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Dietary intake of inulin-type fructans in active and inactive Crohn's disease and healthy controls: a case-control study

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1 **Dietary intake of inulin-type fructans in active and inactive Crohn's disease and healthy**

2 **controls: a case-control study**

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21

24

25 **Short heading:** Fructan intakes in Crohn's disease

26

27   **ABSTRACT**

28   **Background and Aims**

29   Prebiotic inulin-type fructans are widely consumed in the diet and may have contrasting

30   effects in Crohn's disease by stimulating gut microbiota and/or by generating functional

31   gastrointestinal symptoms. The aim of this study was to measure fructan and oligofructose

32   intakes in patients with active and inactive Crohn's disease compared with healthy controls.

33   **Methods**

34   Patients with active Crohn's disease (n=98), inactive Crohn's (n=99) and healthy controls

35   (n=106) were recruited to a case-control study. Dietary intake of inulin-type fructans was

36   measured using a specific food frequency questionnaire and was compared between the three

37   groups and between patients with different disease phenotypes (Montreal classification).

38   Associations between intakes and disease activity (Harvey Bradshaw Index, HBI) were also

39   undertaken.

40   **Results**

41   Patients with active Crohn's disease had lower fructan intakes (median 2.9 g/d, IQR 1.8) than

42   those with inactive Crohn's (3.6 g/d, 2.1, P=0.036) or controls (3.9 g/d, 2.1, P=0.003) and

43   lower oligofructose intakes (2.8 g/d, 1.8) than inactive Crohn's (3.5 g/d, 2.2, P=0.048) or

44   controls (3.8 g/d, 2.1, P=0.003). There were no differences in intakes related to disease site or

45   behaviour. There were negative correlations between HBI wellbeing score and fructan intake

46   (ρ=-0.154, P=0.03) and oligofructose intake (ρ=-0.156, P=0.028) and for the HBI abdominal

47   pain score and fructan (ρ=-0.164, P=0.021) and oligofructose intake (ρ=-0.157, P=0.027).

48   **Conclusions**

49   Patients with active Crohn's disease consume lower quantities of fructans and oligofructose

50   than their inactive counterparts and healthy controls. The impact of lower intakes of prebiotic

51   fructans on gut microbiota are unknown and warrant further research.

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52

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INTRODUCTION

55

56 The aetiology of Crohn's disease includes an inappropriate immune response towards

57 commensal microbiota in genetically susceptible individuals. Many studies utilising in-depth

58 molecular microbiological techniques have consistently demonstrated that the luminal and

59 mucosal microbiota in Crohn's disease are characterised by reduced diversity and lower

60 levels of *Firmicutes* such as Roseburia and *Faecalibacterium prausnitzii*.[1-3] These bacteria

61 ferment dietary substrates, including non-digestible or non-absorbed carbohydrates, to

62 produce short-chain fatty acids such as butyrate,[4] which has been shown to promote

63 immunoregulation.[5] A range of interventions that target the modification of the

64 gastrointestinal microbiota have therefore been investigated in Crohn's disease including

65 antibiotics, probiotics and prebiotics.

66

67 Prebiotics selectively stimulate the growth and/or activity of one or a limited number of

68 microbial genera/species in the gut microbiota that confer(s) health benefits to the host.[6] The

69 most widely investigated prebiotics are the inulin-type fructans, and many studies have

70 shown that dietary supplementation stimulates the numbers of bifidobacteria[6] and some

71 studies also report stimulation of *F. prausnitzii*[7] and the production of short-chain fatty

72 acids.[4,6] These findings are important to Crohn's disease since such changes in the luminal

73 and mucosal environment might therefore elicit immunological and therapeutic benefit, for

74 example the evidence of higher levels of *F. prausnitzii* in those with extended remission.[8]

75

76 Inulin-type fructans consist of D-fructose monomers linked by $\beta 2 \rightarrow 1$ bonds to form linear

77 polymers, some with a terminal glucose molecule. Inulin-type fructans refer to all molecules

78 ranging in length from 2-60 degrees of polymerisation, whilst oligofructose refers only to

79 shorter molecules of 2-10 degrees of polymerisation.[6] Inulin-type fructans are widely

80   consumed in the diet, the majority being present as oligofructose in cereals such as wheat and

81   rye and in vegetables such as onions, leeks, and asparagus, although longer polymers (i.e. 11-

82   60 degrees of polymerisation) are also contained within chicory root and artichokes.[9-11]

