International Journal of Epidemiology, 2019, 385–386f
doi: 10.1093/ije/dyy298
Advance Access Publication Date: 27 January 2019
Cohort Profile

Cohort Profile

Cohort Profile Update: The Swiss Inflammatory Bowel Disease Cohort Study (SIBDCS)

Valérie Pittet [1]* Pierre Michetti,[2,3] Christoph Mueller,[4] Christian P Braegger,[5] Roland von Känel,[6] Alain Schoepfer,[3] Andrew J Macpherson[7,8] and Gerhard Rogler[9] on behalf of the Swiss IBD Cohort Study Group

[1]Institute of Social & Preventive Medicine (IUMSP), Lausanne University Hospital, Lausanne, Switzerland, [2]Crohn and Colitis Center, Gastroentérologie Beaulieu SA, Lausanne, Switzerland, [3]Division of Gastroenterology & Hepatology, Lausanne University Hospital, Lausanne, Switzerland, [4]Institute of Pathology, University of Bern, Bern, Switzerland, [5]Division of Gastroenterology and Nutrition, University Children's Hospital Zurich, Zurich, Switzerland, [6]Department of Consultation-Liaison-Psychiatry and Psychosomatic Medicine, University Hospital Zurich, Zurich, Switzerland, [7]University Clinic of Visceral Surgery and Medicine, Inselspital, Bern, Switzerland, [8]Maurice Muller Laboratories, Department for Biomedical Research, University of Bern, Bern, Switzerland and [9]Division of Gastroenterology & Hepatology, Zurich University Hospital, Zurich, Switzerland

*Corresponding author. E-mail: Valerie.Pittet@chuv.ch

Editorial decision 21 December 2018; Accepted 8 January 2019

The original cohort

The SIBDCS was launched in November 2006 with the aim of enrolling and following patients with inflammatory bowel disease (IBD) throughout Switzerland. Our original sample included incident or prevalent cases, regularly treated in Switzerland, aged 2 and over. Patients were included through their treating gastroenterologist. Data from medical charts and patient self-reported questionnaires were collected annually. Blood samples and biopsies (in case of colonoscopy), collected at baseline and during follow-up, were stored in a biobank. The baseline data collected for the 754 patients recruited in the first 20 months were presented in a previous cohort profile manuscript.[1]

What is the reason for the new focus?

The objectives of the cohort study have been expanded to follow the intense international research activity on IBD. Given the morbidity, unsatisfactory treatments available and their impact on quality of life and costs, much remains to be done to gain more knowledge about IBD pathogenesis and the factors associated with flares or worsening disease. Genetic risk factors alone do not explain the recent increase in disease incidence and are only weakly associated with clinical phenotypes, disease course and severity.[2] In order to increase our understanding of the disease pathogenesis and the triggers or determinants of disease progression, 'omics studies, along with the identification of environmental and epigenetic factors, are increasingly being conducted and have been made possible through the expansion of new technologies and analytical methods. These technologies are, however, highly dependent on a precise and thorough phenotypic characterization of patients. In addition to basic and explanatory research, increasing attempts are made to explore patient-reported outcomes, needs and perceptions of the disease. One reason for this is the willingness to better identify factors that

can affect patients' quality of life, challenge optimal care and improve outcome of patients with chronic diseases through patient-centred initiatives (e.g. patient participative research, patient empowerment programmes). Overall, this objective also focuses on how to improve information and communication about the disease. The final reason was to foster collaborations in the area of chronic gastrointestinal diseases through the optimization in the use of the existing cohort infrastructure. Therefore, we opened the use of our infrastructure and resources to facilitate the development of subcohorts of patients with these diseases.

What will be the new areas of research?

First, we started a core project on microbiome composition, with two main sub-objectives. The first was to analyse how genetic risk factors for IBD can affect the composition of the faecal intestinal microbiota using taxonomy analyses (high-throughput sequencing) and *in vivo* functions (metatranscriptomics). We plan to study the complex interactions between genes and microbiota (e.g. the relevance of the respective risk genes to modulate and alter the intestinal microbiota in living organisms) as well as the potential of the intestinal microbiota to modulate the hitherto quite well-characterized molecular pathways.[3] The second objective was to investigate whether the association between microbiome composition and entero-phenotypes from patients with a different disease course (stricturing, fistulizing etc.) varied according to critical cellular functions (e.g. barrier function, cytokine secretion, autophagy, apoptosis or inflammasome activation). We further plan to investigate whether particular microbiome compositions or communities could promote or prevent the disease recurrences and their variations in timeline and activity. Thanks to the biobank and the detailed phenotypic characterization of the patients, we are able to annotate all the biosamples with detailed clinical information to conduct experiments. A longitudinal collection of stool samples was acquired from a control cohort of patients, to allow study of how the microbiome changes during disease course, under IBD medications (such as anti-TNF agents or steroids). The question as to whether alterations in the microbiome could potentially be used as predictive markers for disease behaviour in both the short and the long term will also be studied.

