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ECCO Topical Review

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European Crohn's and Colitis Organisation Topical Review on Environmental Factors in IBD

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Abstract

This ECCO Topical Review of the European Crohn's and Colitis Organisation [ECCO] focuses on the role of environmental factors with respect to the development of inflammatory bowel disease [IBD] as well as their influence on the course of established IBD. The objective was to reach expert consensus to provide evidence-based guidance for clinical practice.

Key Words: Crohn's disease; ulcerative colitis; European Crohn's and Colitis Organisation; inflammatory bowel disease; environmental; antibiotics; hygiene; perinatal factors

1. Introduction

Within recent years there has been increasing evidence to support the role of the exposome in inflammatory bowel disease [IBD] pathogenesis: a shift from earlier work that highlighted genetic factors. Indeed, the rise in the incidence of IBD far outweighs that which can be explained by genetic drift.[1,2]

Identifying modifiable environmental factors is challenging. Prospective studies and controlled trials are scarce. Whereas, in summation, environmental factors are crucial, each individual factor may confer only a modest risk. This is likely why none of the major gastroenterology societies have clear guidance on environmental factors.

The aim of this paper was to investigate the strength of associations between environmental factors and IBD incidence and relapse.

2. Method

The ECCO Environmental Factors Working Group was selected from applications following response to an ECCO call. A literature search was undertaken by members of the group. The search was conducted via PubMed. Drafting of text and statements was divided between members of the Working Group. Statements were voted upon anonymously. Statements with > 80% agreement from all

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members were included within the paper in accordance with ECCO standards.

3. Results

3.1. Prenatal and perinatal risk factors for IBD

ECCO Current Practice Position 1

The increased rate of caesarean section parallels the incidence of IBD in Western countries

With the increased incidence of IBD, the rate of caesarean section has more than doubled during the past 20 years.[3]

The composition of the intestinal microbiota is directly related to the environment encountered at birth.[4,5] Caesarean section [CS]-born babies acquire skintype microbiota, whereas babies delivered vaginally acquire a vaginal microbiota. A study assessing microbiota composition of 7-year-old children showed children born by CS had significantly fewer *Clostridiae*.[6]

Studies investigating relationship between method of delivery and IBD incidence have yielded conflicting results.[7–10] A questionnaire-based study from Germany reported that prematurity was associated with IBD, but not delivery method,[11] and another questionnaire-based study from Germany found no association.[12] The pooled results of a meta-analysis suggested CS delivery was a risk factor for adult- and paediatric-onset Crohn's disease [CD] (95% confidence interval [CI] 1.12–1.70; $p = 0.003$) but not ulcerative colitis [UC].[13] A population-based study using the Danish National Patient Registry determined that CS was associated with an increased risk of developing IBD before the age of 36 years (incidence rate ratio [IRR] 1.14, 95% CI 1.06–1.22), with the highest risk in children aged under 15 years [IRR 1.29, 95% CI 1.11–1.49].[8] Subanalysis showed the association to be entirely with emergency CS. In contrast, the Norwegian Medical Birth Registry data demonstrated that IBD patients were less likely to have been born by CS [OR 0.27, 95% CI 0.10–0.73].[9]

ECCO Current Practice Position 2

Smaller families and being the older sibling increase the risk of developing IBD; however, data are equivocal

Overall, population-based studies provide evidence that higher birth order and smaller families increase the risk of developing IBD. However, other studies have reported conflicting or equivocal data which casts uncertainty.

Family size in childhood is significantly associated with UC but not CD[14] [OR 0.81 per person of the family, 95% CI 0.68–0.98]. A Canadian study also reported that having a larger family is protective against CD [95% CI 0.79–0.96].[15] These observations are supportive of the 'hygiene hypothesis', as discussed later. However, another study found no association between sibling number and IBD.[16]

3.2. Effects of breastfeeding

ECCO Current Practice Position 3

There is lower incidence of paediatric-onset IBD among those who have been breastfed, with a more pronounced effect in CD and a duration-dependent response

The current evidence relating breastfeeding with IBD is largely based on two meta-analyses. The first[17] included 17 studies published until 2003. The pooled OR were 0.67 [95% CI 0.52–0.86] for CD and 0.77 [0.61–0.96] for UC.

A well-conducted study from northern France,[18] which was not included in the above meta-analysis, paradoxically found breastfeeding to increase the risk of Crohn's disease [OR 2.1, 95% CI 1.3–3.4, $p = 0.01$]. When meta-analysis was re-calculated,[17] the particular study reduced the beneficial effect of breastfeeding on CD [0.62, 95% CI 0.27–0.43] but it significantly increased the heterogeneity of published studies.

The second meta-analysis [2009] included 7 of the 79 articles focusing on paediatric IBD[19] and showed breastfeeding had a significant protective effect in early-onset IBD [OR 0.69, 95% CI 0.51–0.94; $p = 0.02$] but differences for UC [OR 0.72, 95% CI 0.51–1.02; $p = 0.06$] or Crohn's disease [OR 0.64, 95% CI 0.38–1.07; $p = 0.09$] separately were not statistically significant. However, again authors question the quality of data.

Since 2009, several other population studies have been published showing discrepant results.[20–25]

Studies have indicated that breastfeeding might have a duration-response effect, with a minimum 3 months required to influence risk.[26,27] A Slovak case control study found that breastfeeding for less than 6 months increased the risk of both CD and UC.[14] The notion is supported by a recent multinational, multicentre population case-control study from Asia, which demonstrated the strongest effect yet observed: breastfeeding for more than 12 months decreased the risk for both CD [OR 0.10, 95% CI 0.04–0.30] and UC [adjusted OR 0.16, 95% CI 0.08–0.31].[28]

Breastfeeding may reduce the need for surgery in CD [0.42, 95% CI 0.25 – 0.68] and UC [0.21, 95% CI 0.09 – 0.46].[29]

3.3. Other perinatal risk factors

Baron *et al*. conducted a population-based questionnaire-based study to assess the association between paediatric-onset IBD and disease during pregnancy, gestational age at birth, birthweight and length, vaccination, infection, and hospitalisation during the first month of life.[18] Multivariate analyses revealed no association between prenatal factors and CD, whereas disease during pregnancy was associated with increased risk of UC [OR 8.9, 95% CI 1.5–52]. A lack of association between paediatric IBD and similar factors was also declared in another study.[26] Hutfless assessed a wide range of pre- and perinatal environmental factors and demonstrated significant increased risk of IBD in Caucasians and nonsignificant trends for increased risk in maternal age < 20 years, respiratory infection during pregnancy, or hypertension.[30] Another study examined similar factors in the perinatal period and found no associations with IBD with preeclampsia, birthweight, gestational age, and Apgar score.[7] However, investigators found significant associations between CD and maternal smoking during pregnancy [OR 2.04, 95% CI 1.06–3.92] and maternal age > 35 at delivery [OR 4.81, 95% CI 2.32–9.98].