83

84   Despite the potential mechanisms for inulin-type fructans to benefit Crohn's disease through

85   modification of the gastrointestinal microbiota, supplementation studies have failed to result

86   in the induction of remission of active disease.[12,13] Some patients with Crohn's disease also

87   experience functional gastrointestinal symptoms (e.g. abdominal pain, bloating, diarrhoea)

88   that are not the result of active disease, and a significant minority also fulfil criteria for the

89   functional bowel disorder irritable bowel syndrome.[14] Fermentable carbohydrates such as

90   inulin-type fructans have been implicated in the generation of gastrointestinal symptoms in

91   some people with functional bowel disorders.[15,16] This presents a conundrum whereby

92   prebiotic carbohydrates that might beneficially modify the gastrointestinal microbiota and be

93   fermented to produce short-chain fatty acids, may in some also induce functional

94   gastrointestinal symptoms.

95

96   Diet and nutrition play an important role in the management of Crohn's disease and have

97   been identified as issues of primary concern in patients.[17] Many patients believe that diet can

98   induce or exacerbate symptoms[17] and self-imposed diet restrictions have been reported,

99   including of foods rich in inulin-type fructans.[18-20] To our knowledge there are no large

100 studies investigating dietary intakes of inulin-type fructans in Crohn's disease. The aim of

101 this case-control study was to measure intakes of inulin-type fructans and oligofructose in

102 patients with both active and inactive Crohn's disease compared with healthy controls.

103

METHODS

This was a case-control study using interviewer-administered questionnaires to measure intakes of inulin-type fructans from habitual diet in patients with active Crohn's disease, inactive Crohn's disease and healthy controls. This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving patients and healthy controls were approved by the National Research Ethics Service (South East Research Ethics Committee, Bromley Local Research Ethics Committee). Written informed consent was obtained from all participants prior to study enrolment.

Participants

Patients with Crohn's disease were recruited from four inflammatory bowel disease outpatient clinics across London, United Kingdom (UK). Patients were eligible if they had a documented diagnosis of Crohn's disease for at least three months, supported by radiological or histological reports and were aged between 18-65 years. Exclusion criteria included a recent change in medication (e.g. change in immunosuppressant or biologic therapy within 12 weeks, oral 5-aminosalicyclic acid or steroids within 4 weeks, use of rectal preparations during the preceding 2 weeks). Patients completed questionnaires prior to any changes in medication at that appointment to ensure that the measurement of disease activity was reflective of their recent disease activity and coincident to the period of survey of inulin-type fructan intake. Further exclusion criteria included pure perianal Crohn's disease, other gastrointestinal disorders (e.g. short bowel syndrome, previous pan-proctocolectomy / significant colonic resection), other severe major organ disorders (e.g. hepatic, renal, endocrine, respiratory, neurological, or cardiovascular disease or previous diagnosis of cancer with disease-free state $\leq$ 2 years) or self-reported pregnancy or lactation, all of which may otherwise impact on dietary intake.

129

130   Patients were categorised as having active disease if they had a Harvey Bradshaw Index

131   (HBI) of ≥4 together with a C-reactive protein >10 mg/dL and were categorised as having

132   inactive disease if they had an HBI of ≤3 and a C-reactive protein <10 mg/dL. The combined

133   use of clinical and serum inflammatory markers was used to increase the sensitivity and

134   specificity of the active and inactive definitions. Patients not fulfilling both criteria were not

135   recruited.

136

137   Healthy adults (18-65 y) were recruited as controls through a circular email sent to all

138   students and staff at King's College London and through the snowballing technique, in order

139   to recruit subjects from outside of the institution. Exclusion criteria included having Crohn's

140   disease or any other gastrointestinal disorder (e.g. ulcerative colitis, irritable bowel syndrome,

141   chronic constipation, diarrhoea), previous gastrointestinal surgery or other severe major organ

142   disorder as above, including those likely to impact dietary intake (e.g. diabetes,

143   cardiovascular disease) or self-reported pregnancy or lactation.

