or surgery in UC (Table 2). Patients of non-Western origin were more often used biological therapy (OR 10.2; 95%CI 1.7–60.4). UC patients describing their childhood living area as urban were also more likely to need surgery than those living in rural regions (OR 2.3; 95%CI 1.1–4.5). Finally, being underweight during childhood was more often seen in patients that underwent surgery (OR 3.4; 95%CI 1.6–7.0).

Adult exposures. Next, 48 adulthood-related factors were examined (Table 3). In CD and UC, 13 and 7 factors, respectively, showed a nominally significant association with biological use or surgical intervention. In CD, current unemployment was more often seen in patients that underwent surgery (OR 1.9; 95%CI 1.2–3.1) or biological therapy (OR 1.8; 95%CI 1.1–2.9), while no associations were seen for UC (P values ≥ 0.19). CD patients, who were used to work in shifts however, had an approximately threefold increased risk of surgery (OR 2.9; 95%CI 1.0–8.1). Different factors concerning current lifestyle were also associated with course of disease. In CD, current cigarette smoking was more often seen in patients requiring biological therapy (OR 1.8; 95%CI 1.0–3.2) while regular passive smoke exposure increased risk of surgery (OR 2.4; 95% CI 1.1–5.1). The use of cannabis showed a divergent effect, with a reduced in risk of surgery in CD (OR 0.5; 95%CI 0.2–0.8), compared with an approximately twofold increased risk of surgery in UC (OR 2.2; 95%CI 1.0–4.6). The use of amphetamines (OR 6.2; 95%CI 1.6–23.9) as well as cocaine (OR 4.8; 95%CI 1.1–20.0) showed a similar effect in UC but not CD. Although the average amount of alcohol use per day was not associated with biological use or surgery neither for CD nor UC (all P values > 0.30, Table S3), patients choosing beer as preferred alcoholic beverage less often needed biological therapy in CD (OR 0.5; 95%CI 0.2–1.0) and UC (OR 0.3; 95%CI 0.1–0.7). CD patients who had a high physical activity score, however, less often needed biologicals (OR 0.4; 95%CI 0.2–0.8) while abiding to the advised daily activity norm (exercising at least 30 min, 5 days per week) showed no association.[11] Finally, a perceived poor sleep quality was reported by 19.6% of patients with IBD, especially more often in UC patients that underwent surgical intervention (OR 2.8; 95%CI 1.4–5.9) while no associations were observed for duration of sleep or the use of sleep-related medications (all P values > 0.05).

Lifelong exposures. After examining 24 factors unrelated to life stage, no association was seen in UC (Table 4). Different hygiene-related factors were associated with course of CD. While patients brushing their teeth greater than twice per day showed an increased risk of surgery (OR 2.8; 95%CI 1.1–7.3), no effect was seen for the use of mouthwash. Additional adjusting of the LR model for the potential confounding effect of dental state did not alter these findings. A large household size showed an approximately 10-fold reduction in risk for surgical intervention in CD (OR 0.1; 95%CI 0.0–0.6), as the presence of room-wide carpet did for the need for biologicals (OR 0.5; 95%CI 0.3–0.8). A previous appendectomy was seen more often in CD patients underwent IBD-related surgery (OR 2.4; 95%CI 1.2–5.0).

Discussion

In this study, 93 exposures were systematically evaluated for their role in the need for biological therapy and surgery in IBD. Although no statistically significant associations were found, we identified 11 potential novel nominal associations. We also replicated five previously described factors, indicating robustness of these associations. An overview of all nominal associations is shown in Figure 3.

In contrast to disease etiology, childhood-related exposures seem to play less of a role in course of IBD.[3] As differences in disease phenotypes have been previously described, this is the first study describing more biological use in non-Western migrants in UC, but not CD, most likely due to differential inherent responses to environmental triggers.[12,13] Whereas childhood obesity was previously related to several autoimmune diseases including CD, this is the first study associating a poor nutritional status during childhood to a higher risk of surgery later in life in UC patients.[14,15]

Current adulthood-related factors seem to hold stronger associations with the use of biologicals and need for surgery. In line with Spekhorst *et al*,[16] we show a higher risk of complicated disease course in CD in those who are unemployed. Among CD patients currently employed, working shifts was associated with a threefold increased risk of surgical intervention. As working shifts inevitably leads to sleep disruption, a role in not only etiology of IBD but also its course seems plausible.[17,18] The same line of reasoning holds for the shown increased prevalence of poor sleep quality in those requiring surgery, as sleep impairment was previously associated with subclinical inflammation, alterations of gut microbiota, and disease activity.[19–21] The risk-increasing effect of active as well as passive cigarette smoking shown in CD is in line with previous studies.[5,6,22] We found smaller effect sizes than previously reported, which might be due to the decreased number of active smokers in our cohort compared with previous cohorts, following the global decrease of smoking in IBD patients.[23] To our knowledge, this is the first study describing the opposite effect of cannabis in UC and CD. IBD patients were previously shown to be more likely to ever use cannabis than controls. Another small Israeli study showed an improved quality of life and decreased surgery rate.[24–26] We also found and decreased risk for surgery in CD, but an increasing risk in UC. Similar associations are shown for amphetamine and cocaine use. Further research is needed to replicate our findings and study these associations in more detail. The role of alcohol consumption in course of IBD has been scarcely studied in the past.[27] Whereas previous studies have shown a potential increase of symptoms in UC alone, this is the first study examining its role in biological use, showing no association for total alcohol consumption, while beer consumption was seen more often in patients with no history of biological treatment.[28,29] In line with previous studies, this study shows a beneficial effect for physical activity in CD as well as UC.[7,30] As a single work-out was

Table 2 Childhood-related factors and the need for biological therapy and risk of surgery in patients with inflammatory bowel disease