3.4. Childhood vaccinations and the development of IBD

ECCO Current Practice Position 4

There is no support for the hypothesis that vaccinations in childhood predispose to the later development of IBD

There is no evidence that vaccination predisposes to IBD. In a case-control study, neither vaccination with measles, mump,s and rubella [MMR] nor the timing of childhood vaccination influenced future IBD incidence.[31] The analysis of vaccination and the acute onset of

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symptoms of IBD revealed no cases of IBD in individuals who were vaccinated in the 2–4 month period preceding the first symptoms.

In a prospective long-term case-cohort study based on the Copenhagen School Health Records Register, it has been shown that Bacillus Calmette-Guérin [BCG] and smallpox vaccination do not cause IBD later in life.[32] BCG given before 4 months of age has even been shown to decrease the risk of IBD [hazard ratio = 0.43; 95% confidence interval, 0.20–0.93].

A recent meta-analysis of 10 studies investigating 10 vaccine types [BCG, diphtheria, tetanus, poliomyelitis, smallpox, pertussis, measles, rubella, mumps, and MMR vaccine] investigated the association between vaccination and the risk for IBD in 2399 IBD patients and 33 747 controls[33] and found no association between childhood immunisation and IBD.

Environmental factors, including vaccinations before the development of IBD, were assessed also by EpiCom investigators[34]; although reports of vaccination were higher in Eastern European patients, univariate and multivariate regression did not show vaccination to be a risk factor for CD or UC.

3.5. The hygiene hypothesis

ECCO Current Practice Position 5

There is insufficient evidence to support or refute the hygiene hypothesis

The hygiene hypothesis comes from the observation that the increase in incidence of IBD is coincident with improvements in sanitation. According to this theory, growing up in an environment with limited exposure to microbes results in impaired immune response later in life.[35]

An early-life hygiene-related factor could be behind the observation of a decreasing incidence in intestinal tuberculosis and an increasing incidence of IBD in migrant populations translocated to industrialised countries.[36]

Assessing the influence of early-life hygiene factors is very difficult. Until recently, risk factors were assessed with non-standard questionnaires.[37] More recent data are largely derived from case-control retrospective studies that are subject to potentially relevant recall and selection bias. Finally, many factors have been proposed which are usually present together and could have been additive or confounding factors [Table 1].

The association with improved sanitary facilities was not confirmed by the majority of the studies published during the past 15 years.[38] The role of infection is discussed elsewhere in this review.

The association of refrigeration with IBD incidence is known as the cold chain hypothesis.[39] This theory also fits conceptually with the role of altered microbiota composition in IBD pathogenesis and, indeed, the mechanisms of action of the innate immune system.[40,41] However, whereas the theory is compelling, hard evidence to support it is lacking.

3.6. Diet

3.6.1. Animal models and cell lines

Numerous observational studies have attempted to identify dietary patterns that contribute to the risk for IBD. In general, however, studies of the effects of food are limited by the difficulty in accurately capturing dietary intake, as well as the potential for complex interactions between foods.[42] Dietary ingredients with the best evidence so far include dietary fats,[43–47] gluten,[48] maltodextrin,[49] and emulsifiers.[50,51] Meat has been implicated in UC, as have animal proteins and emulsifiers in CD.[52]

Rodent models and cell lines have provided additional insight. High-fat, high-sugar diet induced inflammation with dysbiosis, decreased mucin expression, and increased intestinal permeability. In a pivotal study, wild type and IL10-/- mice exposed to milk fat suffered more severe colitis due to induced taurine conjugation of bile acids. Dietary fat accelerated ileitis, whereas gluten induced inflammation via increased intestinal permeability in a TNFΔAre/wt mouse model.[49] Maltodextrin was shown to alter the function of adherent invasive *E. coli* [*AIEC*][49] whereas emulsifiers deplete the mucous layer, affect *AIEC* translocation,[50–52] and increase mucosa-associated bacteria. Roberts *et al.*[51] demonstrated that certain dietary fibres [plantain, broccoli] might be beneficial in preventing translocation of *AIEC* across M cells.

Le Leu *et al.* demonstrated that dietary red meat aggravates dextran sulphate sodium-induced colitis in mice, whereas resistant starch [a substrate for short-chain fatty acid production] attenuated inflammation.[53] Using the same model, another group demonstrated that exposure to soy protein appeared to be beneficial.[54]

In summary, in several animal models, high-fat/high-sugar diet, gluten, red meat, maltodextrin, and emulsifiers may induce or accelerate intestinal inflammation. Certain dietary fibres and soy protein might be beneficial.

ECCO Current Practice Position 6

Dietary patterns characterised by high animal fat and animal proteins, food additives, and low fibre have been associated with increased incidence of IBD
Conversely, omega-3 fatty acids, medium-chain triglycerides, and fermentable carbohydrates may be protective

3.6.2. Epidemiology and human data

Diet is considered as an essential exposomal factor potentially targeting inflammation-related mechanisms in the host directly via changes to the microbiome.[55] Most studies point to an increased risk of IBD among people who consume greater amounts of meat and fats, particularly polyunsaturated fatty acids [PUFAs] and omega-6 [n-6] fatty acids, and lower risk among people with diets high in fibre, fruits, and vegetables.[56,57] Hou reviewed 19 case-control studies demonstrating a positive association with fat consumption and IBD onset.[56] An extensive review of literature by Spooren *et al.*[58] identified 35 studies investigating onset of IBD. Several studies reported high intake of sugar or sugar-containing foods [n = 7 UC, n = 12 CD], and low intake of fruits and/or vegetables [n = 5 UC, n = 10 CD] associated with an increased onset risk. However, a similar high number of other studies did not confirm these findings. A possible protective role was found for grain-derived products in CD onset, but results were inconsistent for dietary fibre in UC and CD and grain-derived products in UC.[58]

