1 **SUPPLEMENTARY MATERIAL**

2

3 ## *1. SUPPLEMENTARY METHODS*

4 ### 1.1 Trial design

5 Participants arrived at the first study visit after an overnight fast (minimum eight hours
6 fasted), where the pre-intervention (T0) blood sample was drawn, and anthropometric
7 measures were taken. Then the first sensor for the Continuous Glucose Monitoring (CGM)
8 was placed. The study procedure was explained along with handing out the diaries for the
9 bowel function and (gastrointestinal) well-being and sachets for the run-in period. At home,
10 participants filled in the study diary for the past week, collected the first faecal sample
11 (stored directly in-home freezer) and measured their glucose levels using the CGM. Three
12 days after the first study visit, participants started consuming the treatment or placebo. At
13 the end of the run-in period (T1), prior to the second study visit, participants collected the
14 second faecal sample. On the second study visit, participants returned the faecal samples in
15 frozen form and the diaries of the baseline and run-in period along with the empty leftover
16 sachets of the run-in period. Anthropometric measures were taken again, the CGM sensor
17 was replaced and new diaries along with the sachets for the intervention period were
18 handed out. At the end of the intervention period (T2) participants collected the third faecal
19 sample. At the third study visit participants arrived again fasted and the post-intervention
20 blood sample was taken as well as anthropometric measures. The second CGM was
21 removed, and the diaries of the intervention period and the empty and leftover sachets
22 were returned. Participants received the diaries of the wash-out period. At the end of the
23 wash-out period (T3) participants collected the fourth faecal sample, after which the third

24 and fourth faecal sample were transported to the university together with the diaries of the
25 wash-out period.
26 The products were provided as single, daily dosage packed in transparent sachets stored in
27 nontransparent bags for each week of the study. Intervention products were provided by a
28 third, independent researcher. Neither the researchers nor the participants were told which
29 intervention product they received. As the placebo product could not fully match the
30 treatment product in colour, taste and shape, implying the possibility of participants to being
31 not fully blinded, the study was considered investigator-blinded. Participants were
32 instructed to consume the content of one sachet per day, preferably in the morning with
33 their breakfast or morning snack. Compliance was assessed by counting empty and leftover
34 sachets. All participants were instructed to maintain their normal diet and level of physical
35 activity throughout the whole study.
36
37 **1.2 Short-chain fatty analysis in faeces**
38 Faecal samples were collected at home by the volunteers using sterile tubes and directly
39 frozen in the home freezer at -20 °C. The samples were transported in frozen form within
40 one month to the study centre where they were further stored at -80 °C. Quantification of
41 faecal SCFA was done by analysing faecal water using high-performance chromatography
42 (HPLC) similar to previously described methods (Bui et al., 2019). In short, faecal samples
43 were diluted in water by mixing 0.2 g faeces with 0.8 mL water and subsequently centrifuged
44 for 5 min at 21130 RCF at 4 °C. Standards of acetic acid, butyric acid, propionic acid,
45 isobutyric acid and lactate were prepared in concentrations ranging from 2.5-20 mM. Then,
46 160 µL of standard or sample was mixed with 40 µL of 10 mM DSMO in 0.1 N H_2SO_4 as
47 internal standard for analysis. SCFA were quantified using high-performance liquid

48 chromatography on a Shimadzu LC_2030C equipped with a refractive index detector and a
49 Shodex SH1011 column. Ten µL of the sample was injected at an oven temperature of 45 °C
50 with a flow rate of 1.00 mL/min using 0.01 N H_2SO_4 as eluent.
51
52 **1.3 Diaries for bowel function and well-being**
53 Participants were asked to record their bowel function and (gastrointestinal) well-being
54 using weekly questionnaires. Bowel function was assessed as average stool softness over the
55 last week using the Bristol Stool Scale and stool frequency as average number of stools per
56 day during the last week. Gastrointestinal symptoms and satiety feelings were recorded
57 using a 0 - 100 visual analogue scale.
58
59 **1.4 Gut microbiota analysis.**
60 Bacterial DNA was extracted from frozen faecal samples that were thawed on ice, using the
61 repeated bead-beating method as described before (Salonen et al., 2010) and purified using
62 the Maxwell® 16 Tissue LEV DNA Purification Kit. The quantity of the extracted DNA was
63 assessed using a Nanodrop spectrophotometer (Thermo Fisher Scientific). Microbiota
64 composition was analysed by Illumina MiSeq sequencing of the 16S rRNA gene hypervariable
65 V3-V4 region using primers 341F/785R as previously described (Korpela et al., 2018).
66 Sequences were further processed using the mare package in R (Korpela, 2016) that relies on
67 USEARCH (Edgar, 2010). In short, only forward reads were used, primers were cut from the
68 5'-end of each read, and reads were quality filtered with quality score 2 and truncated to a
69 length of 150 bp. The rarest reads, likely sequencing errors, were removed based on a
70 minimum read abundance of 0.005%. After quality filtering, we obtained on average 34952
71 reads per sample, ranging from 3164 to 78916. The reads were taxonomically annotated