144

145   **Data collection**

146   Basic demographic data including sex, age, smoking status and ethnicity were collected at the

147   time of recruitment. For patients with Crohn's disease, a range of clinical information was

148   also recorded. A gastroenterologist recorded each patient's disease activity using the HBI to

149   score general wellbeing, stool frequency, pain, abdominal mass and extra-intestinal

150   manifestations.[21,22] The gastroenterologist also recorded the Crohn's disease phenotype using

151   the Montreal classification to record age at diagnosis, disease location and disease

152   behaviour.[23]

153

154   Intakes of inulin-type fructans (hereon referred to as fructans) and oligofructose were

155   measured using a specific food frequency questionnaire (FFQ).[11] The FFQ comprised 23

156   foods and drinks (eight fruits and vegetables; 15 composite foods e.g. breads, breakfast

157   cereals, pastry products etc) that make contributions to fructan and oligofructose intakes in

158   the UK diet. The FFQ has been shown to be a valid and reliable method for measuring

159   fructan and oligofructose intakes for use in dietary surveys.[11] Patients with Crohn's disease

160   and healthy controls were asked to recall the frequency and portion size of consumption of

161   the 23 items over the preceding week.

162

163   The FFQ was administered by the researcher using standardised questioning procedures in

164   order to minimise administrator bias. Flash cards were available if participants were

165   unfamiliar with some food items (e.g. asparagus, globe artichoke, Jerusalem artichoke,

166   chicory root). Data from the FFQ's were subsequently checked by a dietitian and entered into

167   a bespoke food composition database. Dietary intake of fructans and oligofructose from food

168   commodities (e.g. onion, asparagus etc) was calculated using food composition data.[9] Dietary

169   intake from composite foods was assessed by first calculating the food commodity content

170   (e.g. total wheat, total rye) of each composite food on the FFQ (e.g. breads, pastry products)

171   using the Food Commodity Intake Database (US Department of Agriculture and the US

172   Environmental Protection Agency, United States) and then calculating the fructan and

173   oligofructose content of these food commodities. Values for small, medium and large portion

174   sizes were taken from standard food portion values in the UK.[24]

175

176   **Statistical Analysis**

177   Statistical analyses were performed using SPSS software package version 20 (IBM SPSS

178   Software, NY, US). Categorical data were compared between groups using the chi-square test

179   or the Fisher's Exact test (where more than 25% of cells had counts less than 5). Parametric

180   continuous data (e.g. demographic data) was compared between the groups using an unpaired

181   t-test or one-way analysis of variance (ANOVA), as appropriate. Fructan and oligofructose

182   intakes were tested for equality of variances using Levene's test and for normality using and

183   Kolomogorov-Smirnov and Shapiro-Wilk tests. Where necessary data was transformed to

184   achieve a satisfactory residual plot. Fructan and oligofructose intakes were found to be not

185   normally distributed and therefore were compared between two groups using a Mann

186   Whitney test and between three groups using a Kruskal Wallis test and Bonferroni *post hoc*

187   correction. Fructan and oligofructose intake data was also divided into tertiles, which were

188   compared between groups using the chi-square test. Relationships between fructan and

189   oligofructose intakes and HBI score(s) were analysed using Spearman's rho. The results of all

190   tests were considered significant if P≤0.05. Categorical data is reported as n (%) and

191   continuous data as mean (SD) and/or median (IQR) as appropriate.

192

RESULTS

A total of 303 participants were recruited (98 active Crohn's disease, 99 inactive Crohn's disease, 106 healthy controls). There were no significant differences between the groups in key demographic data including age, sex or ethnicity (**Table 1**). Although not statistically significant, more patients with active Crohn's disease were current smokers (28.6%) than those with inactive disease (17.2%) or healthy controls (19.8%) (P=0.127), perhaps reflecting the impact of smoking on exacerbation of Crohn's disease.[25] Patients in the active group had mild/moderately active Crohn's disease (HBI median 9, min 4 – max 19) and those in the inactive group had only mildly elevated disease (HBI median 1, min 0 – max 3).

There were significant differences in intakes of total fructans (p<0.001) and oligofructose (p=0.001) between groups (**Table 2**). Following *post hoc* corrections, patients with active Crohn's disease were shown to have lower fructan intakes (median 2.9 g/d, IQR 1.8) than both those with inactive Crohn's disease (3.6 g/d, 2.1, P=0.036) or healthy controls (3.9 g/d, 2.1, P=0.003) and lower oligofructose intakes (median 2.8 g/d, IQR 1.8) than those with inactive Crohn's disease (3.5 g/d, 2.2, P=0.048) or healthy controls (3.8 g/d, 2.1, P=0.003). There were no significant differences in intakes of total fructans or oligofructose between the inactive Crohn's disease group and healthy controls. When all 303 participants were divided into tertiles of intake, the highest tertile of fructan intake ($\geq$ 4.19 g/d) consisted of fewer patients with active Crohn's disease (21.4%) than those with inactive Crohn's (35.4%) and healthy controls (42.5%) (P=0.006), with the same pattern for tertiles of oligofructose intake (**Table 2**).