Environmental conditions, unlike genetic risk factors, can be influenced. Thus, knowledge on those risk factors is fundamental. Several studies have attempted to identify such factors.[4,5] These include for example smoking,[6,7] diet and food additives.[8] We plan to address the issue of environmental factors by studying factors linked to life habits, diet and socioeconomic factors, as well as two potential new factors we recently identified (heat waves/climate conditions and high altitude). The 'hygiene hypothesis' suggests that increased hygiene in childhood, associated with reduced exposure to pathogens, may leave the mucosal immune system insufficiently trained and thus prone to uncontrolled inflammation.[9–14] What is, however, unknown is how such factors may be not only related to getting the disease, but also to main clinical typologies at diagnosis. Therefore we conduct a study to collect information on early childhood risk factors from patients and, as a control cohort, from family members and friends. Patients, their mothers (where possible) and friends who grew up in a similar environment were asked to fill out their respective questionnaire.

Second, we had the possibility from the SIBDC to regularly collect patients' self-reported data. We therefore studied new patient-reported measures such as pain, socioeconomic variables, diets and symptoms, and patients' perspectives on health care and treatment, including their concerns and expectations.

Finally, we built a subcohort and opened the recruitment to patients diagnosed with eosinophilic oesophagitis (EoE), a newly identified chronic inflammatory disease of the gastrointestinal tract.[15] EoE shares with IBD a number of characteristics such as treatment options (steroids or anti-TNFα),[16] course of the disease, immune-mediated pathogenesis, genetic susceptibility and environmental disease triggers.[17] However, there also are major distinctions (restriction of location to the oesophagus, role of eosinophils in disease onset). We were interested in comparing these factors between IBD and EoE, to provide new insights into both diseases.

Who is in the cohort?

By the end of 2016, a total number of 3577 IBD patients had been recruited (including 103 new cases in 2016, among which 12 were incident cases). Among those, 2993 (84%) were followed up, 272 (8%) were considered lost to follow-up (i.e. not reachable for 18 months or more) and 312 (9%) explicitly asked to withdraw from the study. Among lost to follow-up reasons were death ($N = 77$) and change of diagnosis ($N = 16$). The evolution of the cohort sample between 2006 and 2016 shows, as in Table 1, that our objective of including 3000 patients in Swiss territory[1] was reached in 2014. Median age of patients was 42 years. with a range between 1 and 94. Table 2 presents basic characteristics of patients with Crohn's disease (phenotype and disease location) and ulcerative colitis (extension). The number of reports made from the medical charts ranged from 1 to 11 per patient, and the number of patient-reported questionnaires completed ranged from 1 to 9 per patient. The Biobank of the SIBDCS stored a total of 45 514 biosamples (5375 biopsies stored in RNAlater,

Table 1. Overview of the number (%) of adult and paediatric patients followed up (FU), stopped, and lost-to-follow-up (LTFU) from 2006 to 2016

	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
Adults											
FU	87 (100)	884 (99.9)	1419 (97.7)	1714 (96.0)	1954 (93.9)	2150 (92.3)	2383 (89.2)	2457 (86.2)	2579 (84.9)	2737 (84.1)	2768 (83.1)
Stopped	0 (0)	0 (0)	15 (1.0)	37 (2.1)	76 (3.7)	97 (4.2)	150 (5.6)	208 (7.3)	244 (8.0)	274 (8.4)	300 (9.0)
LTFU	0 (0)	1 (0.1)	19 (1.3)	35 (2.0)	51 (2.5)	82 (3.5)	140 (5.2)	184 (6.5)	214 (7.0)	243 (7.5)	262 (7.9)
Total (*N*)	87	885	1453	1786	2081	2329	2673	2849	3037	3254	3330
Paediatrics											
FU			12 (100)	33 (97.1)	50 (94.3)	66 (93.0)	89 (92.7)	114 (91.9)	155 (91.2)	196 (92.0)	225 (91.1)
Stopped			0 (0)	1 (2.9)	3 (5.7)	5 (7.0)	5 (5.2)	5 (4.0)	8 (4.7)	9 (4.2)	12 (4.9)
LTFU			0 (0)	0 (0)	0 (0)	0 (0)	2 (2.1)	5 (4.0)	7 (4.1)	8 (3.8)	10 (4.0)
Total (*N*)			12	34	53	71	96	124	170	213	247
All											
FU	87 (100)	884 (99.9)	1431 (97.7)	1747 (96.0)	2004 (93.9)	2216 (92.3)	2472 (89.3)	2571 (86.5)	2734 (85.3)	2933 (84.6)	2993 (83.7)
Stopped	0 (0)	0 (0)	15 (1.0)	38 (2.1)	79 (3.7)	102 (4.3)	155 (5.6)	213 (7.2)	252 (7.9)	283 (8.2)	312 (8.7)
LTFU	0 (0)	1 (0.1)	19 (1.3)	35 (1.9)	51 (2.4)	82 (3.4)	142 (5.1)	189 (6.4)	221 (6.9)	251 (7.2)	272 (7.6)
Total (*N*)	87	885	1465	1820	2134	2400	2769	2973	3207	3467	3577

