- Letter
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Quantitative microbiome profiling disentangles inflammation- and bile duct obstruction-associated microbiota alterations across PSC/IBD diagnoses

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Abstract

Recent work has highlighted the importance of confounder control in microbiome association studies[1,2]. For instance, multiple pathologies previously linked to gut ecosystem dysbiosis display concomitant changes in stool consistency[3,4,5,6], a major covariate of microbiome variation[2,7]. In those cases, observed microbiota alterations could largely reflect variation in faecal water content. Moreover, stool moisture variation has been linked to fluctuations in faecal microbial load, inducing artefacts in relative abundance profile analyses[8,9]. Hence, the identification of associations between the gut microbiota and specific disease manifestations in pathologies with complex aetiologies requires a deconfounded, quantitative assessment of microbiome variation. Here, we revisit a disease association microbiome data set comprising 106 patients with primary sclerosing cholangitis (PSC) and/or inflammatory bowel disease[10]. Assessing quantitative taxon abundances[9], we study microbiome alterations beyond symptomatic stool moisture variation. We observe an increased prevalence

of a low cell count *Bacteroides* 2 enterotype across the pathologies studied, with microbial loads correlating inversely with intestinal and systemic inflammation markers. Quantitative analyses allow us to differentiate between taxa associated with either intestinal inflammation severity (*Fusobacterium*) or cholangitis/biliary obstruction (*Enterococcus*) among previously suggested PSC marker genera. We identify and validate a near-exclusion pattern between the inflammation-associated *Fusobacterium* and *Veillonella* genera, with *Fusobacterium* detection being restricted to Crohn's disease and patients with PSC–Crohn's disease. Overall, through absolute quantification and confounder control, we single out clear-cut microbiome markers associated with pathophysiological manifestations and disease diagnosis.