Findings from the European Investigation into Cancer and Nutrition [EPIC] Study and the Nurses' Health Study [NH] are particularly noteworthy because of their prospective design.[59–61] The EPIC study associated greater consumption of linoleic acid [an n-6 PUFA present in high concentrations in red meat, cooking oils, and margarine] with a higher incidence of UC.[59] In contrast, people who consumed higher levels of omega-3 [n-3] PUFA docosahexanoic acid were less likely to be diagnosed with UC. In the NH study, greater consumption of long-chain n-3 PUFAs and a higher ratio of n-3:n-6 PUFAs again appeared to protect against development of UC.[62] The NH study has also examined the association between fibre intake and incident IBD. Nurses consuming large amounts of fibre, particularly fruits, were approximately 40% less likely to be subsequently diagnosed with CD, although no association was observed for UC.[62] Similar findings

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Table 1. Early life hygiene factors and risk of inflammatory bowel disease.

Hygiene factor	Studies endorsing the hygiene theory	Studies not confirming hygiene theory	Studies against the hygiene theory
Family size and birth order	Han DY, 2010. CD, being only child: OR 1.54 [1.09–2.16] Klement E, 2008. Small number of siblings: OR 2.63 [1.49–4.62] Montgomery SM, 2002. UC, older siblings: OR 1.15 [1.07–1.24] CD, younger siblings: OR 0.83 [0.76–0.90] Hampe J, 2003. Higher birth rank [> = 3]: OR 0.68 [0.51–0.91] Chu KM, 2013. CD, shared housing: OR 0.1 [0.04–0.4] UC, shared housing: OR 0.1 [0.01–0.4] Bernstein CN, 2006. Having larger families: OR 0.87 [0.76–0.96] Hlavaty T, 2013. UC, having larger families: OR 0.82 [0.68–0.98] Ko Y, 2015. CD, Middle Eastern migrants in Australia; bedroom sharing during childhood: OR 0.36 [0.16–0.80] CD, Caucasian Australians; bedroom sharing during infancy: OR 0.43 [0.23–0.80]	Castiglione F, 2012. ≤ 1 sibling, UC: OR 0.95 [0.71–1.15] ≤ 1 sibling, CD: OR 1.02 [0.76–1.37] Firstborn, UC: OR 0.91 [0.65–1.27] Firstborn, CD: OR 0.73 [0.52–1.02] Sicilia B, 2008. OR not available. Thompson NP, 2000 [*]. CD, first child: OR 0.92 [0.34–2.47] UC, first child: OR 1.34 [0.57–3.17] Radon K, 2007. ≥ 2 older siblings: CD 10.1, UC 14.5, controls 16.9% [$p > 0.05$] ≥ 2 younger siblings: CD 12%, UC 5.3, control 12.9 [$p > 0.05$]	Baron S, 2005. UC, increased risk in bedroom sharing: OR 7.1 [1.9–27.4] Jakobsen C, 2013. Increased risk in bedroom sharing: OR 2.1 [1.0–4.3] Sood A, 2014. UC, private bedroom: OR 0.37 [0.26–0.53] Amre DK, 2006. CD, less crowded families: OR 0.3 [0.2–0.9] Klement E, 2008. Increased risk in younger siblings: OR 2.35 [1.47–3.77] Boneberger SF, 2011. UC, having older siblings: OR 2.2 [1.1–4.4]
Sanitary facilities	Pugazhendi S, 2011. Safe drinking water: OR 1.59, 1.02–2.47	Thompson NP, 2000 [*]. CD, poor amenities: OR 1.25 [0.44–3.47] UC, poor amenities: OR 0.61 [0.21–.1.61] Hansen TS, 2011. Running water: OR 0.5 [0.15–1.66]	Baron S, 2005. Regular drinking of tap water: OR 0.56 [0.3–1] Sood A, 2014. Flush toilet: OR 0.47 [0.27–0.81] Van Kruiningen HJ, 2005. Tap water: OR 0.34 [0-18-0.66]
Pets and farm animals	Hlavaty T, 2013. CD, cats: OR 0.6 [0.4–0.9] Ng SC, 2015. CD, dogs: OR 0.54 [0.35 to 0.83] Ko Y, 2015. CD, Middle Eastern migrants in Australia; pet during infancy: OR 0.12 [0.03–0.43] CD, Middle Eastern migrants in Australia; farm animals during infancy: OR 0.12 [0.03–0.43] Timm S, 2014. Raised on a livestock farm: OR 0.54 [0.31–0.94] Bernstein CN, 2006. CD, cats: OR 0.66 [0.46–0.96] Radon K, 2007. CD, farm animals: OR 0.5 [0.3–0.9] UC, farm animals: OR 0.4 [0.2–0.8] UC, cats: OR 0.5 [0.3–0.8] Van Kruiningen HJ, 2005. CD, bird: OR 0.45 [0.22–0.93]CD, dog: OR 0.49 [0.270.02] CD, cat: OR 0.13 [0.06–0.29]	Castiglione F, 2012. CD, animals in childhood: OR 0.96 [0.75–1.24] UC, animals in childhood: OR 1.08 [0.85–1.37] Boneberger SF, 2011. UC, pets: IBD 65%, controls 73.6%, $p = 0.25$ UC, farm animals: IBD 36.5%, controls 40.8%, $p = 0.58$ Hafner S, 2008. Pets: CD 77%, UC 75%, controls 81% [$p > 0.05$] Ko Y, 2015. Australian Caucasians; farm animals in infancy: OR 0.95 [0.48–1.89]	Han DY, 2010. CD, pets, 6–11 years old: OR 1.98 [1.28, 3.06] Amre DK, 2006. CD, pets: OR 2.0 [0.9–4.5] Sood A, 2014. UC, pets: OR 2.54 [1.53–4.21] Ko Y, 2015. Australian Caucasians; pet during childhood: OR 2.87 [1.58–5.21]

Associations [when available] shown as: OR [95% confidence interval].
IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis; OR, odds ratio.
[*], nested case-control study in a cohort study.