In all participants, the majority of total fructans and oligofructose came from wheat, onion, banana and garlic, with a range of other commodities contributing very small amounts

218   ('other' e.g. leeks, rye, artichoke). There were significant differences in the contribution of

219   the major food commodities to intakes of total fructans and oligofructose between groups

220   (**Table 3**). Following *post hoc* corrections, patients with active Crohn's disease consumed a

221   greater proportion of total fructans from wheat (median 69.6%, IQR 40.6%) than both those

222   with inactive Crohn's disease (62.8%, 37.5%, P=0.039) or healthy controls (57.9%, 34.4%,

223   P=0.003) and a greater proportion of oligofructose from wheat (median 70.5%, IQR 39.8)

224   than those with inactive Crohn's disease (64.6%, 34.6%, P=0.042) or healthy controls

225   (60.9%, 32.0%, P=0.006). Furthermore, those with active Crohn's disease consumed a lower

226   proportion of total fructans (median 12.8%, IQR 25.3%) and oligofructose (13.4%, 25.7%,)

227   from onion than patients with inactive Crohn's disease (fructan 20.1%, 22.4 P=0.042;

228   oligofructose 20.9%, 22.4 P=0.033). Healthy controls consumed considerably more fructans

229   and oligofructose form other sources (e.g. leeks, rye, artichoke) than patients with Crohn's

230   disease, irrespective of whether disease was active or not (**Table 3**).

231

232   In terms of Montreal disease classification, neither disease site nor disease behaviour had a

233   significant effect on intakes of total fructans or oligofructose, either when data was analysed

234   for the combined Crohn's disease population or when active and inactive groups were

235   analysed separately (**Table 4**).

236

237   There was a significant, though small, negative correlation between patients' HBI wellbeing

238   score and both total fructan intake (ρ= -0.154, P=0.03) and oligofructose intake (ρ= -0.156,

239   P=0.028) and for the HBI abdominal pain score and total fructan (ρ= -0.164, P=0.021) and

240   oligofructose intake (ρ= -0.157, P=0.027) (**Table 5**). As the scores for these increased,

241   indicating poorer wellbeing and more severe abdominal pain, total fructan and oligofructose

242   intakes decreased. When analysed within patient groups, there was only a significant

243   correlation between higher abdominal pain score and intakes of total fructans (ρ= -0.216,

244   P=0.032) and oligofructose (ρ= -0.208, P=0.040) in patients with active Crohn's disease.

245   There were no significant associations between intakes of total fructans and oligofructose and

246   any of the other components of the HBI.

247

248   **DISCUSSION**

249   This is the first study to report intakes of fructans and oligofructose in a large sample of

250   patients with Crohn's disease, and therefore to our knowledge there are no data with which to

251   directly compare our findings. We identified lower intakes of total fructans and oligofructose

252   in patients with active disease compared to those with inactive disease and healthy controls,

253   despite no differences between patients with inactive Crohn's disease and healthy controls.

254   There were small but significant associations between lower intakes of fructans and

255   oligofructose and both impaired wellbeing and more severe abdominal pain, especially in

256   those with active disease.

257

258   The lower intakes of fructans and oligofructose in active Crohn's disease could be the result

259   of a variety of factors, including the result of specific diets to induce remission, the restriction

260   of foods or food components to reduce gastrointestinal symptoms or impaired overall dietary

261   intake.

262

263   Firstly, patients with active Crohn's disease could be following specific diets to induce

264   remission. Elimination diets such as the low fat, fibre limited, exclusion (LOFFLEX) diet are

265   sometimes used during active disease to assist in induction of remission,[26] although in the

266   current study nobody reported to be following a specific elimination diet. A systematic

267   review of randomised controlled trials recently reported little evidence of benefit of fibre

268   restriction or fibre supplementation for inducing remission in Crohn's disease.[27] Secondly,

269   patients with Crohn's disease sometimes restrict fibre intake in order to reduce

270   gastrointestinal symptoms, with dietary fibre exclusion the most common form of dietary

271   advice provided by gastroenterologists to patients with inflammatory bowel disease in the

272   UK.[28] Consequently, some studies report lower fibre intakes in active Crohn's disease

273   compared with inactive disease.[29]

274

275   However, it is important to highlight that reducing fibre intake does not necessarily equate to

276   reducing fructan intake. For example, the major dietary source of fructan is wheat, and

277   switching from wholemeal bread to refined white bread will reduce fibre intake but would

278   have little impact on fructan intake.[30] Therefore, the lower fructan intake in active Crohn's

279   disease reported here is unlikely to be merely the result of patients reducing their fibre intake

280   to induce disease remission or to reduce gastrointestinal symptoms.