	Inflammatory bowel disease				Crohn's disease				Ulcerative colitis			
a. Childhood-related factors and the need for biological therapy in patients with inflammatory bowel disease												
	No biologics	Biologics	MV-adj. LR model		No biologics	Biologics	MV-adj. LR model		No biologics	Biologics	MV-adj. LR model	
	n; %	*n*; %	OR (95%CI)	*P*	*n*; %	*n*; %	OR (95%CI)	*P*	*n*; %	*n*; %	OR (95%CI)	*P*
Birth non-Western country	**5; 1.1**	**10; 3.9**	**3.7 (1.2–11.1)**	**0.02**	2; 1.3	7; 3.8	3.3 (0.7–16.5)	0.14	**3; 1.1**	**3; 4.9**	3.8 (0.7–19.7)	0.12
Migration status												
Dutch native	**456; 97.6**	**235; 92.2**	Reference	**0.004***	154; 96.9	173; 93.0	Reference	0.13*	**279; 98.2**	**54; 88.5**	Reference	**0.012***
Second gen. migrant	**6; 1.3**	**10; 3.9**	2.5 (0.9–7.2)	0.09	3; 1.9	6; 3.2	1.4 (0.3–5.8)	0.68	**2; 0.7**	**4; 6.6**	**10.2 (1.7–60.4)**	**0.011**
First gen. migrant	**5; 1.1**	**10; 3.9**	**3.8 (1.3–11.5)**	**0.017**	2; 1.3	7; 3.8	3.4 (0.7–16.8)	0.14	3; 1.1	3; 4.9	4.1 (0.8–21.7)	0.095
Birth through C-section	14; 4.1	8; 3.3	0.5 (0.2–1.3)	0.16	4; 2.7	8; 4.4	1.2 (0.3–4.4)	0.74	11; 4.1	0; 0.0		
Living area first 5 years												
Rural	224; 51.0	126; 53.4	Reference	0.57*	82; 54.7	95; 55.2	Reference	0.90*	129; 48.7	27; 48.2	Reference	0.56*
Large village/small city	126; 28.7	64; 27.1	0.8 (0.5–1.1)	0.18	35; 23.3	41; 23.8	0.8 (0.5–1.5)	0.51	85; 32.1	21; 37.5	1.1 (0.6–2.1)	0.80
Urban	89; 20.3	46; 19.5	1.0 (0.6–1.5)	0.83	33; 22.0	36; 20.9	1.0 (0.6–1.8)	0.97	51; 19.2	8; 14.3	0.7 (0.3–1.7)	0.44
Childhood underweight	46; 9.9	23; 9.1	1.0 (0.6–1.7)	0.94	14; 8.9	15; 8.1	1.1 (0.5–2.3)	0.90	30; 10.6	6; 9.8	1.0 (0.4–2.5)	0.96
b. Childhood-related factors and risk of surgery in patients with inflammatory bowel disease												
	No surgery	Surgery	MV-adj. LR model		No surgery	Surgery	MV-adj. LR model		No surgery	Surgery	MV-adj. LR model	
	n; %	*n*; %	OR (95%CI)	*P*	*n*; %	*n*; %	OR (95%CI)	*P*	*n*; %	*n*; %	OR (95%CI)	*P*
Birth non-Western country	9; 1.9	6; 2.3	1.6 (0.5–4.6)	0.40	6; 3.7	3; 1.6	0.6 (0.1–2.7)	0.49	3; 1.1	3; 4.0	3.5 (0.7–18.1)	0.13
Migration status												
Dutch native	448; 96.1	248; 95.2	Reference	0.23*	154; 93.9	176; 95.7	Reference	0.69*	265; 97.4	70; 93.3	Reference	0.09*
Second gen. migrant	9; 1.9	7; 2.7	1.7 (0.6–4.7)	0.32	4; 2.4	5; 2.7	1.4 (0.4–5.7)	0.63	4; 1.5	2; 2.7	2.1 (0.4–12.3)	0.39
First gen. migrant	9; 1.9	6; 2.3	1.6 (0.5–4.7)	0.40	6; 3.7	3; 1.6	0.6 (0.1–2.7)	0.49	3; 1.1	3; 4.0	3.6 (0.7–18.6)	0.12
Birth through C-section	21; 4.8	5; 2.0	0.5 (1.2–1.3)	0.17	**9; 5.8**	**3; 1.7**	0.4 (0.1–1.7)	0.23	9; 3.5	2; 2.9	0.9 (0.2–4.3)	0.87
Living area first 5 years												
Rural	228; 52.4	125; 51.7	Reference	0.24*	85; 54.5	95; 56.2	Reference	0.69*	**128; 51.0**	**29; 40.8**	Reference	**0.03***
Large village/small city	130; 29.9	61; 25.2	0.9 (0.6–1.3)	0.55	39; 25.0	37; 21.9	0.9 (0.5–1.6)	0.75	**84; 33.5**	**23; 32.4**	1.2 (0.6–2.2)	0.62
Urban	77; 17.7	56; 23.1	1.4 (0.9–2.1)	0.13	32; 20.5	37; 21.9	0.9 (0.5–1.7)	0.73	**39; 15.5**	**19; 26.8**	**2.3 (1.1–4.5)**	**0.02**
Childhood underweight	**36; 7.7**	**34; 13.2**	**1.8 (1.0–3.0)**	**0.03**	11; 6.7	18; 10.0	1.2 (0.5–2.9)	0.68	**21; 7.7**	**75; 21.3**	**3.4 (1.6–7.0)**	**0.001**

P indicates *P* value of MV-adj. LR model. "*" indicates *P*-trend. All associations with *P* value < 0.05 are shown in bold.

CI, confidence interval; C-section, cesarean section; LR, logistic regression; MV, multivariate; *n*, number; OR, odds ratio.