72 using USEARCH (Edgar, 2010) to map to the SILVA 16S rRNA reference database version 115
73 (Quast et al., 2013). OTUs (operational taxonomic unit), with clustering at 97% identity, were
74 used to calculate the diversity and richness measures. Further analyses were performed
75 using the mare package. The data has been submitted to the European Nucleotide Archive
76 (ENA) under the accession number PRJEB47230. To attain species level annotations, the
77 same reads were annotated using the BLAST function (Camacho et al., 2009) in the mare
78 package.
79
80 **1.5 Trophic chain *in vitro* experiment - synthetic co- and tri-cultures**
81 As a proof-of-concept a trophic chain experiment with dried chicory root (WholeFiber™) was
82 performed using synthetic co- and tri-cultures with strains having the canonical functionality
83 of the genera of interest. For this purpose *Bifidobacterium animalis subsp. lactis* BLC1
84 (obtained from Dr L Morelli Sacco SRL), *Anaerostipes rhamnosivorans* 1Y2^T (Laboratory of
85 Microbiology, Wageningen University & Research) and *Bacteroides xylanisolvens* HMP
86 (obtained from the Human Microbiome Program as HMP 2_1_22) were grown in co- or
87 tricultures. Bacteria were routinely maintained in a modified yeast extract, casitone fatty
88 acid (YCFA) medium (Duncan et al., 2009) supplemented with 20 mM xylose and 20 mM
89 galactose for *Bacteroides xylanisolvens* HMP or 20 mM glucose for *Bifidobacterium animalis*
90 *subsp. lactis* BLC1 and *Anaerostipes rhamnosivorans* 1Y2^T. All growth experiments were
91 performed in duplicate in the modified YCFA medium (Duncan et al., 2009) containing 5 g/L
92 WholeFiber™. Equal amounts of the overnight preculture of the three individual bacteria
93 (5%, v/v) were simultaneously added to the media to complete the tri-culture. In parallel,
94 same amounts of *Bacteroides xylanisolvens* HMP and *Bifidobacterium animalis subsp. lactis*
95 BLC1 were added in the modified YCFA medium with dried chicory roots. All cultures were

96 subsequently incubated at 37°C up to seven days. Gas and liquid samples were collected at
97 different time intervals for H_2 and organic acid analysis, respectively, as previously described
98 (Bui et al., 2019).

99 **1.6 Circulating short-chain fatty analysis in plasma**

100 Fasting blood samples were collected after antecubital venepuncture into BD® EDTA K2E
101 vacutainers (4 mL). Samples were centrifuged for 10 min at 4 °C and 12,000 x g and
102 subsequently stored at -80 °C until further analysis. Fasting circulating short-chain fatty acids
103 in plasma were derivatized prior to measurement on a liquid-chromatography triple
104 quadrupole mass-spectrometry (LC-MS/MS) as previously described (Han et al., 2015) and
105 optimized (van Dongen et al., 2021). The protocol was further adapted as described in the
106 following. All chemicals were prepared at room temperature (RT). Plasma samples were first
107 centrifuged for 5 min at RT and 14,000 x g. The supernatant was spiked with a mix of each
108 1 mM deuterated acetate (acetate-d_4) and butyrate (butyrate-d_7) by adding 5 µL of the
109 deuterated SCFA mix to 45 µL of sample to achieve a concentration of 0.1 mM in the sample.
110 The sample was subsequently cleaned by adding 50 µL spiked sample to 150 µL 100%
111 acetonitrile (ratio 1:3) at RT and mixing by inversion. Subsequently, samples were
112 centrifuged for 20 min at 14,000 x g. A volume of 100 µL of the supernatant was transferred
113 in a low-binding Eppendorf tube to which 100 µL 200 mM 3-nitrophenylhydrazine (3NPH) in
114 40% acetonitrile and 100 µL 120 mM 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC)
115 with 6% pyridine in 40% acetonitrile were added. All reagents were prepared freshly in glass
116 tubes at RT. After mixing by inversion the samples were derivatized by heating at 40 °C for
117 30 min while shaking in a thermomixer. Subsequently, samples were cooled on ice for 1 min,
118 100 µL of ice-cold water was added and samples were mixed by inversion. Derivatized
119 samples were centrifuged for 5 min at 14,000 x g. A volume of 90 µL of the sample was