18 346 serum, 16 118 plasma, 5675 buffy coat/genomic DNA) from 2700 patients. A total of 14 918 biosamples have been used so far for approved research projects. Patients provided the biobank with 1 to 21 blood samples and 1 to 26 biopsies.

What has been measured?

Genetic data

Single nucleotide polymorphism (SNP) analyses of 2330 IBD patients for 389 SNPs with an established or a potential association with IBD have been performed, and the corresponding information was stored at the central databank in Lausanne. Since February 2016, the SIBDCS biobank also collects biosamples (biopsies and blood samples) for the EoE sub-cohort.

Intestinal microbiota data

To characterize the microbial community of IBD patients, we have processed so far 1255 biopsy samples of 159 ulcerative colitis (UC) and 187 Crohn's disease (CD) patients obtained from the SIBDCS biobank, generating 35 billion high-quality 16S rDNA, which were clustered into more than 359 000 taxa.

Diet, life habits and socioeconomic factors

In 2013, we collected data on birth and breastfeeding [number of respondents (N) = 1263] and in 2014, we collected the following information on diet and lifestyle: alcohol consumption and smoking habits ($N = 384$). Type of specific diets like vegetarianism, veganism and gluten-free ($N = 1254$), and other socioeconomic factors like physical activity, income, alcohol consumption and deprivation in primary care (DiPCare-Q) ($N = 1349$) were collected in 2015.

Environmental factors

General and specific early childhood life conditions were collected using a questionnaire previously tested in the German IBD cohort. Variables comprise: moves and size of municipalities, access to running water, fridge acquisition, presence and type of pets, livestock proximity, hives or farmland, family composition, household organization, nursery stays, trips in Europe and abroad, exposure to passive smoking, childhood surgeries or diseases, vaccination, lifestyle, breastfeeding and birth conditions, milk and sugar intake, special diets, obesity, family history of cancer, antibiotics and non-steroidal anti-inflammatory drug (NSAID) use. In September 2016, questionnaires were sent to all patients, and for patients aged 50 and under

Table 2. Characteristics of the cohort population by the end of 2016

	Median (IQR / range) unless indicated
Overall characteristics	
Ratio male/female	1.03
Age at diagnosis (years)	26.3 (18.9-36.8, 0.5-82.7)
Age at enrolment (years)	37.2 (25.7–49.4, 1.3–87.6)
Disease duration at enrolment (years)	5.5 (1.5–13.5, 0.0–52.5)
Age at latest follow-up (FU) (years)	41.7 (29.7–54.7, 1.3–93.9)
Total time in the cohort (years)	5.8 (3.1–8.5, 0.0–10.5)
Total patient-years in the cohort	20'499.5
Number of physician-reported FU per patient	4 (2–7, 1–11)
Number of patient-reported FU per patient	3 (1–5, 0–9)
Total number of reports to the cohort	7 (4–12, 1–20)
Number (%) of patients with blood samples collected	2617 (73.1)
Number of blood samples collected per patient	1 (0–3, 0–21)
Number (%) of patients with colon biopsies collected	960 (26.8)
Number of colon biopsies collected per patient	0 (0–1, 0–26)
Crohn's disease basic characteristics, *N* (%)	
Disease location	
Ileal	585 (29.1)
Colonic	654 (32.5)
Ileocolonic	689 (34.3)
Upper gastrointestinal only	48 (2.4)
Unknown/unclear	35 (1.7)
Disease behaviour	
Inflammatory	1108 (55.1)
Stenosing	599 (29.8)
Fistulizing	304 (15.1)
Perianal disease	726 (36.1)
Ulcerative colitis basic characteristics, *N* (%)	
Pancolitis	662 (42.1)
Left-sided colitis	583 (37.1)
Proctitis	297 (18.9)
Unknown/unclear	29 (1.9)

additionally to their mothers and friends. Among the 2071 patients who received the questionnaire, 1107 (53%) replied. Among the 1250 patients aged <=50 we received 371 (29%) questionnaires back from mothers and friends, and 393 (31%) from friends.