Table 3 Adulthood-related factors and the need for biological therapy and risk of surgery in patients with inflammatory bowel disease

	Inflammatory bowel disease				Crohn's disease				Ulcerative colitis			
a. Adulthood-related factors and the need for biological therapy in patients with inflammatory bowel disease												
	No biologics	Biologics	MV-adj. LR model		No biologics	Biologics	MV-adj. LR model		No biologics	Biologics	MV-adj. LR model	
	n; %	*n*; %	OR (95%CI)	*P*	*n*; %	*n*; %	OR (95%CI)	*P*	*n*; %	*n*; %	OR (95%CI)	*P*
Educational level												
Lower level	70; 15.6	35; 13.9	Reference	0.30*	28; 18.2	22; 12.0	Reference	0.83*	40; 14.8	11; 18.6	Reference	0.14*
Average level	164; 36.5	103; 41.0	0.9 (0.5–1.5)	0.64	55; 35.7	79; 42.9	1.3 (0.6–2.6)	0.47	96; 35.4	20; 33.9	0.6 (0.2–1.4)	0.22
High level	215; 47.9	113; 45.0	0.8 (0.5–1.3)	0.34	71; 46.1	83; 45.1	1.2 (0.6–2.4)	0.65	135; 49.8	28; 47.5	0.5 (0.2–1.2)	0.10
Current unemployment	**261; 58.5**	**127; 50.8**	**1.8 (1.3–2.6)**	**0.001**	68; 45.0	95; 51.6	**1.8 (1.1–2.9)**	**0.016**	105; 38.6	25; 42.4	1.5 (0.8–2.8)	0.19
Working in shifts	26; 10.0	14; 11.3	1.0 (0.5–2.0)	0.99	10; 12.0	9; 10.2	0.7 (0.3–2.0)	0.51	15; 9.0	5; 15.6	1.8 (0.6–5.6)	0.28
Active smoking at Dx	**94; 24.2**	**73; 33.0**	**1.8 (1.2–2.6)**	**0.004**	49; 35.8	66; 40.0	1.4 (0.8–2.2)	0.20	42; 18.2	5; 10.2	0.6 (0.2–1.6)	0.27
Currently actively smoking	**55; 12.9**	**60; 24.8**	**2.2 (1.4–3.3)**	**2.4×10^{-4}**	30; 20.3	54; 29.7	1.6 (1.0–2.7)	0.07	25; 9.7	4; 7.7	0.7 (0.2–2.2)	0.55
Smoking habits since Dx												
Never smoked	**198; 46.3**	**100; 41.3**	Reference	**0.001***	60; 40.5	68; 37.4	Reference	0.053*	133; 51.8	30; 57.7	Reference	0.23*
Quit smoking pre-Dx	**83; 19.4**	**37; 15.3**	1.2 (0.7–2.0)	0.49	23; 15.5	21; 11.5	1.2 (0.5–2.6)	0.69	49; 19.1	14; 36.9	1.4 (0.6–3.2	0.44
Quit smoking after Dx	**92; 21.5**	**45; 18.6**	1.2 (0.8–2.0)	0.34	35; 23.6	39; 21.4	1.3 (0.7–2.3)	0.40	50; 19.5	4; 7.7	0.4 (0.1–1.3)	0.15
Started/stayed smoking	**55; 12.9**	**60; 24.8**	**2.4 (1.5–3.7)**	**1.7×10^{-4}**	30; 20.3	54; 29.7	**1.8 (1.0–3.2)**	**0.049**	25; 9.7	4; 7.7	0.7 (0.2–2.2)	0.53
Pack years smoked (median; IQR)	9.8; 4–21	8.5; 3–20	1.0 (1.0–1.0)	0.58	11.0; 5–21	8.8; 3–20	1.0 (1.0–1.0)	0.19	9.0; 4–20	5.0; 2–20	1.0 (0.9–1.0)	0.30
Passive smoke exposure, current												
Never	**364; 85.8**	**186; 77.8**	Reference	0.48	**118; 79.7**	**130; 72.6**	Reference	0.77	225; 88.9	50; 96.2	Reference	0.11