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were reported by the EpiCom inception cohort.[34] Presumably diet alone is inadequate to cause IBD, but there is evidence for a gene/diet interaction, in which variants in genes for fatty acid metabolism affect the relationship between IBD risk and PUFA consumption.[63]

Another aspect is the growing evidence that dietary changes, most notably high-fat and high-sugar Western diets, have had substantial effects on taxonomic, genetic, and metabolic features of our microbiota.[64–66] Long-term dietary habits determine distinct microbiota patterns as demonstrated in children in Europe and Burkina Faso, although other differences such as housing, sanitation, and medication also are involved.[67] More specifically, diets enriched in fat, phosphatidylcholine, and L-carnitine and animal proteins might promote inflammation. Conversely, other dietary factors such as carbazoles or tryptophan-enriched proteins have anti-inflammatory properties [Table 2].[68]

3.7. Coffee and caffeine

There is no clear evidence that coffee or caffeine alter the likelihood of developing IBD. The possible exception are patients with primary sclerosing cholangitis [PSC]; a large retrospective cohort study showed patients with PSC were more likely to have never consumed coffee than healthy controls.[69] Questionnaire-based studies of coffee consumption among IBD sufferers are difficult to interpret. A significant group of IBD sufferers, especially CD patients, avoid coffee as they believe it worsens symptoms.[70]

A small double-blind trial suggests that a combination of myrrh, caffeine, and camomile protects against remission of UC. The protection offered is not significantly different from that associated with mesalazine.[71]

3.8. Alcohol

Data regarding alcohol intake are conflicting. One case-controlled study of 384 subjects showed alcohol use to be protective against UC onset with an odds ratio of 0.57 [95% CI 0.37–0.86].[72] However, this trend has not been replicated in all cohorts; a separate case-controlled study of 177 UC subjects showed no correlation,[73] whereas a prospective evaluation of dietary risk factors for relapse in UC identified an association between alcohol consumption and relapse.[74]

3.9. Microbiome

ECCO Current Practice Position 7

Dysbiosis is associated with IBD phenotype. Environmental factors including diet and antibiotics may be associated with dysbiosis; however, causation is not proven

Recent advances in culture-independent techniques have improved our understanding of the gut microbiota as well as the importance of its interaction with the mucosal immune system in the pathogenesis of IBD.[75] Dysbiosis—the decrease in the diversity and stability of both mucosa-associated bacteria and faecal bacteria reported in IBD patients—is likely to be the result of environmental factors, including antibiotics and various intestinal micro-organisms that cause imbalance in the interplay between the gut microflora and the immune system, thereby functioning as causative or triggering agents for IBD.

Over the years, many different micro-organisms have been proposed as aetiological agents for IBD. *Mycobacterium avium* subspecies *paratuberculosis* [MAP] causes Johne's disease, a chronic granulomatous ileitis in cattle similar to CD, and has been intensively studied. Several studies have found a higher prevalence of MAP in CD patients compared with controls[76–81] but many have found no association.[82–84]

Other studies have shown that gastrointestinal infections,[85,86] especially with *Campylobacter* and *Salmonella*,[87] are associated with developing IBD in the first year after infection. A meta-analysis of nine studies found a significant association between *Campylobacter* spp. and IBD (pooled OR 3.0 [95% CI 1.3–6.6]).[88] A subset of *Escherichia coli* with adherent and invasive properties (adherent-invasive *Escherichia coli* [AIEC]) has been found to be highly prevalent in CD.[89–91] AEIC are able to adhere to intestinal epithelial cells and to penetrate the epithelial barrier, as well as to replicate within both epithelial cells and macrophages.[92,93] *Helicobacter pylori* infection, on the other hand, is associated with a reduced risk for IBD with a pooled OR of 0.4 [95% CI 0.4–0.5] regardless of age, type of IBD, and ethnicity.[94]

Table 2. Effect of different food components on microbiota and gut immune system [adapted from Tilg *et al.*].

Effect	Food components	Interaction with microbiota	Immunological effect
Inflammatory	Red meat, eggs, milk, animal proteins	Yes [decrease of SCFA-producing bacteria]	↑ Pro-inflammatory cytokines
	High-fat diet [saturated fats]	Yes + increased intestinal permeability	Endotoxaemia ↑ Intestinal cytokine expression
	Milk-derived fat [saturated fats]	Yes [expansion of pathobionts]	↑ Pro-inflammatory cytokines, Th1-driven
	Omega-6 PUFA	Yes	↑ Pro-inflammatory cytokines
	Long-chain triglycerides	Unknown	Stimulation of inflammatory T cells
Anti-inflammatory	Cruciferous vegetables [carbazoles]	Yes	↑ IL-22, mucosal protection
	Vegetables, fish [tryptophan]	Yes	
	Soluble fibre [complex carbohydrates]	Yes + generation of SCFA	↑ Production of mucus and IgA↓ Proinflammatory cytokines, ↑ Tregs
	Mediterranean diet [enriched in omega-3]	Unknown	↓ Pro-inflammatory cytokines
	Medium-chain triglycerides	Unknown	Reduce inflammation

PUFA, polyunsaturated fatty acids; SCFA, short-chain fatty acids.

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Dysbiosis of gut microbiota and aberrant function of the intestinal epithelial barrier and innate and acquired immune system predispose to the development of IBDs. Mutual relationship between gut microbiota, intestinal epithelial cells, and intestinal immune cells provides a homeostatic environment in the intestine.[95] IBD patients have lower microbial diversity and Firmicutes and Bacteroidetes phyla.[96] Many studies have shown an association with IBD-gene risk loci that regulate sensing and response to microbiota [NOD2, ATG16L1, IRGM, IL23R, JAK2, IL12B, IL10, MUC19, SLC22A5, GPR35, IL27, ECM1, PTPN22, IKBL].[97] Studies profiling the gut microbiota in patients with IBD compared with controls have consistently shown changes in microbiota composition as well as reduction in overall biodiversity. Disease state is associated with a drop in abundance of several taxa. *Faecalibacterum prausnitizi* is decreased in ileal CD and it is increased during the recovery phase of UC.[98,99] Other studies showed increased numbers of adherent-invasive *E. coli*, *Enterobacteria*, *Fusobacteria*, MAP, and *Clostridium difficile* aside from *Bacteroides, Clostridia, Bifidobacteria*, and *Ruminococcaceae* in IBD patients.[97]