281

282   Thirdly, gastrointestinal symptoms (e.g. abdominal pain, bloating) may be triggered by other

283   foods or food components and patients with active Crohn's disease may reduce their intake of

284   these to avoid such symptoms.[17] For example, one study found that 19% of patients with

285   Crohn's disease reported wheat triggered gastrointestinal symptoms,[17] whilst another found

286   that gastrointestinal symptoms were induced by a range of fructan-containing food items,

287   including breakfast cereals (15.2%), breads (18.2%), cakes and biscuits (22.6%) and

288   vegetables (19.6%).[18] A randomised controlled trial in active Crohn's disease reported greater

289   abdominal pain, flatulence and borborygmi during fructan/oligofructose supplementation,

290   albeit in doses of up to 15 g/d.[12] However, in the current study those with more severe

291   abdominal pain (higher HBI abdominal pain score) actually had lower intakes of fructan.

292   Rather than suggesting low intakes result in pain it is likely that patients with more severe

293   pain choose to avoid consumption of foods that exacerbate symptoms, such as fructan-

294   containing foods. In the current study, patients with active Crohn's disease consumed lower

295   proportions of fructan and oligofructose from onion and other vegetables (e.g. leeks,

296　asparagus, artichokes). This perhaps may be the result of a move towards consumption of less

297　diverse diets and the adoption of more basic dietary intake.

298

299　Functional gastrointestinal symptoms including abdominal pain, flatulence and diarrhoea are

300　common in Crohn's disease, with up to 44% of patients with active disease and 35% of

301　patients with inactive disease also fulfilling criteria for the functional bowel disorder irritable

302　bowel syndrome.[14] Indeed a retrospective uncontrolled study found that restriction of a range

303　of short-chain fermentable carbohydrates (fermentable oligo-, di- and monosaccharides and

304　polyols, termed FODMAPs) resulted in a significant reduction of abdominal pain (50% of

305　patients), flatulence (56%) and diarrhoea (46%) in patients with Crohn's disease, with

306　ongoing dietary restriction of fructans being a significant factor associated with reduction in

307　gastrointestinal symptoms.[31] The current study only measured intakes of fructans, and did not

308　measure intakes of other FODMAPs (e.g. α-galacto-oligosaccharides, polyols etc) that are

309　relevant to gastrointestinal symptom generation, and such studies are now warranted.

310

311　Surprisingly we showed no association between liquid stools and fructan intake. However,

312　the HBI is a validated measure of disease activity rather than a specific measure of stool

313　output and it records liquid stools, rather than liquid/loose stools or the subjective symptom

314　of diarrhoea.[21,22] We also failed to show that disease location or disease behaviour had a

315　significant effect on fructan intake. Other studies have also shown no difference across

316　Crohn's disease types in the intake of micronutrients[32] or in the prevalence of fructose

317　malabsorption.[33]

318

319　Our study showed no difference in intakes of fructans and oligofructose between patients

320　with inactive Crohn's disease and healthy controls. Indeed a number of studies,[29,34] though

321   not all,[35] fail to find any differences in total energy intake (as a marker of global food intake)

322   between inactive Crohn's disease and healthy controls. The lack of difference in fructan

323   intakes between inactive disease and the healthy controls is unlikely due to poor estimates of

324   intake in the latter (e.g. due to sampling bias) as intakes in our healthy control population

325   (fructans 3.9 g/d, oligofructose 3.8 g/d) were similar to that previously reported in the UK

326   (fructans 4.0 g/d, oligofructose 3.8 g/d).[11]

327

Clinical consequences and clinical application

329   The consequence of lower intakes of fructans and oligofructose in active Crohn's disease is

330   unclear. On one hand it may be viewed as an attempt by patients to select foods that do not

331   trigger gastrointestinal symptoms, whereas alternatively there may be concern that lower

332   intakes may negatively impact the gastrointestinal microbiota. Numerous studies indicate that

333   fructans stimulate the numbers of bifidobacteria and some studies also report stimulation of

334   *Faecalibacterium prausnitzii*.[6,7] These microbiological findings are important since higher

335   bifidobacteria have been associated with greater IL-10 positive dendritic cells and higher *F.*

336   *prausnitzii* are associated with lower IL-6 positive dendritic cells.[36] In addition, patients with

337   higher *F. prausnitzii* are more likely to have extended remission.[8] The differences in

338   gastrointestinal microbiota between active and inactive Crohn's disease has been extensively

339   investigated,[1-3] but the potential modifying effect of differences in dietary intake on this

340   association (including that of fructan and oligofructose) has not been explored and is now

341   warranted.