Weekly	**29; 6.8**	**31; 13.0**	1.5 (0.9–2.7)	0.14	**10; 6.8**	**29; 16.2**	1.9 (0.9–4.2)	0.11	17; 6.7	1; 1.9	0.2 (0.0–1.7)	0.13
Daily	**31; 7.3**	**22; 9.2**	1.1 (0.6–2.0)	0.86	**20; 13.5**	**20; 11.2**	0.7 (0.3–1.5)	0.33	11; 4.3	1; 1.9	0.3 (0.0–2.8)	0.32
Preferred alcohol: beer	**82; 19.2**	**28; 11.7**	**0.4 (0.2–0.7)**	**0.001**	24; 16.3	21; 11.7	**0.5 (0.2–1.0)**	**0.046**	52; 20.2	5; 9.6	0.3 (0.1–0.7)	0.011
Preferred alcohol: white wine	**29; 6.8**	**29; 12.1**	1.5 (0.8–2.6)	0.17	**8; 5.4**	**22; 12.2**	2.2 (0.9–5.3)	0.066	20; 7.8	6; 11.5	1.6 (0.6–4.3)	0.39
Cannabis; ever use	88; 20.8	61; 25.7	0.8 (0.5–1.2)	0.30	28; 19.4	49; 27.4	1.0 (0.6–1.8)	0.95	55; 21.5	10; 20.0	0.8 ()0.3–1.9)	0.57
Amphetamines; ever use	12; 2.8	10; 4.2	1.0 (0.4–2.4)	0.98	4; 2.8	8; 4.4	1.0 (0.3–3.7)	0.97	8; 3.1	2; 4.0	0.9 (0.2–4.7)	0.91
Cocaine; ever use	12; 2.8	8; 3.4	0.7 (0.3–1.9)	0.50	3; 2.1	7; 3.9	1.0 (0.2–4.2)	0.99	8; 3.1	1; 2.0	0.4 (0.0–3.5)	0.41
Physical activity score												
Low	**118; 29.4**	**88; 40.7**	Reference	**0.001**	45; 31.9	69; 42.9	Reference	**0.006**	**65; 27.0**	**19; 38.8**	Reference	0.49
Medium	**140; 34.8**	**66; 30.6**	**0.6 (0.4–0.9)**	**0.007**	48; 34.0	53; 32.9	0.6 (0.4–1.1)	0.14	**86; 35.7**	**9; 18.4**	0.3 (0.1–0.8)	0.012
High	**144; 35.8**	**62; 28.7**	**0.5 (0.3–0.7)**	**0.001**	48; 34.0	39; 24.2	**0.4 (0.2–0.8)**	**0.006**	**90; 37.3**	**21; 42.9**	0.7 (0.-1.5)	0.39
Physical activity daily norm	**252; 55.7**	**118; 54.6**	**0.7 (0.5–0.9)**	**0.021**	83; 58.9	88; 54.7	0.8 (0.5–1.3)	0.33	**160; 66.4**	**26; 53.1**	0.6 (0.3–1.1)	0.09
Sports duration												
None	220; 55.7	134; 63.2	Reference	**0.023**	88; 64.7	103; 66.0	Reference	0.59	117; 48.8	27; 54.0	Reference	0.29
Less than 1 h/week	44; 11.1	23; 10.8	0.8 (0.5–1.4)	0.46	13; 9.6	15; 9.6	1.0 (0.4–2.4)	0.94	29; 12.1	7; 14.0	0.9 (0.4–2.4)	0.91
More than 1 h/week	131; 33.2	55; 25.9	**0.6 (0.4–0.9)**	**0.024**	35; 25.7	38; 24.4	0.8 (0.5–1.5)	0.57	94; 39.2	16; 32.0	0.7 (0.3–1.4)	0.29
Sports activity score												
Low	221; 55.9	138; 65.1	Reference	**0.009**	88; 64.7	106; 67.9	Reference	0.49	118; 49.2	28; 56.0	Reference	0.18
Medium	31; 7.8	16; 7.5	0.9 (0.4–1.7)	0.64	10; 7.4	9; 5.8	0.9 (0.3–2.4)	0.82	19; 7.9	6; 12.0	1.2 (0.4–3.4)	0.70
High	143; 36.2	58; 27.4	**0.6 (0.4–0.9)**	**0.009**	38; 27.9	41; 26.3	0.8 (0.5–1.4)	0.49	103; 42.9	16; 32.0	0.6 (0.3–1.2)	0.17