Metagenomic studies revealed more stability of functionality than microbiota at phylogenetic level. One study identified only nine bacterial classes associated with UC patients compared with controls, but 21 differences in functional and metabolic pathways, with similar findings for CD patients.[100] By systematically sampling both mucosa- and lumen-associated microbiota, Lavella *et al*. found significant differences in both UC and control patients.[101]

Apart from bacteria, there are fungi and viruses in the microbiome. Few studies investigated the role of fungal signatures in IBD patients.[102,103] Two decades ago, *S. cerevisia* mannan [ASCA] was found in the sera of CD patients. Fungi and *C. albicans* are particularly prevalent in CD patients, as in first-degree healthy relatives of them.[104] Paediatric IBD is associated with reduced diversity in both fungal and bacterial gut microbiota. Specific Candida taxa were found to be increased in abundance in the IBD samples.[81]

Microbiota also have a predictive value for disease recurrence in IBD. Presence of *R. gnavus, B. vulgatus,* and *C. perfringens* and absence of *Blautia* and *Roseburia* in faecal samples of patients with UC before surgery are associated with a higher risk of pouchitis.[105] Early endoscopic Crohn's recurrence was associated with high counts of *E. coli, Bacteroides*, and *Fusobacteria*.[106] A lower proportion of *F. prausnitzii* on resected ileal Crohn's mucosa was associated with endoscopic recurrence at 6 months [$p = 0.03$], suggesting that there may be a microbial signature, detectable at the time of resection, that can inform about disease behaviour and the risk of recurrence postoperatively.[107]

3.10. Pollution

ECCO Current Practice Position 8

A positive association between urban air pollution and IBD has been described. However, it is difficult to interpret whether this is a direct consequence of pollution

The main sources of air pollution are derived from transportation and industry.[108] Composition depends on the exact source. Air pollution is composed of a number of components: volatile organic compounds and particulate matter [PM]. PM includes pollen, biological components, sulphates, nitrates, organic carbon, mineral dust, polycyclic aromatic hydrocarbons, metals, and ions. PM is classified according to size, as either fine particles [diameter < 2.5 μm] or coarse [diameter < 10 μm].[10]

Pollutants enter the gastrointestinal tract either through the mucociliary clearance of inhaled pollutants from the lungs or via contaminated food.[109] These may activate or exacerbate inflammatory pathways. However, there is no direct evidence of how pollutants contribute towards IBD.[29,110]

In a case-control study, Kaplan *et al.* examined the association between pollution and IBD.[111] Overall there was no such association for newly diagnosed cases of IBD. However, an association was revealed in some subgroups. Individuals under 23 years of age were more likely to be diagnosed with CD if they lived in regions of higher pollution [OR 2.31], with a linear association between risk and increased air nitrogen oxide [NO] levels. There was a trend towards more CD diagnosis with increasing PM exposure [OR 1.73]. UC was associated with higher sulphur dioxide [SO2] levels for individuals under 25 years of age [OR 2.0]. Patients who developed CD between 44 and 57 years of age were less likely to have lived in areas of elevated NO [OR 0.56].[111] These findings may suggest that traffic-related pollutants and industrial-based pollutants may have age-specific effects on the development of IBD.

In most nations, urban regions are associated with higher air pollution levels. Some studies demonstrated that an urban household was associated with a higher incidence of IBD.[15,112,113] A systematic review and meta-analysis demonstrated a positive association between the urban environment and both CD and UC.[114] Li *et al.* demonstrated that the standardised incidence ratio for adults employed in 'driving' occupations showed that they were at an increased risk of developing CD.[115]

Clustering of IBD cases, above all in CD, occur occasionally. Exposure to contaminated surface water with bacteria has been suggested as a possible cause.[116]

Although these studies correlate air pollutants and IBD, they must be interpreted with caution as they are subject to a number of biases and further studies are required. There is no evidence correlating water pollution with IBD.

3.11. Smoking

ECCO Current Practice Position 9

Smoking is a risk factor for CD. Continuing smoking after diagnosis is a risk factor for a more severe disease course. Smoking cessation improves disease outcome
Smoking is protective against UC. Smoking cessation has a negative influence on disease course. However, due to the increased risk of death associated with smoking, starting or continuing smoking is not a treatment option

CD is 4-fold more common in smokers and also has increased prevalence in ex-smokers.[117-119] Conversely, UC is relatively rare among smokers.[117] Smoking cessation is a risk factor for UC, incurring a greater risk than never smoking.[120,121]

3.11.1. Smoking and disease course

Smokers with CD experience more strictures and fistulae, perianal involvement,[122] hospital admissions, surgery,[123,124] postoperative complications,[125] and extraintestinal manifestations.[126]

Smoking is also known to impact on response to treatment. Although meta-analysis suggests that smoking does not impact on initial tumour necrosis factor [TNF] response,[127] it is a risk factor for

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subsequent relapse.[128] The PRECISE study showed smoking to be a risk factor for loss of response to certolizumab.[129]

Studies on the impact of smoking on established UC have yielded mixed results. Smokers are prescribed fewer courses of steroids.[121] Some studies demonstrated less hospitalisation and lower rates of colectomy, whereas others showed no differences.[119,121,122] One study found smoking to be protective against pouchitis[130] and PSC.[131] However, a systematic review of 16 studies on the impact of smoking on colectomy, disease activity, proximal disease extension, and development of pouchitis found that smoking does not alter the natural history of UC.[132]

3.11.2. Smoking cessation

Smoking cessation benefits smokers with CD but can be detrimental to smokers with UC.

An interventional study investigated the impact of intensive smoking cessation advice in 474 smokers with CD.[133] After 1 year, disease patterns within the ex-smoking group were those of non-smokers. Disease flare and hospitalisation rates were significantly decreased in ex-smokers, with a benefit comparable to azathioprine as maintenance therapy.[134]

Recent ex-smokers with UC are more likely to have active disease and require medical therapy,[135] and have higher rates of hospitalisation.