120 transferred to a LC-MS/MS vial to which 10 µL of an internal standard was added, which
121 consisted 0.15 mM acetate, 0.1 mM butyrate and 0.1 mM propionate derivatized using
122 isotope labelled $^{13}C_6$-3NPH instead of 3NPH as described before (van Dongen et al., 2021).
123 For quantification, a calibration curve was made by derivatizing known concentrations of
124 acetate, butyrate and propionate in the range of 0-60 µM as described above, of which 90 µL
125 was mixed with 10 µL of the internal standard as done for the samples. Samples were stored
126 at 4 °C until measurement on the same or subsequent day using a Shimadzu Nexera XR LC-
127 20AD XR UPLC system coupled to a Shimadzu LCMS-8050 triple quadruple mass
128 spectrometer (Kyoto, Japan). 10 µL of sample were injected onto a Phenomenex C18 column
129 (50 x 2.1 mM, 1.7 µm) at 40 °C. The mobile phase consisted of a gradient made from
130 ultrapure water with 0.1% formic acid (v/v) (mobile phase A) and acetonitrile with 0.1%
131 formic acid (v/v) (mobile phase B). The gradient started with 100% mobile phase A, reaching
132 70% mobile phase A at 6 min, and further decreasing to 30% mobile phase A at 8 min. At
133 9 min 0% mobile phase A was reached and was kept until 10 min, returning to 100% mobile
134 phase A at 10.5 min and kept at these initial conditions up to 15 min. The LCMS-8050 was
135 equipped with an electrospray ionization (ESI) source and used for multiple reaction
136 monitoring (MRM) quantification in negative mode with the MRM transitions from precursor
137 to product with corresponding retention times as given in **Table S1.** A nebulizing gas flow of
138 3 L/min was combined with a heating gas flow of 10 L/min, an interface temperature of
139 300 °C, a desolvation temperature of 526 °C, a desolvation line temperature of 250 °C and a
140 heat block temperature of 400 °C. The drying gas flow was set at 10 L/min.
141 To quantify SCFA concentrations the peak areas of the calibration curve standards were
142 divided by the peak area of their corresponding ^{13}C isotope-labelled SCFA. Concentrations of
143 SCFA in the samples were then calculated in the same way by dividing each SCFA peak area

144 for its corresponding ^{13}C isotope-labelled internal standard peak area. The variation
145 measured by the ratio of the spiked-in deuterated acetate and butyrate corrected for their
146 corresponding ^{13}C isotope labelled SCFA was found to be 13% and 10%, respectively. As
147 butyrate is partially consumed by enterocytes (Deleu et al., 2021), circulating butyrate levels
148 were close to the quantification threshold and, in certain cases, negative (mostly in the
149 placebo group after the study). Hence all negative values were set equal to zero before
150 further analysis and non-parametric distributions were assumed for the statistical analysis of
151 this SCFA.

152

153 **Table S1 Retention times and reaction monitoring transitions for detection of the derivatized short chain**
154 **fatty acids by liquid-chromatography triple quadrupole mass-spectrometry.**

Short-chain fatty acid	**Retention time (min)**	**Precursor ion *(m/z)***	**Product ion *(m/z)***	**Collision energy (V)**
Acetate 3NPH	4.35	194.0	137.1	17.0
Acetate $^{13}C_6$-3NPH	4.35	200.1	143.1	17.0
Acetate-d_4 3NPH	4.32	197.1	137.1	17.0
Propionate 3NPH	5.41	208.0	137.1	19.0
Propionate $^{13}C_6$-3NPH	5.41	214.1	143.1	19.0
Butyrate 3NPH	6.54	222.1	137.1	19.0
Butyrate $^{13}C_6$-3NPH	6.54	228.1	143.1	19.0
Butyrate-d_7 3NPH	6.54	229.1	137.1	19.0

155 **3NPH, 3-nitrophenylhydrazine**
156

157 **1.7 Glucose homeostasis markers**

158 Fasting blood samples were collected after antecubital venepuncture into BD® sodium
159 fluoride vacutainers (2 mL) for glucose measurement and into BD® EDTA K2E vacutainers
160 (4 mL) for insulin. Samples were centrifuged for 10 min at 4 °C and 12,000 x g and