Pregnancy and birth outcomes

In 2015, we conducted a sub-study with women who became pregnant during follow-up, to assess course of pregnancy, medications used, smoking, birth and pregnancy outcomes. Eighty women out of 120 answered the questionnaire.

Patient-reported signs and symptoms

Between 2012 and 2015, information on signs and symptoms derived from clinical activity indexes were analysed. A total of 1385 patients answered these questions one to four times, corresponding to more than 2453 analysable assessments. Pain was assessed in 2015 by collecting information in terms of intensity, location, treatment and impact on daily life and social activities ($N = 1263$).

Patient-reported perspectives on treatment and health care

Patients' needs for information were collected in 2009 through open-ended questions ($N = 728$). Data on patient-reported risks and benefits of drug treatments, concerns and expectations were gathered through closed and open-ended questions in 2015 ($N = 1102$).

EoE clinical, treatment and patient data

Patients diagnosed with EoE have been recruited since January 2016.[18] Baseline and follow-up information collected by the physician comprised the following: clinical activity, endoscopic activity, endoscopic activity of concomitant gastro-oesophageal reflux disease, histological activity, blood eosinophilia, current therapy, disease activity, management decisions, past medical history and, past therapies. We collected self-rated clinical activity and quality of life during study visits. In particular, follow-up data comprised monthly assessment of clinical activity, drug-related adverse events, new medical examinations and complications.

What has it found? Key findings and publications

As yet, more than 220 manuscripts have been published using data from the SIBDCS. A substantial part of the manuscripts report on data of the initial core projects. We performed epidemiological studies to assess risk factors associated with disease complications,[19–27] surgery[28–30] or disease course,[30–33] stratified by treatments or not. We found that three-quarters of CD patients were diagnosed within 24 months, as compared with 12 months for UC.[34] In a study conducted on 1245 UC patients, we found that the time from diagnosis to major surgery, i.e. colectomy, decreased in patients diagnosed after 2003.[29] We observed a linear decrease of colectomy rates between 2005 and 2017 [β= -0.210 (-0.323–-0.097); $P < 0.001$]. We found that 43% of CD and 31% of UC patients presented with at least one extraintestinal comorbidity.[21] Inflammatory

articular disease was the most common extraintestinal manifestation in CD, women and older patients.[35] We showed that early use of immunomodulators or biologics in CD reduced the risk of developing bowel strictures over time by 50% to 70%.[36] Main findings were also made related to psychosocial and psychosomatic factors, including anxiety and depression, health-related quality of life,[37–40] social support, job stress and coping,[41–48] appropriateness of treatments,[49,50] health economics[51,52] and patients' perspectives.[53–57] In a study based on 2007 adult IBD patients, we found an association of clinical disease recurrence with signs of anxiety [hazard ratio (HR) = 1.215 (1.078-1.370); $P = 0.0014$] and with signs of depression [HR = 1.417 (1.229-1.635); $P = 0.000001$].[44] We found that 5-aminosalicylates were prescribed in 60% of adults[49] and 47% paediatric CD patients,[58] which highly contrasted with scientific evidence. Around half of patients still sought for information on disease and treatments, regardless of the disease stage,[56] and their great est concern was about cancer.[55]

We also examined association between genetic variants and the disease course. We found that the C-allele of PTPN2 single nucleotide polymorphism (SNP) was associated with more severe disease and higher likelihood of response to anti-TNF-α biologic treatments.[59]

What are the main strengths and weaknesses?

The SIBDCS is a disease-oriented prospective cohort study. It was not planned to be population-based, except for specific geographicl regions, e.g. the Cantons of Vaud, Solothurn and Uri.[1] We have not achieved this goal now for several reasons. The federal organization of the Swiss health care system makes it almost impossible to ensure full coverage of all IBD cases. Moreover, specialist clinics that provide care for IBD patients did not exist in Switzerland at the beginning of the cohort study. As a result, it was rather difficult to identify patients with IBD. The study was open to all gastroenterologists practising in Switzerland, including private practices. The development of specialized clinics, however, only began in 2011.

Patients with IBD are also very difficult to follow through a long-term observational study because of the characteristics of the disease itself. The burden on patients is high, and when they experience a long-expected remission, they would like to continue living without having to think about the disease, or they may even feel cured, which has frequently resulted in them asking to stop their participation in the study, making attrition a big challenge.