Patients with IBD are often unaware of the impact of smoking.[136,137]

3.12. Cannabis

Population-based studies have shown that IBD patients are more likely to use cannabis than those without IBD.[138] Chronic analgesia requirements, surger and low quality of life scores are all predictors of cannabis use among IBD patients.[139] Both retrospective and small prospective studies have shown cannabis use to be associated with improved quality of life, weight gain, and symptom control. Cannabis has even been positively associated with the ability to work.[140]

However, there is no compelling evidence that cannabis improves disease outcome. In fact, a case-controlled study showed long-term cannabis use was associated with a 5-fold higher rate of surgery [OR 5.03, 95% CI 1.45–17.46], although the authors themselves note that the study was not designed to prove causality.[141]

3.13 Medication

3.13.1. NSAIDS and aspirin

ECCO Current Practice Position 10

There is evidence linking long-term non-steroidal anti-inflammatory drug use with future IBD onset. However, the evidence to support such an association with aspirin is conflicting

The evidence linking non-steroidal anti-inflammatory drug [NSAID] use with IBD flare is inconsistent; it is unlikely that a short-term use is detrimental

The evidence that acetylsalicylic acid and NSAIDs are risk factors for IBD is conflicting.

Several studies show a positive association between NSAID use and disease onset.[142,143] A study of IBD incident cases demonstrated high rates of current and recent NSAID use [respective ORs 2.96 and 2.51, CIs 1.32–6.64 and 1.13–5.55].[144] A case-controlled study of newly diagnosed colitis demonstrated substantially higher NSAID and aspirin use in comparison with hospital controls [OR 6.2, CI 3.2–13.5].[145] Subsequently there have been two large prospective studies on the impact of NSAIDS and aspirin, which drew different conclusions. The first was a long-term follow-up of medication and health of nurses within the USA. This study showed a moderately increased risk of incident CD (HR 1.59 [95% CI 0.99–2.56]) and UC (HR 1.87, [95% CI 1.16–2.99]) following frequent NSAID use, and no association with aspirin.[146] The second involved a European cohort study looking exclusively at aspirin use and showed a 6-fold increase in the incidence of CD, with no additional incidence of UC.[147]

The evidence linking NSAIDs and disease flare is also conflicting. Two studies, one case-controlled and one retrospective cohort, did not demonstrate an association.[148,149] There has been one challenge study investigating the administration of paracetamol, aspirin, or a variety of NSAIDs to patients with quiescent IBD.[150] No patients taking aspirin, paracetamol, or nimesulide had a flare of disease within the 4 weeks. In those taking non-selective NSAIDs [naproxen, indomethacin, diclofenac, nabumetone], 17–28% experienced a relapse, with symptoms starting within days of taking the drug.

3.13.2. Oral contraceptives and hormone replacement therapy

ECCO Current Practice Position 11

Oral contraception is a risk factor for the development of CD and UC. However, once CD or UC is established, the use of hormonal contraception does not increase the risk of flare

A meta-analysis comparing the rate of IBD between subjects exposed and not exposed to the combined oral contraceptive [COC] pill showed an increased risk of both CD and UC in the exposed group (hazard ratio 1.46 [95% CI 1.26–1.70] and 1.28 [95% CI 1.06–1.54] respectively).[151]

A meta-analysis of five studies did not demonstrate an increased risk of flare in current COC users.[152] Indeed, a recent retrospective questionnaire-based study suggested 20% women noticed an improvement in cyclical IBD symptoms, whereas only 5% felt that oral contraception worsened symptoms.[153]

3.13.3. Hormone replacement therapy

Studies investigating a link between hormone replacement therapy [HRT] and IBD in postmenopausal women are limited. In a prospective cohort study, HRT was associated with an increased incidence of UC (odds ratio 1.71 [95% CI 1.07–2.74]) but not of CD.[154]

3.13.4. Isotretinoin

ECCO Current Practice Position 12

There is no evidence for a causal relationship between isotretinoin and IBD onset

Isotretinoin is a vitamin A analogue used for the treatment of moderate to severe acne vulgaris. A potential association of isotretinoin with inflammatory bowel disease has been proposed by case reports and small case series.[155–160] Indeed, Reddy *et al.* assessed causality of isotretinoin use with IBD in 85 cases filed with the Food and Drug Administration [FDA] [1997–2002] and concluded that isotretinoin might trigger IBD in some patients.[161] Although positive associations have been found most frequently with UC,[162] a meta-analysis of published epidemiological studies [1990–2014] found an increased risk with isotretinoin use for developing CD but not UC.[163] However, the most recent large, population-based

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case-control studies from Canada[164–166] and France[167,168] and a meta-analysis[169] of these studies have cast doubts on the proposed association.

ECCO Current Practice Position 13

Within Europe and North America, exposure to antibiotics is positively associated with the development of IBD, especially CD. This association is even stronger in paediatric-onset IBD and almost exclusively seen in CD

3.13.5. Antibiotics

In a Canadian nested case-control analysis including 2234 IBD subjects and 22 346 controls, antibiotic dispensations were associated with both CD and UC; the association was stronger for UC and paralleled the number of antibiotic dispensations.[170] However, a recent meta-analysis of eight case-control and three cohort studies encompassing 7208 subjects suggested that previous antibiotic use was positively associated with newly diagnosed CD [OR 1.74, 95% CI 1.35–2.23] but not with UC [OR 1.08, 95% CI 0.91–1.27]. The strength of this association was greatestest among paediatric-onset IBD. Metronidazole and fluoroquinolones were most strongly associated.[171]

A recent prospective population-based case-control study in eight Asian countries and Australia suggested that antibiotic use prevented the development of CD [adjusted OR 0.19, 95% CI 0.07–0.52] and UC [adjusted OR 0.48, 95% CI 0.27–0.87] in Asians.[28] However, this study may suffer recall bias as the population consisted of patients older than 25 years.

In children with paediatric-onset IBD, antibiotic use within the first year of life was 19% higher than in age-matched controls without IBD.[172] Nationwide Finnish[173] and Danish[174] case-control studies showed that the risk of paediatric CD but not UC is increased with the number of antibiotic purchases from birth to the index date.