161 subsequently stored at -80 °C until further analysis. Fasting glucose concentrations were
162 analysed in the automated systems of the local hospital “De Gelderse Vallei” (Ede, The
163 Netherlands). Fasting insulin concentrations were measured with enzyme-linked
164 immunosorbent assay (ELISA) (Mercodia Ultrasensitive Insulin ELISA, Uppsala, Sweden).
165 HOMA-ir values were calculated from fasting glucose and fasting insulin values using the
166 HOMA2 calculator (https://www.dtu.ox.ac.uk/homacalculator) (Levy et al., 1998; Matthews
167 et al., 1985).
168
169 **1.8 Continuous Glucose Monitoring**
170 Abbott’s FreeStyle Libre Flash was used for Continuous Glucose Monitoring (CGM; Abbott,
171 Marne-la-Vallée, France). The system used in this study measured for up to 14 days every
172 15 min the glucose profiles in the interstitial fluid using a sensor and a reader. The CGM
173 sensor was placed on the upper back of the arm preferred by the participant and following
174 the manufacturer instructions. If necessary, the sensors were additionally secured by
175 covering them with medical tape (leaving a hole in the middle on top of the sensor for
176 moisture removal). When a sensor was lost before the end of the 14-day period, it was
177 replaced with a new one. Every participant received an accompanying reader and was
178 instructed to read out the sensor every eight hours. The screen of the reader was covered to
179 ensure that participants were blinded to their own glucose read-outs. Each participant wore
180 a CGM twice; the first covering baseline and the run-in period and second during the first 14
181 days of the intervention period. At the end of each period data was transferred from the
182 reader to a computer using the available Freestyle Libre App.
183 CGM readouts were analysed by an in-house developed open-source R script, CGM
184 Shiny (Hangelbroek, 2021). CGM metrics were calculated for periods of three consecutive

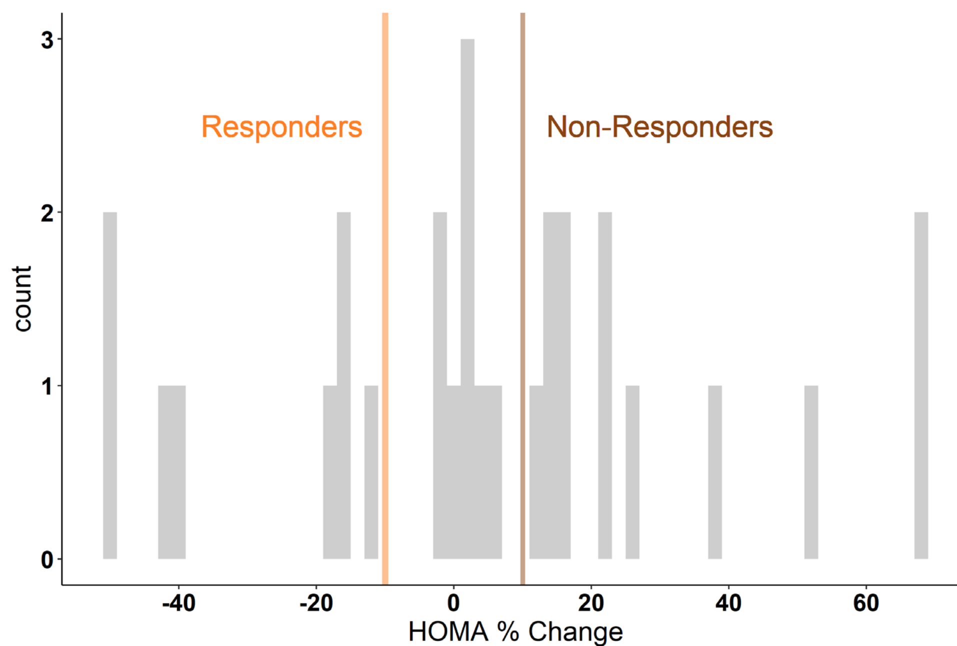
185 days covering the same weekdays (Tuesday, Wednesday, Thursday) in the baseline, the run-
186 in and the intervention period. We omitted the first hours until midnight from analysis, also
187 when sensors were replaced due to sensor loss. The first day of sensor readings was omitted
188 from analysis as recommended (Bailey et al., 2015). Calculations of CGM metrics started at
189 midnight (12 am). CGM Shiny can calculate metrics using either data from all 24 h of a day
190 (starting at midnight), or from the period subjects are awake (6:00 am to 12:00 am) or asleep
191 (12:00 am to 6:00 am) as recommended (Danne et al., 2017). Despite precise instructions, it
192 proved difficult for participants to scan the sensor every 8 h to transfer data to the reader.
193 Data gaps of less than an hour (<4 datapoints) were linearly interpolated. Larger gaps were
194 left as missing data. One subject was excluded from data analysis due to sensor failure. From
195 the CGM metrics available we selected the coefficient of variation as a measure of glucose
196 variability expressed as percentage, since it is generally well understood (Danne et al., 2017)
197 and as we observed that it strongly correlated with other glucose variability CGM metrics. To
198 understand the effect of missing data on the outcomes of the CV we conducted a sensitivity
199 analysis. We assessed the percentages of missing data and determined a threshold at 20%
200 missing data. Consequently, the subjects that had more than 20% missing data were
201 excluded from the analysis (n=4 for the placebo and n=6 for the treatment group).
202 Furthermore, we identified and extreme outlier in the placebo group (more than three times
203 interquartile range above third quartile or below first quartile), which appeared to
204 substantially influence the result and, hence, was excluded during the sensitivity analysis.
205 Similarly, an outlier was excluded from analysis when investigating differences in CV after
206 *Blautia* baseline segmentation. Following data exclusion, baseline CV was 21.3% for
207 treatment versus 19.7% for placebo with (p = 0.25).
208