Despite these limitations, the SIBDCS still follows a large number of patients, with two methods of data collection, through medical visits and self-reported patient questionnaires all over Switzerland, except in the Italian-speaking part which is expected to join by the end of 2018. Our cohort comprises both paediatric and adult patients, which provides the unique opportunity to study transitions (of the disease, but within the health care system) over time. Moreover, the SIBDCS has developed a close and widespread network of scientists, allowing them to address basic research questions in many domains.

Can I get hold of the data? Where can I find out more?

Due to legal and ethical restrictions, original data are available upon request from the SIBDCS, conditional on approval by the SIBDCS Scientific Board and within the frame of ethical approval. SIBDCS data can be used for projects that conform with the SIBDCS guidelines. All information on how to submit project proposals can be found at [www.ibdcohort.ch]. Requests for data consultation should be addressed to the SIBDC scientific committee through the email address: [sibdcs-submission@chuv.ch].

Update in a nutshell

- The SIBDCS started in 2006. Recruitment and yearly follow-up consisting of medical visits and self-reported questionnaires were presented to paediatric and adult inflammatory bowel disease (IBD) patients in Switzerland. Patients were included through their gastroenterologist in university hospitals, regional hospitals or private practices.
- By the end of 2016, 3577 IBD patients had been recruited and 2993 (84%) were followed up. Median age of patients was 42 years and ranged from 1 to 94.
- A broad range of data and biological samples were collected over time, including disease and treatments characteristics, sociodemographic data, health resource consumptions, life habits, psychosocial and psychosomatic measures, environmental data and data on patients' preferences.
- The cohort also generated secondary data from blood samples, biopsies and faecal samples, including genetic and microbiota composition data.
- We share our infrastructure for the development of other cohorts of inflammatory chronic gastrointestinal diseases, with the example of eosinophilic oesophagitis.

Acknowledgements

Members of the SIBDCS Study Group: Claudia Anderegg, Peter Bauerfeind, Christoph Beglinger, Stefan Begré, Dominique Belli, José M Bengoa, Luc Biedermann, Beat Bigler, Janek Binek, Mirjam Blattmann, Stephan Boehm, Jan Borovicka, Christian P. Braegger, Nora Brunner, Patrick Bühr, Bernard Burnand, Emanuel Burri, Sophie Buyse, Matthias Cremer, Dominique H. Criblez, Philippe de Saussure, Lukas Degen, Joakim Delarive, Christopher Doerig, Barbara Dora, Gian Dorta, Mara Egger, Tobias Ehmann, Ali El-Wafa, Matthias Engelmann, Jessica Ezri, Christian Felley, Markus Fliegner, Nicolas Fournier, Montserrat Fraga, Pascal Frei, Remus Frei, Michael Fried, Florian Froehlich, Christian Funk, Raoul Ivano Furlano, Suzanne Gallot-Lavallée, Martin Geyer, Marc Girardin, Delphine Golay, Tanja Grandinetti, Beat Gysi, Horst Haack, Johannes Haarer, Beat Helbling, Peter Hengstler, Denise Herzog, Cyrill Hess, Klaas Heyland, Thomas Hinterleitner, Philippe Hiroz, Claudia Hirschi, Petr Hruz, Rika Iwata, Res Jost, Pascal Juillerat, Céline Keller, Christina Knellwolf, Christoph Knoblauch, Henrik Köhler, Rebekka Koller, Claudia Krieger-Grübel, Gerd Kullak-Ublick, Patrizia Künzler, Markus Landolt, Rupprecht Lange, Frank Serge Lehmann, Andrew Macpherson, Philippe Maerten, Michel H. Maillard, Christine Manser, Michael Manz, Urs Marbet, George Marx, Christoph Matter, Rémy Meier, Martina Mendanova, Pierre Michetti, Benjamin Misselwitz, Bernhard Morell, Patrick Mosler, Christian Mottet, Christoph Müller, Pascal Müller, Beat Müllhaupt, Claudia Münger-Beyeler, Leilla Musso, Andreas Nagy, Michaela Neagu, Cristina Nichita, Jan Niess, Andreas Nydegger, Nicole Obialo, Carl Oneta, Cassandra Oropesa, Ueli Peter, Daniel Peternac, Laetitia Marie Petit, Franziska Piccoli-Gfeller, Julia Beatrice Pilz, Valérie Pittet, Nadia Raschle, Ronald Rentsch, Sophie Restellini, Jean-Pierre Richterich, Sylvia Rihs, Marc Alain Ritz, Jocelyn Roduit, Daniela Rogler, Gerhard Rogler, Jean-Benoît Rossel, Vanessa Rueger, Gaby Saner, Bernhard Sauter, Mikael Sawatzki, Michela Schäppi, Michael Scharl, Sylvie Scharl, Martin Schelling, Susanne Schibli, Hugo Schlauri, Sybille Schmid Uebelhart, Jean-François Schnegg, Alain Schoepfer, Frank Seibold, Mariam Seirafi, Gian-Marco Semadeni, David Semela, Arne Senning, Marc Sidler, Christiane Sokollik, Johannes Spalinger, Holger Spangenberger, Philippe Stadler, Michael Steuerwald, Alex Straumann, Bigna Straumann-Funk, Michael Sulz, Alexandra Suter, Joël Thorens, Sarah Tiedemann, Radu Tutuian, Stephan Vavricka, Francesco Viani, Jürg Vögtlin, Roland Von Känel, Alain Vonlaufen, Dominique Vouillamoz, Rachel Vulliamy, Jürg Wermuth, Helene Werner, Paul Wiesel, Reiner Wiest, Tina Wylie, Jonas Zeitz, Dorothee Zimmermann.