3.14. Appendectomy and tonsillectomy

ECCO Current Practice Position 14

Appendectomy appears to be protective against UC onset. In contrast, appendectomy might be a risk factor for CD Previous tonsillectomy is associated with CD. There is no such association with UC onset

Appendectomy when performed for true appendicitis appears protective against UC. A Swedish population study confirmed that the incidence of UC following appendectomy is lower than in controls [OR 0.74, 95% CI 0.64–0.86].[175] This is consistent with an earlier meta-analysis of the association between appendectomy and UC incidence.[176] Until recently, appendectomy was associated with a less severe course of colitis and lower rates of colectomy among UC sufferers [OR 0.4, 95% CI 0.2–0.78].[177] However, a recent study from the IBD Genetics Consortium database of UC patients found the opposite; appendectomy was positively associated with colectomy [OR 2.2, 95% CI 1.14.5].[178]

With CD, results have been conflicting. A Swedish population study showed appendectomy to be positively associated with development of CD for up to 20 years following surgery [OR 1.85, 95% CI 1.10–3.18].[179] Meta-analysis of risk of CD following appendectomy also supported this association, despite heterogeneity between studies [OR 1.61, 95% CI 1.26–2.02].[180] However, this risk is particularly high within a year of surgery, and indeed one study which attempted to remove bias of appendectomy at diagnosis actually showed appendectomy to be protective [OR 0.34, 95% CI 0.23–0.51].[181] Thus it is possible that a proportion of CD sufferers may undergo appendectomy before IBD diagnosis, due to clinicians mistaking ileocaecal CD for an acute appendicitis.[20]

A case-controlled study of a Danish inception cohort showed tonsillectomy to be protective against IBD [OR 0.49, 95% CI 0.31–0.78] but this finding has not been replicated in other cohorts.[182–184] A recent meta-analysis of 23 observational studies involving 19 569 patients demonstrated [after adjustment for smoking] that tonsillectomy was associated with an increased risk of developing CD [pooled OR 1.66, 95% CI 1.03–2.68] but was not with UC [OR 1.03, 95% CI 0.74–1.44].[184] Interestingly, previous tonsillectomy among Middle Eastern migrants within Australia was strongly associated with both CD and UC, but the association was weak amongst Caucasians residents.

3.15. Stress, anxiety, and depression

ECCO Current Practice Position 15

Stress, anxiety, and depression have not been proven to be risk factors for later development of IBD. However, all have shown to worsen the course of IBD. Managing these conditions optimally has been associated with a positive outcome

The relationship between psychiatric illness and IBD is bi-directional.[185] Concurrent medical illness worsens depression, and is associated with treatment resistance.[186,187] IBD suffers are known to have a greater incidence of both anxiety and depression.[188,189] Both are linked with increased rates of IBD flare,[190] as well as negative symptom perception and worse impact of IBD on lifestyle.[191]

A Canadian prospective longitudinal study suggested a causal relationship; self-reports of stress preceded increased disease activity.[192] However, a single study suggests that faecal calprotectin does not correlate with perceived stress.[193]

Managing psychological comorbidities pharmacologically is associated with a positive IBD outcome,[194] with fewer relapses and reduced steroid use.[195]

It is difficult to ascertain whether psychiatric illness is a risk factor for IBD onset. Rates of psychiatric illness, in particular anxiety and depression, are consistently higher amongst IBD patients. Walker *et al.* found that the majority of their cohort with mood disorders or anxiety suffered psychological morbidity 2 years prior to IBD diagnosis.[196] Other studies have drawn conflicting conclusions.[197–199]

3.16. Exercise

ECCO Current Practice Position 16

Data on the protective effect of exercise on later development of IBD are inconclusive. However, regular exercise in patients with quiescent or mild disease may improve outcome

A meta-analysis[200] and systematic review[201] yielded no conclusive evidence that exercise reduced IBD onset. However, a more recent prospective study of women [the Nurses' Health Study] showed

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an inverse relationship between exercise and CD incidence, and no relationship with UC.[202] A longitudinal follow-up of male military workers recruited in adolescence showed exercise at the time of recruitment was indeed protective of future IBD.[203]

Regular exercise in patients with quiescent or mild disease may improve outcome.[204,205]

3.17. Occupation

ECCO Current Practice Position 17

White-collar occupations as well as sedentary occupations are associated with IBD onset. However, prospective epidemiological studies are missing, and as such data must be interpreted with caution

In a retrospective database analysis, sedentary occupations were associated with a 2-fold increase in IBD incidence. However, individuals with IBD were also twice as likely to be out of the labour force.[206] Furthermore, a retrospective survey of a Chinese population found that the increase in UC prevalence was paralleled by higher socioeconomic status.[207] The limited number of studies prevents definitive conclusions.

3.18. Seasonal variation

ECCO Current Practice Position 18

Data regarding the impact of seasonality on IBD onset and flare are conflicting

An earlier Scandinavian population-based study, published in 1991, of 845 CD and 1330 UC patients born between 1924 and 1957, provided evidence for clustering by birth for CD and to a lesser extent UC.[208] In a cohort of 844 Jewish IBD patients an increased risk to develop CD was found in patients born in winter; the risk was reduced for patients born in spring. No association with seasonal variations was noted for UC.[209] Two additional studies from Italy and China, respectively, have found an increasing risk of onset of CD in spring and summer.[210,211] A further retrospective controlled observational study from Switzerland demonstrated an increased risk of IBD flares at times of heatwaves.[212] In a recent Canadian case-control study, men with CD had significantly more often been born between April and June [OR 1.13, 95% CI 1.03–1.25].[213] In contrast, in a Belgian cohort, being born in June was associated with a significantly reduced risk of developing CD [OR = 0.636, 95% CI 0.447–0.906; p = 0.012].[214] Furthermore an English study, comparing the months of birth of 634 patients with CD with those of the general population, could not find a statistically significant association.[215]

Ulcerative colitis showed a peak incidence in winter/early spring in a study from Turkey.[216] In a retrospective study of a Korean cohort of 727 IBD patients, birth in January and February was associated with increased risk of IBD with a nadir in autumn, though in a subgroup analysis this was only significant for UC but not CD [$\chi^2_{[3\ df]}$ = 9.668, p = 0.022].[217] In a Norwegian cohort of 420 UC patients and 142 CD patients, there was monthly seasonality [p = 0.028] in onset of symptoms from December through January for UC but not for CD.[218] Finally, other studies have not found any association between seasonality and onset of IBD. These discrepancies may be attributed to methodological differences.