342

343   Recent guidelines for the dietetic management of patients with Crohn's disease have

344   recommended that exclusion diet be considered in maintenance of Crohn's disease, and that

345   restriction of short-chain fermentable carbohydrates may potentially be useful in those who

346 experience functional gastrointestinal symptoms.[37] However, only a minority of patients with

347 inflammatory bowel disease are given tailored dietary advice by a gastroenterologist or

348 dietitian[17,28] and therefore patients with IBD may seek alternative and potentially less

349 evidence-based alternatives.[26] This may lead to the unnecessary avoidance of foods that

350 contribute important nutritional and non-nutritional components to the diet.

351

352 **Strengths and limitations**

353 The data presented here are from a large cohort of patients with active and inactive Crohn's

354 disease and a large healthy control group with similar demographic characteristics. The use of

355 prebiotic supplements containing fructans and/or oligofructose is generally low in this patient

356 group[38] and none of the patients in the current study were using such supplements and

357 therefore the fructan intakes reported here constitute the total amounts consumed. However,

358 we did not measure body weight, body mass index or total dietary intake, and therefore the

359 findings may reflect lower intake of all foods, rather than just those containing fructans and

360 oligofructose specifically. However the evidence for reduction in global food intake during

361 active Crohn's disease is equivocal.

362

363 The FFQ used in this study has been validated in a healthy population, but not in patients

364 with Crohn's disease. Whilst our cohort were similar in gender and age to those in the

365 validation study, dietary assessment tools should be validated in the population in which they

366 are to be used. It was also developed using the standard food composition data available at

367 the time[9] which did not include subsequent data for the fructan and oligofructose content of a

368 wider range of foods including various other vegetables[40] and cereals.[41] We may therefore

369 have underestimated fructan and oligofructose intakes, although this would have occurred

370 consistently across all three groups, unless these additional foods are differentially consumed

371 between active and inactive disease and health. Finally, the FFQ measured short-term intake

372 only. We therefore cannot comment on longer term intakes of fructans and oligofructose and

373 do not attempt to make any associations with the pathogenesis of disease activity. Further

374 research on whole diet intake in Crohn's disease that includes analysis of intakes of a range

375 of carbohydrates is required in order to explore the relationship between diet, disease activity

376 and gastrointestinal symptoms further.

377

378 **CONCLUSION**

379 Patients with active Crohn's disease consume lower amounts of fructans and oligofructose

380 than their inactive counterparts and healthy controls. This is particularly the case for those

381 with poorer well-being and more severe abdominal pain. Vegetable such as onion, leeks and

382 artichokes etc contributed lower proportions to fructan and oligofructose intakes in patients

383 with active Crohn's disease. The lower intakes of fructan and oligofructose may be the result

384 of specific diets to induce remission, the restriction of foods or food components to reduce

385 gastrointestinal symptoms or impaired dietary intake. The impact of the lower intakes of

386 these prebiotic compounds in active Crohn's disease are unknown and warrant further

387 research.

388

389

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394

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399   Protection Agency for the use of the Food Commodity Intake Database.

400

401   **AUTHORSHIP**

402   KW, JOL and AJS formulated the research question; JLA and KW designed the study; JLA,

403   CRH, JLB, AK, SN, AH, AF and JOL recruited participants and performed all

404   measurements; JLA and KW analysed data; JLA and KW wrote the manuscript; all authors

405   critically commented on and approved the final manuscript.