(Continues)

Table 3 (Continued)

	Inflammatory bowel disease				Crohn's disease				Ulcerative colitis			
a. Adulthood-related factors and the need for biological therapy in patients with inflammatory bowel disease												
	No biologics	Biologics	MV-adj. LR model		No biologics	Biologics	MV-adj. LR model		No biologics	Biologics	MV-adj. LR model	
	n; %	*n*; %	OR (95%CI)	*P*	*n*; %	*n*; %	OR (95%CI)	*P*	*n*; %	*n*; %	OR (95%CI)	*P*
Perceived sleep quality												
Good	197; 45.9	100; 42.6	Reference	0.45	63; 43.8	74; 42.5	Reference	0.73	121; 46.4	21; 38.9	Reference	0.52
Moderate	149; 34.7	87; 37.0	1.2 (0.8–1.7)	0.36	53; 36.8	61; 35.1	1.0 (0.6–1.6)	0.92	91; 34.9	25; 46.3	1.8 (1.0–3.6)	0.07
Bad	83; 19.3	48; 20.4	1.1 (0.7–1.8)	0.55	28; 19.4	39; 22.4	1.1 (0.6–2.1)	0.68	49; 18.8	8; 14.8	1.1 (0.4–2.6)	0.91
Use of sleep medication												
Never	380; 87.8	196; 82.4	Reference	**0.039**	126; 86.3	142; 80.7	Reference	0.14	232; 88.2	48; 87.3	Reference	0.94
Less than once per week	21; 4.8	13; 5.5	1.2 (0.6–2.5)	0.66	8; 5.5	8; 4.5	1.0 (0.3–2.7)	0.94	13; 4.9	4; 7.3	1.8 (0.6–6.2)	0.32
One to two times per week	10; 2.3	8; 3.4	1.5 (0.6–4.1)	0.40	3; 2.1	6; 3.4	1.3 (0.3–5.5)	0.75	6; 2.3	2; 3.6	2.2 (0.4–11.8)	0.37
Three times or more per week	22; 5.1	21; 8.8	1.9 (1.0–3.6)	0.055	9; 6.2	20; 11.4	1.9 (0.8–4.6)	0.13	12; 4.6	1; 1.8	0.5 (0.1–3.9)	0.50
b. Adulthood-related factors and risk of surgery in patients with inflammatory bowel disease												
	No surgery	Surgery	MV-adj. LR model		No surgery	Surgery	MV-adj. LR model		No surgery	Surgery	MV-adj. LR model	
	n; %	*n*; %	OR (95%CI)	*P*	*n*; %	*n*; %	OR (95%CI)	*P*	*n*; %	*n*; %	OR (95%CI)	*P*
Educational level												
Lower level	63; 13.9	44; 17.4	Reference	0.05*	18; 11.0	33; 18.5	Reference	0.15*	**41; 15.8**	**11; 15.1**	Reference	**0.039***
Average level	164; 36.3	105; 41.5	1.0 (0.6–1.6)	0.88	68; 41.7	68; 38.2	0.7 (0.3–1.5)	0.39	**80; 30.9**	**36; 49.3**	1.5 (0.7–3.4)	0.33
High level	225; 49.8	104; 41.1	0.7 (0.4–1.1)	0.13	77; 47.2	77; 43.3	0.6 (0.3–1.2)	0.16	**138; 53.3**	**26; 35.6**	0.6 (0.3–1.4)	0.25
Current unemployment	**183; 40.7**	**128; 51.0**	**1.6 (1.1–2.2)**	**0.011**	**67; 41.4**	**97; 55.1**	**1.9 (1.2–3.1)**	**0.011**	102; 39.2	30; 41.1	1.2 (0.7–2.2)	0.50
Working in shifts	25; 9.5	15; 12.3	1.5 (0.7–3.0)	0.27	7; 7.4	12; 15.2	**2.9 (1.0–8.1)**	**0.049**	17; 10.9	3; 7.1	0.7 (0.2–2.5)	0.57
Active smoking at Dx	**89; 22.8**	**78; 35.1**	**1.7 (1.1–2.4)**	**0.008**	49; 34.3	66; 41.0	1.1 (0.7–1.9)	0.68	36; 16.2	11; 18.6	1.2 (0.6–2.5)	0.67
Currently actively smoking	66; 15.2	50; 20.9	1.5 (1.0–2.3)	0.06	39; 24.5	46; 26.4	1.1 (0.6–1.9)	0.70	25; 10.1	4; 6.3	0.6 (0.2–1.8)	0.39
Smoking habits since Dx												
Never smoked	**194; 44.6**	**106; 44.4**	Reference	0.18*	60; 37.7	70; 40.2	Reference	0.71*	128; 51.8	35; 55.6	Reference	0.74*
Quit smoking pre-Dx	**91; 20.9**	**30; 12.6**	0.7 (0.4–1.3)	0.26	26; 16.4	18; 10.3	0.7 (0.4–1.2)	0.36	52; 21.1	12; 19.0	1.1 (0.5–2.6)	0.75
Quit smoking after Dx	**84; 19.3**	**53; 22.2**	1.0 (0.6–1.6)	0.98	34; 21.4	40; 23.0	0.7 (0.4–1.3)	0.26	42; 17.0	12; 19.0	1.2 (0.5–2.6)	0.69
Started/stayed smoking	**66; 15.2**	**50; 20.9**	1.4 (0.9–2.2)	0.14	39; 24.5	46; 26.4	0.9 (0.5–1.7)	0.82	25; 10.1	4; 6.3	0.7 (0.2–2.0)	0.46
Pack years smoked (median; IQR)	8.4; 3–19	12.9; 5–21	1.0 (1.0–1.0)	0.44	**8.1; 3–16**	**13.0; 5–21**	1.0 (1.0–1.0)	0.77	8.5; 3–20	8.9; 4–20	1.0 (1.0–1.0)	0.83
Passive smoke exposure, current												
Never	**367; 85.7**	**186; 77.8**	Reference	**0.005**	125; 79.6	125; 72.3	Reference	**0.035**	217; 89.7	59; 92.2	Reference	0.86
Weekly	**35; 8.2**	**25; 10.5**	**1.8 (1.0–3.2)**	**0.044**	17; 10.8	22; 12.7	**2.4 (1.1–5.1)**	**0.022**	15; 6.2	3; 4.7	0.8 (0.2–2.7)	0.66
Daily	**26; 6.1**	**28; 11.7**	**2.2 (1.1–4.0)**	**0.020**	15; 9.6	26; 15.0	1.9 (0.8–4.4)	0.141	10; 4.1	2;3.1	1.1 (0.2–5.2)	0.94
Preferred alcohol: beer	**81; 18.7**	**30; 12.6**	0.7 (0.4–1.2)	0.17	25; 15.8	21; 12.2	0.9 (0.4–1.8)	0.7	48; 19.5	9; 14.1	0.7 (0.3–1.6)	0.39
Preferred alcohol: white wine	42; 9.7	16; 6.7	0.7 (0.4–1.3)	0.24	19; 12.0	11; 6.4	0.5 (0.2–1.3)	0.15	22; 8.9	4; 6.3	0.7 (0.2–2.3)	0.61
Cannabis; ever use	104; 24.1	45; 19.3	0.8 (0.5–1.2)	0.26	**51; 32.5**	**26; 15.4**	**0.5 (0.2–0.8)**	**0.011**	48; 19.6	17; 27.4	**2.2 (1.0–4.6)**	**0.045**