Data on seasonality in established IBD are also conflicting.

3.19. Vitamin D

ECCO Current Practice Position 19

Vitamin D deficiency may influence the pathogenesis and disease course of IBD but the mechanisms are not understood

Vitamin D influences the immune system at various levels, including regulation of innate and adaptive immunity, antibacterial response, and antigen presentation.

A recent meta-analysis of 12 studies reporting on vitamin D deficiency in CD showed that 570 participants with CD had significantly higher odds of vitamin D deficiency compared with 778 controls [OR 1.63, 95% CI 1.24–2.13; p = 0.0004]. A meta-analysis of seven studies reporting on prevalence of vitamin D deficiency in UC showed that 177 participants with UC had more than double the odds of vitamin D deficiency compared with 362 controls [OR 2.28, 95% CI 1.18–4.41; p = 0.01].[219]

Several studies, in both established and newly diagnosed IBD, have reported high prevalence of vitamin D deficiency, especially in CD. However, vitamin D deficiency is also common in other chronic diseases and even in healthy subjects.[220,221] Several factors contribute to vitamin D deficiency in IBD, including inadequate sunlight exposure, inadequate dietary intake, smoking, impaired absorption, impaired conversion to active vitamin D metabolites, increased catabolism, and increased excretion. In a prospective study from the USA in women, higher predicted levels of 25[OH]D significantly reduced the risk of CD [OR 0.54, 95% CI 0.30–0.90].[222,223]

There are limited clinical data supporting an association between low levels of vitamin D and increased disease activity, especially in CD.

Data on the therapeutic use of vitamin D supplementation in patients with IBD are scarce. Only two small open-label trials and one randomised controlled trial [RCT] have shown a positive effect on disease activity in patients with CD.[224]

3.20. Geographical gradients

ECCO Current Practice Position 20

Geographical gradients correlating with the incidence of IBD have been found in various studies, though a proof of association is still missing

In a prospective study in women enrolled in the Nurses' Health Study I [NHS I] and in the NHS II, increasing latitude of residence was associated with a higher incidence of CD and UC. This north-south gradient hypothesis might in part be explained by different levels of sun exposure. Thus, the incidence of CD is higher in the northern part of the USA; compared with women residing in northern latitudes at age 30, the multivariate-adjusted HR for women residing in southern latitudes was 0.48 [95% CI 0.30–0.77] for CD and 0.62 [95% CI 0.42–0.90] for UC.[225] Increased ultraviolet light exposure has been associated with a reduced risk of inpatient surgery in CD patients.[226] In a French study, higher levels of residential sun exposure were related to significantly decreased risk of CD when adjusted for vitamin D intake [0.29, 95% CI 0.11–0.80], with no association regarding UC.[227] In a recent systematic review of high-quality population-based studies published from 2003 to 2013, Holmes *et al.* reported only a modest increase in the incidence of paediatric CD with higher latitude.[228]

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3.21. Moving to areas of different IBD incidence

ECCO Current Practice Position 21

Moving to areas of high-incidence increases the risk of IBD, particularly UC. It is not known whether moving to low-incidence areas protects against IBD

The IBD incidence varies between countries.

Migration studies support a strong environmental component in disease onset, especially with UC.[229,230] A large population study of South Asian immigrants to the UK showed IBD incidence among first-generation immigrants to be much higher than that among South Asians within Asia.[231] Subsequent follow-up showed incidence rates in the second generation to be even higher.[232] Disease phenotype among first-generation immigrants was often milder than in Caucasians; however, by the second generation it was as severe, with additional studies showing more severe disease with increased perianal involvement in patients with CD.[233]

In contrast, a Canadian population study showed lower disease incidence in first-generation immigrants.[234] However, second-generation immigrants had IBD incidence [as children] comparable to that of non-immigrant Canadians. A Swedish study of IBD in immigrant populations showed lower IBD rates compared with the native populations; however, rates were in fact higher in those who had migrated from developing nations.[235]

Little is known as to whether migration from areas of high prevalence to low prevalence is protective.

3.22. Travel and altitude

3.22.1. Impact of travel on IBD incidence

ECCO Current Practice Position 22

There is no evidence that short-term travel is an independent risk factor for IBD onset. The data on the impact of travel on established disease are conflicting

Travel poses at least a theoretical risk of IBD onset. Travel to an endemic area may expose to local environmental factors. It is known that changes to the microbiota occur relatively quickly in response to dietary changes.[65]

A study of newly diagnosed colitis showed that of the 61 patients subsequently confirmed to have IBD, 10/61 initially developed symptoms while abroad.[236] That said, there have been no large-scale prospective or population-based studies which demonstrate a clear link.

3.22.2. Impact of travel on established disease

A case-controlled study comparing those IBD patients with at least one relapse in the past year, with those in remission, showed a positive association of journey to high altitude with relapse (21/52 [40.4%] vs 8/51 [15.7%]; p = 0.005).[237] A recent case-controlled study of environmental factors did not show a link between travel and disease activity [31.8% flares vs 29.4% controls; $p = 0.85$, OR 1.12, 95% CI 0.537–2.336].[238]

Working Groups

WG1: Early life events, e.g. breast feeding, vaccination: leader, Ebbe Langholz, Denmark; Y-ECCO, Eduards Krustins, Latvia; members, Vicent Hernandez Ramirez, Spain, Konstantinos Katsanos, Greece, Elif Saritas Yuksel, Turkey.

WG2: Gut-environment interface, e.g. diet, microbiome: leader, Vito Annese, Italy, Y-ECCO, Johan Burisch, Denmark; members, Pierre Ellul, Malta, Tarkan Karakan, Turkey, Arie Levine, Israel.

WG3: Lifestyle, e.g. smoking, appendectomy: leader, Christian Maaser, Germany; Y-ECCO, Hannah Gordon, UK; members, Gerassimos John Mantzaris, Greece, Hans Strid, Sweden, Colm O' Morain, Ireland.

Reviewers on behalf of GuiCom: Andreas Sturm, Germany, Stephan Vavricka, Switzerland.

Conflict of Interest

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