406

407

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531

532 **Table 1 Participant demographic and clinical data**

	Active Crohn's (n= 98)		Inactive Crohn's (n=99)		Healthy controls (n=106)		P value
Age, *y, mean (SD)*	38. 5	(12.8)	36.2	(11.2)	36.6	(8.5)	0.283[*]
Females, *n (%)*	61	(62.2)	54	(54.5)	64	(60.4)	0.516[†]
Current smoker, *n (%)*	28	(28.6)	17	(17.2)	21	(19.8)	0.127[†]
Ethnicity, *n (%)*							0.651[†]
White	67	(68.4)	74	(74.7)	76	(71.7)	
Asian	22	(22.4)	15	(15.2)	23	(21.7)	
Black	5	(5.1)	8	(8.1)	5	(4.7)	
Mixed/other	4	(4.1)	2	(2.0)	2	(1.9)	
Harvey Bradshaw Index, *median (IQR)*	9	(4)	1	(2)	-	-	<0.001[‡]
Montreal Classification							
Disease duration, *y, mean (SD)*	10.5	(7.6)	14.0	(10.6)	-	-	0.008[§]
Disease Location, *n (%)*							0.061[†]
L1 Ileal	13	(13.3)	26	(26.3)	-	-	
L2 Colon	22	(22.4)	22	(22.2)	-	-	
L3 Ileocolonic	63	(64.3)	51	(51.5)	-	-	
L4 Disease site modifier	4	(4.1)	6	(6.1)	-	-	0.747[‖]
Disease Behaviour, *n (%)*						-	-	0.454[†]
B1 Non-stricturing/penetrating	50	(51)	57	(57.6)	-	-	
B2 Stricturing	29	(29.6)	29	(29.3)	-	-	
B3 Penetrating	19	(19.4)	13	(13.1)	-	-	
P Perianal disease modifier	20	(20.4)	22	(22.2)	-	-	0.862[‖]

533 [*] P values are the result of an ANOVA

534 [†] P values are the result of a chi-squared test

27

535   ‡ P values are the result of a Mann Whitney test

536   § P values are the result of an unpaired t-test

537   ∥ P values are the result of a Fisher's exact test

538

539   **Table 2 Total fructan and oligofructose intakes (g/d) and tertiles of intake among**

540   **patients with Crohn's disease and healthy controls**

	Active Crohn's (n=98)		Inactive Crohn's (n=99)		Healthy controls (n=106)		P value
Total fructans							
Daily intakes, g/d, *median (IQR)*	2.9	(1.8)[a]	3.6	(2.1)[b]	3.9	(2.1)[b]	<0.001[*]
Tertiles of fructan intake, *n (%)*							0.006[†]
Low (≤ 2.77 g/d)	45	(45.9)	30	(30.3)	26	(24.5)	
Medium (2.78 - 4.18 g/d)	32	(32.7)	34	(34.3)	35	(33.0)	
High (≥ 4.19 g/d)	21	(21.4)	35	(35.4)	45	(42.5)	
Oligofructose							
Daily intakes, g/d, *median (IQR)*	2.8	(1.8)[a]	3.5	(2.2)[b]	3.8	(2.1)[b]	0.001[*]
Tertiles of oligofructose intake, *n (%)*							0.018[†]
Low (≤ 2.69 g/d)	44	(44.9)	30	(30.3)	27	(25.5)	
Medium (2.70 – 4.05 g/d)	32	(32.7)	34	(34.3)	35	(33.0)	
High (≥ 4.06 g/d)	22	(22.4)	35	(35.4)	44	(41.5)	

541   Values within a row with unlike superscript letters were significantly different following a

542   Mann Whitney test and Bonferroni *post hoc* correction.

543   [*] P values are the result of a Kruskal Wallis test

544   [†] P values are the result of a chi-squared test

545

546   **Table 3 Percentage contribution of food commodities to intakes of total fructans and**

547   **oligofructose among patients with Crohn's disease and healthy controls**

Percentage contribution to intakes, *median (IQR)*	Active Crohn's (n=98)		Inactive Crohn's (n=99)		Healthy controls (n=106)		P value[*]
Total fructans							
Wheat	69.6	(40.6)[a]	62.8	(37.5)[b]	57.9	(34.3)[b]	0.003
Onion	12.8	(25.3)[a]	20.1	(22.4)[b]	17.4	(23.6)[a,b]	0.048
Banana	0.0	(5.8)[a]	2.2	(7.3)[a]	2.8	(8.0)[b]	0.033
Garlic	0.9	(2.1)[a]	1.8	(4.1)[b]	0.9	(3.3)[a,b]	0.001
Other[†]	0.02	(6.3)[a]	0.03	(9.6)[a]	7.4	(27.0)[b]	<0.001
Oligofructose							
Wheat	70.5	(39.8)[a]	64.6	(34.6)[b]	60.9	(32.0)[b]	0.005
Onion	13.4	(25.7)[a]	20.9	(22.4)[b]	17.6	(23.6)[a,b]	0.036
Banana	0.0	(6.2)[a]	2.2	(7.3)[a]	3.1	(8.5)[b]	0.026
Garlic	0.4	(0.8)[a]	0.7	(1.9)[b]	0.4	(1.4)[a,b]	0.001
Other[†]	0.02	(5.5)[a]	0.03	(6.8)[a]	5.3	(22.5)[b]	<0.001