(Continues)

Table 3 (Continued)

b. Adulthood-related factors and risk of surgery in patients with inflammatory bowel disease

	No surgery	Surgery	MV-adj. LR model		No surgery	Surgery	MV-adj. LR model		No surgery	Surgery	MV-adj. LR model	
	n; %	*n*; %	OR (95%CI)	*P*	*n*; %	*n*; %	OR (95%CI)	*P*	*n*; %	*n*; %	OR (95%CI)	*P*
Amphetamines; ever use	15; 3.5	7; 3.0	1.1 (0.4–2.9)	0.80	**10; 6.3**	**2; 1.2**	0.3 (0.1–1.3)	0.10	**5; 2.0**	**5; 8.1**	**6.2 (1.6–23.9)**	**0.008**
Cocaine; ever use	13; 3.0	7; 3.0	1.2 (0.5–3.2)	0.72	7; 4.4	3; 1.8	0.5 (0.1–2.3)	0.38	5; 2.4	4; 6.5	**4.8 (1.1–20.0)**	**0.032**
Physical activity score												
Low	126; 31.4	82; 37.1	Reference	0.13*	49; 33.6	66; 41.5	Reference	0.06*	70; 30.3	15; 25.0	Reference	0.21*
Medium	135; 33.7	72; 32.6	0.8 (0.6–1.3)	0.39	49; 33.6	53; 33.3	0.8 (0.4–1.4)	0.46	77; 33.3	18; 30.0	1.2 (0.5–2.5)	0.69
High	140; 34.9	67; 30.3	0.7 (0.5–1.1)	0.13	48; 32.9	10; 25.2	0.5 (0.3–1.0)	0.05	84; 36.4	27; 45.0	1.6 (0.8–3.3)	0.22
Physical activity daily norm	247; 61.6	124; 56.1	0.7 (0.5–1.01)	0.06	85; 58.2	87; 54.7	0.7 (0.4–1.1)	0.13	149; 64.5	37; 61.7	0.9 (0.5–1.6)	0.74
Sports duration												
None	**215; 54.6**	**142; 65.7**	Reference	**0.02***	85; 60.4	108; 70.6	Reference	0.16	113; 49.1	32; 52.5	Reference	0.81
Less than 1 h/week	**49; 12.4**	**18; 8.3**	0.6 (0.3–1.1)	0.08	16; 11.3	12; 7.8	0.8 (0.3–1.9)	0.57	30; 13.0	6; 9.8	0.7 (0.3–1.9)	0.48
More than 1 h/week	**130; 33.0**	**56; 25.6**	**0.6 (0.4–1.0)**	**0.03**	40; 28.4	33; 21.6	0.7 (0.4–1.2)	0.17	87; 37.8	23; 37.7	0.9 (0.5–1.7)	0.83
Sports activity score												
Low	**219; 55.6**	**143; 66.2**	Reference	**0.016***	87; 61.7	107; 71.2	Reference	0.11*	115; 50.0	32; 52.5	Reference	0.98*
Medium	**33; 8.4**	**14; 6.5**	**0.7 (0.3–1.3)**	**0.27**	8; 5.7	11; 7.2	1.4 (0.5–4.0)	0.54	22; 9.6	3; 4.9	0.5 (0.1–1.7)	0.26
High	**142; 33.0**	**59; 27.3**	**0.6 (0.4–0.9)**	**0.018**	46; 32.6	33; 21.6	0.6 (0.3–1.1)	0.09	93; 40.4	26; 42.6	1.0 (0.6–1.9)	0.96
Perceived sleep quality												
Good	204; 47.7	96; 40.0	Reference	0.16*	66; 43.4	74; 43.8	Reference	0.65*	**121; 49.0**	**21; 30.4**	Reference	**0.004***
Moderate	145; 33.9	92; 38.3	1.3 (0.9–1.9)	0.15	51; 33.6	63; 37.3	1.1 (0.7–1.9)	0.69	**88; 35.6**	**29; 42.0**	**1.9 (1.0–3.7)**	**0.046**
Bad	79; 18.5	52; 21.7	1.3 (0.8–2.1)	0.23	35; 23.0	32; 18.9	0.8 (0.4–1.6)	0.53	**38; 15.4**	**19; 27.5**	**2.8 (1.4–5.9)**	**0.005**
Use of sleep medication												
Never	337; 87.1	203; 83.9	Reference	0.18*	**131; 84.5**	**141; 82.9**	Reference	0.31*	221; 88.8	60; 85.7	Reference	0.33*
Less than once per week	21; 4.8	13; 5.4	1.0 (0.5–2.1)	0.98	**6; 3.9**	**10; 5.9**	1.4 (0.4–4.3)	0.59	14; 5.6	3; 4.3	0.8 (0.2–2.8)	0.69
One to two times per week	14; 3.2	4; 1.7	0.4 (0.1–1.4)	0.16	**8; 5.2**	**1; 0.6**	0.1 (0.0–1.2)	0.066	5; 2.0	3; 4.3	1.9 (0.4–8.7)	0.39
Three times or more per week	21; 4.8	22; 9.1	**2.0 (1.0–3.8)**	**0.04**	**10; 6.5**	**18; 10.6**	2.1 (0.9–4.9)	0.10	9; 3.6	4; 5.7	1.7 (0.5–6.0)	0.40

P indicates *P* value of MV-adj. LR model. Dx indicates diagnosis. "*" indicates *P*-trend. All associations with *P* value < 0.05 are shown in bold.

CI, confidence interval; C-section, cesarean section; IQR, interquartile range; LR, logistic regression; MV, multivariate; *n*, number; OR, odds ratio.

Table 4 Lifelong factors and the need for biological treatment and risk of surgery in patients with inflammatory bowel disease