Conflict of interest: None declared.

References

1. Pittet V, Juillerat P, Mottet C *et al*. Cohort Profile: The Swiss inflammatory bowel disease cohort study (SIBDCS). *Int J Epidemiol* 2009;**38**:922–31.
2. Cleynen I, Gonzalez JR, Figueroa C *et al*. Genetic factors conferring an increased susceptibility to develop Crohn's disease also influence disease phenotype: results from the IBDchip European Project. *Gut* 2013;**62**:1556–65.
3. Jostins L, Ripke S, Weersma RK *et al*. Host-microbe interactions have shaped the genetic architecture of inflammatory bowel disease. *Nature* 2012;**491**:119–24.
4. Molodecky NA, Panaccione R, Ghosh S *et al*. Challenges associated with identifying the environmental determinants of the inflammatory bowel diseases. *Inflamm Bowel Dis* 2011;**17**:1792–9.
5. Molodecky NA, Kaplan GG. Environmental risk factors for inflammatory bowel disease. *Gastroenterol Hepatol (N Y)* 2010;**6**:339–46.
6. Cosnes J. Tobacco and IBD: relevance in the understanding of disease mechanisms and clinical practice. *Best Pract Res Clin Gastroenterol* 2004;**18**:481–96.
7. Cosnes J, Carbonnel F, Beaugerie L *et al*. Effects of cigarette smoking on the long-term course of Crohn's disease. *Gastroenterology* 1996;**110**:424–31.
8. Cosnes J. Smoking, physical activity, nutrition and lifestyle: environmental factors and their impact on IBD. *Dig Dis* 2010;**28**:411–7.
9. Ng SC, Bernstein CN, Vatn MH *et al*. Geographical variability and environmental risk factors in inflammatory bowel disease. *Gut* 2013;**62**:630–49.
10. Hafner S, Timmer A, Herfarth H *et al*. The role of domestic hygiene in inflammatory bowel diseases: hepatitis A and worm infestations. *Eur J Gastroenterol Hepatol* 2008;**20**:561–6.
11. Castiglione F, Diaferia M, Morace F *et al*. Risk factors for inflammatory bowel diseases according to the 'hygiene hypothesis': a case-control, multi-centre, prospective study in Southern Italy. *J Crohns Colitis* 2012;**6**:324–9.
12. Klement E, Lysy J, Hoshen M *et al*. Childhood hygiene is associated with the risk for inflammatory bowel disease: a population-based study. *Am J Gastroenterol* 2008;**103**:1775–82.
13. Guarner F, Bourdet-Sicard R, Brandtzaeg P *et al*. Mechanisms of disease: the hygiene hypothesis revisited. *Nat Rev Gastroenterol Hepatol* 2006;**3**:275–84.
14. Guarner F. Hygiene, microbial diversity and immune regulation. *Curr Opin Gastroenterol* 2007;**23**:667–72.
15. Furuta GT, Katzka DA. Eosinophilic esophagitis. *N Engl J Med* 2015;**373**:1640–8.
16. Molina-Infante J, Schoepfer AM, Lucendo AJ *et al*. Eosinophilic esophagitis: what can we learn from Crohn's disease? *United European Gastroenterol J* 2017;**5**:762–72.
17. Sherrill JD, Rothenberg ME. Genetic dissection of eosinophilic esophagitis provides insight into disease pathogenesis and treatment strategies. *J Allergy Clin Immunol* 2011;**128**:23–32; quiz 33-4.
18. Safroneeva E, Saner C, Rossel J-B *et al*. Cohort profile: The Swiss eosinophilic esophagitis cohort study (SEECS). *Inflamm Intest Dis* 2017;**2**:163–70.
19. Fraga M, Fournier N, Safroneeva E *et al*. Primary sclerosing cholangitis in the Swiss inflammatory bowel disease cohort study: prevalence, risk factors, and long-term follow-up. *Eur J Gastroenterol Hepatol* 2017;**29**:91–7.
20. Schoepfer AM, Dehlavi MA, Fournier N *et al*. Diagnostic delay in Crohn's disease is associated with a complicated disease course and increased operation rate. *Am J Gastroenterol* 2013;**108**:1744–53.
21. Vavricka SR, Brun L, Ballabeni P *et al*. Frequency and risk factors for extraintestinal manifestations in the Swiss inflammatory bowel disease cohort. *Am J Gastroenterol* 2011;**106**:110–9.