548   Values within a row with unlike superscript letters were significantly different following a

549   Mann Whitney test and Bonferroni *post hoc* correction.

550   [*] P values are the result of a Kruskal Wallis test

551   [†] "Other" represents the combined percentage contribution from leeks, asparagus, barley,

552   globe artichoke, jerusalem artichoke, rye and dandelion; each of which contributed <1% of

553   total fructan and oligofructose OF intake for >80% participants.

554

555 **Table 4 Total fructan and oligofructose intakes of patients with Crohn's disease**

556 **comparing different Montreal disease classifications**

Disease Site	Ileal		Colonic		Ileocolonic		P value[*]
Total fructan intakes, g/d, *median (IQR)*							
All Crohn's disease (n=39, 44, 114)	3.4	(2.1)	3.3	(2.1)	3.1	(2.3)	0.265
Active Crohn's (n=13, 22, 63)	2.8	(2.4)	2.7	(1.6)	3.0	(1.9)	0.942
Inactive Crohn's (n=26, 22, 51)	3.9	(3.4)	3.6	(1.9)	3.2	(2.6)	0.224
Oligofructose intakes, g/d, *median (IQR)*							
All Crohn's disease	3.4	(1.7)	3.2	(2.0)	2.9	(2.1)	0.281
Active Crohn's	2.8	(2.1)	2.5	(1.6)	2.9	(1.9)	0.910
Inactive Crohn's	3.6	(3.4)	3.5	(1.8)	2.9	(2.7)	0.215

Disease Behaviour	Non stricturing, non-penetrating		Stricturing		Penetrating		P value[*]
Total fructan intakes, g/d, *median (IQR)*							
All Crohn's disease (n=107, 58, 32)	3.1	(2.3)	3.3	(2.7)	2.9	(1.3)	0.597
Active Crohn's (n=50, 29, 19)	2.5	(1.7)	3.2	(2.0)	2.9	(1.7)	0.508
Inactive Crohn's (n=57, 29, 13)	3.6	(1.9)	3.6	(3.3)	3.1	(1.5)	0.832
Oligofructose intakes, g/d, *median (IQR)*							
All Crohn's disease	3.1	(2.1)	3.2	(2.6)	2.9	(1.3)	0.498
Active Crohn's	2.3	(1.8)	3.0	(2.0)	2.8	(1.7)	0.424
Inactive Crohn's	3.4	(1.8)	3.6	(3.0)	3.1	(1.5)	0.832

557 [*] P values are the result of a Kruskal Wallis Test

558

559 **Table 5 Spearman's rho correlation between Harvey Bradshaw Index total score, and**

	All Crohn's (n=197)		Active Crohn's (n=98)		Inactive Crohn's (n=99)	
	ρ^*	P value	ρ^*	P value	ρ^*	P value
Total fructan intake						
HBI Total Score	-0.131	0.066	-0.081	0.429	0.182	0.071
Wellbeing	-0.154[†]	0.030	-0.115	0.260	0.082	0.417
Abdominal Pain	-0.164[†]	0.021	-0.216[†]	0.032	0.170	0.093
Liquid stools	-0.127	0.075	-0.001	0.990	0.141	0.163
Abdominal Mass	-0.040	0.573	0.034	0.740	-	-
Complications	-0.014	0.844	0.162	0.112	0.027	0.787
Oligofructose intake						
HBI Total Score	-0.128	0.073	-0.084	0.413	0.169	0.095
Wellbeing	-0.156[†]	0.028	-0.114	0.262	0.051	0.615
Abdominal Pain	-0.157[†]	0.027	-0.208[†]	0.040	0.152	0.132
Liquid stools	-0.121	0.089	-0.004	0.970	0.146	0.149
Abdominal Mass	-0.033	0.648	0.038	0.712	-	-
Complications	-0.010	0.891	0.158	0.120	0.028	0.785

560 **component scores, and intakes of total fructans and oligofructose**

561 [*] Spearman's rho correlation coefficient (ρ)

562 [†] Correlation is significant at the 0.05 level (2-tailed)

563