	Inflammatory bowel disease				Crohn's disease				Ulcerative colitis			
a. Lifelong factors and need for biological treatment in patients with inflammatory bowel disease												
	No biologics	Biologics	MV-adj. LR model		No biologics	Biologics	MV-adj. LR model		No biologics	Biologics	MV-adj. LR model	
	n; %	*n*; %	OR (95%CI)	*P*	*n*; %	*n*; %	OR (95%CI)	*P*	*n*; %	*n*; %	OR (95%CI)	*P*
Vacationing in mountains	43; 10.8	22; 10.0	0.9 (0.5–1.6)	0.73	9; 6.3	17; 10.3	1.7 (0.7–4.0)	0.22	32; 13.6	4; 8.3	0.6 (0.2–1.8)	0.36
Vitamin D supplementation	156; 36.7	88; 37.3	1.1 (0.8–1.6)	0.49	59; 39.9	65; 36.5	1.0 (0.6–1.6)	0.98	92; 36.1	18; 36.0	1.0 (0.5–1.9)	0.95
Use of antibiotics, ever	357; 93.2	206; 94.1	1.1 (0.5–2.2)	0.81	124; 93.9	159; 97.0	2.1 (0.7–6.9)	0.21	213; 92.6	41; 85.4	0.5 (0.2–1.4)	0.21
History of appendectomy	**34; 8.1**	**33; 13.9**	**2.0 (1.2–3.3)**	**0.012**	16; 11.3	30; 16.7	1.7 (0.9–3.4)	0.11	17; 6.7	3; 6.0	1.0 (0.3–3.6)	1.00
Frequency of tooth brushing												
Up to once per day	81; 19.8	44; 19.3	Reference	0.36	32; 22.4	33; 19.1	Reference	0.28*	45; 18.3	9; 19.1	Reference	0.79*
Twice per day	290; 70.7	154; 67.5	0.9 (0.6–1.4)	0.60	96; 67.1	116; 67.1	1.1 (0.6–1.9)	0.93	177; 72.0	33; 70.2	1.0 (0.4–2.3)	0.98
More than twice per day	39; 9.5	30; 13.2	1.5 (0.8–2.8)	0.21	15; 10.5	24; 13.9	1.7 (0.7–3.9)	0.23	24; 9.8	5; 10.6	1.2 (0.4–4.3)	0.73
Frequency of washing hair												
Less than once per week	**18; 3.9**	**12; 4.7**	Reference	0.37*	**5; 3.2**	**9; 4.9**	Reference	0.11*	9; 3.2	2; 3.3	Reference	0.93*
Once to twice per week	**133; 29.0**	**46; 18.1**	0.5 (0.2–1.2)	0.13	**53; 34.0**	**31; 16.8**	0.3 (0.1–1.0)	0.06	75; 26.9	13; 21.3	0.8 (0.2–4.3)	0.80
Twice to four times per week	**204; 44.4**	**130; 51.2**	0.8 (0.4–1.7)	0.54	**68; 43.6**	**96; 51.9**	0.6 (0.2–2.0)	0.43	126; 45.2	31; 50.8	1.1 (0.2–5.4)	0.92
More than four times per week	**104; 22.7**	**66; 26.0**	0.8 (0.3–1.8)	0.55	**30; 19.2**	**49; 26.5**	0.7 (0.2–2.4)	0.55	69; 24.7	15; 24.6	0.9 (0.2–4.5)	0.87
Household size												
Living alone	77; 16.7	49; 19.2	Reference	0.38*	26; 16.6	39; 21.0	Reference	0.20*	46; 16.4	9; 14.8	Reference	0.48*
Two persons	195; 42.3	97; 38.0	0.8 (0.5–1.2)	0.27	60; 38.2	70; 37.6	0.8 (0.4–1.6)	0.57	124; 44.3	22; 36.1	1.0 (0.4–2.3)	0.94
Three to five persons	167; 36.2	100; 39.2	0.8 (0.5–1.3)	0.41	63; 40.1	70; 37.6	0.7 (0.4–1.3)	0.22	97; 34.6	28; 45.9	1.4 (0.6–3.2)	0.47
More than five persons	22; 4.8	9; 3.5	0.6 (0.3–1.5)	0.30	8; 5.1	7; 3.8	0.7 (0.2–2.2)	0.50	13; 4.6	2; 3.3	0.9 (0.2–4.8)	0.88
Bedroom flooring												
Smooth	**284; 63.7**	**184; 74.8**	Reference	**0.02***	**85; 55.6**	**132; 73.3**	Reference	**0.004***	181; 67.3	44; 75.9	Reference	0.39*
Smooth with rug	**16; 3.6**	**6; 2.4**	0.5 (0.2–1.5)	0.23	**5; 3.3**	**6; 3.3**	0.7 (0.2–2.5)	0.60	8; 3.0	0; 0.0		
Room wide carpet	**146; 32.7**	**56; 22.8**	**0.7 (0.5–0.9)**	**0.024**	**63; 41.2**	**42; 23.3**	**0.5 (0.3–0.8)**	**0.004**	80; 29.7	14; 24.1	0.8 (0.4–1.5)	0.452
Character; self-consciousness												
Low score	155; 49.5	75; 46.0	Reference	NA	50; 52.1	57; 47.5	Reference	NA	94; 48.2	16; 43.2	Reference	NA
High score	158; 50.5	88; 54.0	1.3 (0.8–1.9)	0.26	46; 47.9	63; 52.5	1.3 (0.7–2.4)	0.34	101; 51.8	21; 56.8	1.1 (0.5–2.3)	0.77
b. Lifelong factors and risk of surgery in patients with inflammatory bowel disease												
	No surgery	Surgery	MV-adj. LR model		No surgery	Surgery	MV-adj. LR model		No surgery	Surgery	MV-adj. LR model	
	n; %	*n*; %	OR (95%CI)	*P*	*n*; %	*n*; %	OR (95%CI)	*P*	*n*; %	*n*; %	OR (95%CI)	*P*
Vacationing in mountains	**51; 12.7**	**14; 6.3**	**0.4 (0.2–0.8)**	**0.01**	15; 10.1	11; 6.7	0.6 (0.2–1.4)	0.22	33; 14.4	3; 5.4	0.3 (0.1–1.1)	0.065
Vitamin D supplementation	**142; 33.2**	**103; 43.5**	**1.5 (1.1–2.2)**	**0.016**	51; 32.7	73; 42.2	1.4 (0.9–2.3)	0.17	82; 33.6	29; 46.8	1.7 (1.0–3.0)	0.075
Use of antibiotics, ever	**353; 91.7**	**212; 95.9**	0.1 (0.9–4.6)	0.08	132; 95.0	153; 95.6	1.2 (0.4–4.0)	0.78	197; 89.5	57; 96.6	3.0 (0.7–13.6)	0.15
History of appendectomy	**32; 7.5**	**36; 15.5**	**2.1 (1.2–3.6)**	**0.006**	**14; 9.0**	**33; 19.6**	**2.4 (1.2–5.0)**	**0.018**	17; 7.0	3; 4.8	0.6 (0.2–2.3)	0.48
Frequency of tooth brushing												
Up to once per day	**86; 20.6**	**39; 17.4**	Reference	**0.031***	**31; 20.0**	**34; 20.7**	Reference	0.11*	49; 20.8	5; 8.6	Reference	0.071*

(Continues)

Table 4 (Continued)

b. Lifelong factors and risk of surgery in patients with inflammatory bowel disease