22. Vavricka SR, Spigaglia SM, Rogler G *et al*. Systematic evaluation of risk factors for diagnostic delay in inflammatory bowel disease. *Inflamm Bowel Dis*; 2011.
23. Voegtlin M, Vavricka SR, Schoepfer AM *et al*. Prevalence of anaemia in inflammatory bowel disease in Switzerland: a cross-sectional study in patients from private practices and university hospitals. *J Crohns Colitis* 2010;**4**:642–8.
24. Pepe J, Zawadynski S, Herrmann FR *et al*. Structural basis of bone fragility in young subjects with inflammatory bowel disease: a high-resolution pQCT study of the SWISS IBD cohort (SIBDC). *Inflamm Bowel Dis* 2017;**23**:1410–7.
25. Alatri A, Schoepfer A, Fournier N *et al*. Prevalence and risk factors for venous thromboembolic complications in the Swiss inflammatory bowel disease cohort. *Scand J Gastroenterol* 2016; **51**:1200–5.
26. Greuter T, Bertoldo F, Rechner R *et al*. Extraintestinal manifestations of pediatric inflammatory bowel disease: prevalence, presentation, and anti-TNF treatment. *J Pediatr Gastroenterol Nutr* 2017;**65**:200–6.
27. Herzog D, Fournier N, Buehr P *et al*. Prevalence of intestinal complications in inflammatory bowel disease: a comparison between paediatric-onset and adult-onset patients. *Eur J Gastroenterol Hepatol* 2017;**29**:926–31.
28. Pittet V, Rogler G, Michetti P *et al*. Penetrating or stricturing diseases are the major determinants of time to first and repeat resection surgery in Crohn's disease. *Digestion* 2013;**87**:212–21.
29. Parragi L, Fournier N, Zeitz J *et al*. Colectomy rates in ulcerative colitis are low and decreasing: 10-year-follow-up data from the Swiss IBD cohort study. *J Crohns Colitis*; 2018.
30. Manser CN, Frei P, Grandinetti T *et al*. Risk factors for repetitive ileocolic resection in patients with Crohn's disease: results of an observational cohort study. *Inflamm Bowel Dis* 2014;**20**: 1548–54.
31. Biedermann L, Zeitz J, Mwinyi J *et al*. Smoking cessation induces profound changes in the composition of the intestinal microbiota in humans. *PLoS One* 2013;**8**:e59260.
32. Biedermann L, Brulisauer K, Zeitz J *et al*. Smoking cessation alters intestinal microbiota: insights from quantitative investigations on human fecal samples using FISH. *Inflamm Bowel Dis* 2014;**20**:1496–501.
33. Fagagnini S, Heinrich H, Rossel JB *et al*. Risk factors for gallstones and kidney stones in a cohort of patients with inflammatory bowel diseases. *PLoS One* 2017;**12**:e0185193.
34. Vavricka SR, Spigaglia SM, Rogler G *et al*. Systematic evaluation of risk factors for diagnostic delay in inflammatory bowel disease. *Inflamm Bowel Dis* 2012;**18**:496–505.
35. Ditisheim S, Fournier N, Juillerat P *et al*. Inflammatory articular disease in patients with inflammatory bowel disease: result of the Swiss IBD cohort study. *Inflamm Bowel Dis* 2015;**21**: 2598–604.
36. Safroneeva E, Vavricka SR, Fournier N *et al*. Impact of the early use of immunomodulators or TNF antagonists on bowel damage and surgery in Crohn's disease. *Aliment Pharmacol Ther* 2015; **42**:977–89.
37. Werner H, Braegger C, Buehr P *et al*. Shorter time since inflammatory bowel disease diagnosis in children is associated with lower mental health in parents. *Acta Paediatr* 2015;**104**: e32–8.
38. Mueller R, Ziade F, Pittet V *et al*. Quality of life in Swiss paediatric inflammatory bowel disease patients: do patients and their parents experience disease in the same way? *J Crohns Colitis* 2015.
39. Werner H, Landolt MA, Buehr P *et al*. Validation of the IMPACT-III quality of life questionnaire in Swiss children with inflammatory bowel disease. *J Crohns Colitis* 2014;**8**:641–8.
40. Werner H, Landolt MA, Buehr P *et al*. Changes in health-related quality of life over a 1-year follow-up period in children with inflammatory bowel disease. *Qual Life Res* 2017;**26**:1617–26.