	No surgery	Surgery	MV-adj. LR model		No surgery	Surgery	MV-adj. LR model		No surgery	Surgery	MV-adj. LR model	
	n; %	*n*; %	OR (95%CI)	*P*	*n*; %	*n*; %	OR (95%CI)	*P*	*n*; %	*n*; %	OR (95%CI)	*P*
Twice per day	**300; 71.8**	**148; 66.1**	**1.0 (0.7–1.6)**	**0.91**	**115; 74.2**	**100; 61.0**	**0.9 (0.5–1.6)**	**0.62**	165; 69.9	46; 79.3	2.5 (0.9–6.6)	0.075
More than twice per day	**32; 7.7**	**37; 16.5**	**2.2 (1.2–4.2)**	**0.013**	**9; 5.8**	**30; 18.3**	**2.8 (1.1–7.3)**	**0.037**	22; 9.3	7; 12.1	3.0 (0.9–10.9)	0.087
Frequency of washing hair												
Less than once per week	18; 3.9	13; 5.0	Reference	0.40*	4; 2.5	10; 5.5	Reference	0.48*	10; 3.7	2; 2.7	Reference	0.48
Once to twice per week	119; 26.0	61; 23.5	0.7 (0.3–1.6)	0.40	40; 24.8	45; 24.6	0.5 (0.1–2.0)	0.32	72; 27.0	16; 21.3	1.1 (0.2–5.8)	0.88
Twice to four times per week	212; 46.3	124; 47.7	0.9 (0.4–2.1)	0.85	80; 49.7	85; 46.4	0.7 (0.2–2.9)	0.63	119; 44.6	39; 52.0	1.7 (0.4–8.4)	0.51
More than four times per week	109; 23.8	62; 23.8	0.9 (0.4–2.1)	0.89	37; 23	43; 23.5	0.7 (0.2–3.0)	0.65	66; 24.7	18; 24.0	1.4 (0.3–7.3)	0.67
Household size												
Living alone	77; 16.6	51; 19.8	Reference	0.20	27; 16.5	39; 21.4	Reference	**0.036**	45; 16.4	11; 14.9	Reference	0.97
Two persons	189; 40.8	104; 40.3	0.9 (0.6–1.4)	0.72	58; 35.4	72; 39.6	0.9 (0.4–1.7)	0.67	116; 43.1	31; 41.9	1.3 (0.6–3.0)	0.47
Three to five persons	171; 36.9	98; 38.0	1.0 (0.6–1.6)	0.97	68; 41.5	67; 36.8	0.7 (0.4–1.3)	0.28	94; 34.9	31; 41.9	1.5 (0.7–3.3)	0.34
More than five persons	26; 5.6	5; 1.9	**0.2 (0.1–0.7)**	**0.008**	11; 6.7	4; 2.2	**0.1 (0.0–0.6)**	**0.007**	14; 5.2	1; 1.4	0.3 (0.0–2.4)	0.25
Bedroom flooring												
Smooth	302; 67.1	168; 68.0	Reference	0.58	104; 64.2	115; 66.1	Reference	0.22	174; 67.4	51; 71.8	Reference	0.57
Smooth with rug	18; 4.0	4; 1.6	0.4 (0.1–1.3)	0.12	7; 4.3	4; 2.3	0.7 (0.2–2.7)	0.62	8; 3.1	0; 0.0		
Room wide carpet	130; 28.9	75; 30.4	0.9 (0.6–1.3)	0.67	51; 31.5	55; 31.6	0.7 (0.4–1.2)	0.23	76; 29.5	20; 28.2	0.9 (0.5–1.6)	0.66
Character; self-consciousness												
Low score	164; 51.4	68; 42.2	Reference	NA	59; 56.2	49; 43.4	Reference	NA	92; 48.9	19; 41.3	Reference	NA
High score	155; 48.6	93; 57.8	**1.5 (1.0–2.2)**	**0.048**	46; 43.8	64; 56.6	1.7 (0.9–3.0)	0.08	96; 51.1	27; 58.7	1.3 (0.7–2.6)	0.42

P indicates *P* value of MV-adj. LR model. Dx indicates diagnosis. "*" indicates *P*-trend. All associations with *P* value < 0.05 are shown in bold.
CI, confidence interval; C-section, cesarean section; LR, logistic regression; MV, multivariate; *n*, number; OR, odds ratio.

shown to inhibit monocyte tumor necrosis factor secretion in healthy individuals, these findings seem biologically plausible.[31]

Regardless of life-stage, the role of appendectomy has been widely studied in disease etiology as well as course of disease. Although an increased prevalence of stricturing CD has been associated with history of appendectomy, this is the first study showing an increased surgery rate while disease behavior is unaffected (data not shown).[32] For UC, no associations were seen, in line with a previous meta-analysis.[33] Surprisingly, several proxies of current hygiene were also associated with biological use or surgery in the current study. CD patients living in a large household were less likely to require surgery. A similar effect was shown for the presence room-wide carpet. Personality, evaluated using principal component analysis, identified no associations to course of disease for the two distinct personality traits neuroticism and conscientiousness. While an independent role of personality in the exposome can be argued, it is likely of influence on other important exposome factors such as stress. In future studies, it would be of great interest to evaluate interactions between personality and other exposome factors involved. Finally, this study is the first to describe a potential association between frequency of tooth brushing and the need for surgery in CD. Whereas this finding could just be another proxy in the previously suggested hygiene hypothesis, there is also the microparticle theory. In this theory, microparticles such as titanium dioxide and aluminum silicate, as present in toothpaste, are hypothesized to play a role in CD by forming strong stimulators of T-lymphocytes and microphages in experimental models.[34,35] However, this theory remains controversial, and further studies investigating the exact effect of microparticles in IBD are needed.

We acknowledge several limitations to the current study. First, questionnaire-based studies are at risk of recall bias. Although recall bias can never be prevented completely, the smart design of the validated web-based GIEQ limits its effects as described elsewhere.[8] Following the example of studies in the field of genetics, starting at single-gene studies and progressing to genome-wide association studies, using structured statistical approach while correcting for multiple testing, similar steps are crucial to further our knowledge on the exposome in IBD. The current study, however, has shown that for using this approach, larger cohorts are crucial. A power calculation indicated an 80% power to detect ORs below 1.45 within the current cohort. To allow for identification of exposures with moderate effect sizes while correcting for multiple testing in future studies, approximately 1300 patients per disease subtype are needed.

Also, an increase of participants and this power would allow for studying more precise disease outcomes, that is subphenotypes of disease, hospitalizations, and flares. Lastly, the current cross-sectional method is not suitable to study causality. As knowledge of the exposome in course of IBD is limited, it merely forms a stepping stone providing potential novel targets for future prospective studies. A key strength of this study is formed by the wide scope of exposome factors examined in this study, the largest to date, while using a previously validated questionnaire. Also, participants are all enrolled in the 1000IBD cohort ensuring correct and up to date information on disease course, preventing misclassification of diagnosis and complication development.

In this study, we present an overview of novel as well as replicated exposome factors potentially associated with the need for biologicals and surgery in IBD. Future prospective studies in large cohorts are crucial to confirm these findings, further clarifying the role of the exposome in disease course, as the exposome could potentially be used to stratify those at risk of complicated disease and guide both research on biological pathways involved, tailor-made intervention and preventive strategies in IBD.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Baseline characteristics of 1000IBD cohort.
Table S2. Principal component analysis personality traits.
Table S3. (Excel file).