41. Camara RJ, Juillerat P, Pittet V *et al*. Quality of life: a potentially useful measure to indicate subclinical flares in Crohn disease. *Intern Med J* 2012;**42**:e145–51.
42. Camara RJ, Lukas PS, Begre S *et al*. Effects of social support on the clinical course of Crohn's disease. *Inflamm Bowel Dis* 2011; **17**:1277–86.
43. Camara RJ, Schoepfer AM, Pittet V *et al*. Mood and nonmood components of perceived stress and exacerbation of Crohn's disease. *Inflamm Bowel Dis* 2011;**17**:2358–65.
44. Mikocka-Walus A, Pittet V, Rossel JB *et al*. Symptoms of depression and anxiety are independently associated with clinical recurrence of inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2016;**14**:829–35 e1.
45. Schreiner P, Biedermann L, Rossel JB *et al*. Prevalence and determinants of job stress in patients with inflammatory bowel disease. *Inflamm Bowel Dis* 2017;**23**:310–7.
46. Camara RJ, Begre S, von Kanel R *et al*. Avoidance and inhibition do not predict nonrespondent bias among patients with inflammatory bowel disease. *J Epidemiol* 2011;**21**:44–51.
47. Rogler D, Fournier N, Pittet V *et al*. Coping is excellent in Swiss children with inflammatory bowel disease: results from the Swiss IBD cohort study. *J Crohns Colitis* 2014;**8**:409–20.
48. Herzog D, Landolt MA, Buehr P *et al*. Low prevalence of behavioural and emotional problems among Swiss paediatric patients with inflammatory bowel disease. *Arch Dis Child* 2013;**98**:16–9.
49. Schoepfer AM, Bortolotti M, Pittet V *et al*. The gap between scientific evidence and clinical practice: 5-aminosalicylates are frequently used for the treatment of Crohn's disease. *Aliment Pharmacol Ther* 2014;**40**:930–7.
50. Maillard MH, Bortolotti M, Vader JP *et al*. Appropriateness and long-term discontinuation rate of biological therapies in ulcerative colitis. *J Crohns Colitis* 2014;**8**:825–34.
51. Sulz MC, Siebert U, Arvandi M *et al*. Predictors for hospitalization and outpatient visits in patients with inflammatory bowel disease: results from the Swiss inflammatory bowel disease cohort study. *Eur J Gastroenterol Hepatol* 2013;**25**:790–7.
52. Siebert U, Wurm J, Gothe RM *et al*. Predictors of temporary and permanent work disability in patients with inflammatory bowel disease: results of the Swiss inflammatory bowel disease cohort study. *Inflamm Bowel Dis* 2013;**19**:847–55.
53. Burkhalter H, Stucki-Thur P, David B *et al*. Assessment of inflammatory bowel disease patient's needs and problems from a nursing perspective. *Digestion* 2015;**91**:128–41.
54. Pittet V, Rogler G, Mottet C *et al*. Patients' information-seeking activity is associated with treatment compliance in inflammatory bowel disease patients. *Scand J Gastroenterol* 2014;**49**:662–73.
55. Pittet V, Vaucher C, Froehlich F *et al*. Patient self-reported concerns in inflammatory bowel diseases: a gender-specific subjective quality-of-life indicator. *PLoS One* 2017;**12**:e0171864.

56. Pittet V, Vaucher C, Maillard MH *et al*. Information needs and concerns of patients with inflammatory bowel disease: what can we learn from participants in a bilingual clinical cohort? *PLoS One* 2016;**11**:e0150620.
57. Vaucher C, Maillard MH, Froehlich F *et al*. Patients and gastroenterologists' perceptions of treatments for inflammatory bowel diseases: do their perspectives match? *Scand J Gastroenterol* 2016;**51**:1056–61.
58. Sokollik C, Fournier N, Rizzuti D *et al*. The use of 5-aminosalicylic acid in children and adolescents with inflammatory bowel disease. *J Clin Gastroenterol* 2017.
59. Spalinger MR, Voegelin M, Biedermann L *et al*. The clinical relevance of the IBD-associated variation within the risk gene locus encoding protein tyrosine phosphatase non-receptor type 2 in patients of the Swiss IBD Cohort. *Digestion* 2016;**93**:182–92.