1.9 Statistical analysis

The study samples size was based on the detection of a mean within-individuals reduction in fasting insulin levels of 29 pmol/L with a two-sided 5% significance level and a power of 80% requiring 27 subjects per study arm. This sample size is sufficient to detect a mean decrease of 29 pmol/L, which is lower than the 34 pmol/L found earlier with ITF (Guess et al., 2016). To account for a potential dropout rate of 10%, a final sample size of 60 patients (30 per study arm) was used. Normality of the outcome variables was assessed by inspecting Q-Q-plots. Depending on normality corresponding parametric or nonparametric testing was applied. For baseline characteristics data was expressed as mean and SD or median and IQR depending on normality to indicate spread in the study population. Changes in biochemical markers, anthropometric measures, and bowel function were expressed as absolute change and as percentage change (relative change). Statistical inference was performed on absolute changes only. The R package mare (Korpela, 2016) was used for gut microbiota analysis uses tools from the R packages vegan (Oksanen et al., 2019), nlme (Pinheiro et al., 2020), MASS (Venables & Ripley, 2002) and glmmADMB (Fournier et al., 2012; Skaug et al., 2016). Multivariate analysis for microbial composition was done using implemented Principle Coordinates Analysis with Bray-Curtis dissimilarities (Korpela, 2016). Changes in levels of individual taxa were assessed by implemented repeated measures analysis, for which the mare package uses subjects as random factor and also automatically performs false-discovery rate correction. The package checks model assumptions and consecutively fits alternative models, which in case of assumption violation by all fitted models leads to the production of no *P*-values and estimates (Korpela, 2016). To assesses differences in changes in levels of faecal SCFA over the intervention periods between the treatment groups we used using linear mixed models, as implemented in the lme4 R package (Bates et al., 2015) that

233 uses by default an unstructured variance-covariance matrix. We included SCFA as dependent
234 variable and as fixed effect intervention group and intervention period as well as their
235 interaction term and as random effect the subject. Statistical significance levels were
236 calculated using the lmerTest R package (Kuznetsova et al., 2017), which estimated degrees
237 of freedom and *P*-values based on the Satterthwaite's method. Changes over time in stool
238 softness and glycaemic variability were analysed by repeated measures mixed ANOVA (RM
239 ANOVA) with intervention group as between-subject factor, intervention period as within-
240 subject factor, intervention × study period as interaction term and pairwise t-test as post-
241 hoc test with FDR correction. Changes in stool frequency were assessed by Friedman's test
242 with Wilcoxon signed rank-test as post-hoc test with FDR correction. RM ANOVA and
243 Friedman test were performed using the rstatix R package (Kassambara, 2021). Static
244 glycaemic markers and circulating SCFA levels were assessed for differences after the study
245 period between treatment groups by ANCOVA (using baseline as covariate) and for changes
246 over baseline and comparison between groups by paired or unpaired t-test to explore the
247 modulatory potential of the treatment on biomarkers.
248
249 **1.10 Responder and further subgroup analysis**
250 To further explore gut microbiota differences in relation to metabolic responses, we divided
251 the treatment group based on the relative change in HOMA-ir into responders and non-
252 responders. Subjects with a reduction in HOMA-ir larger than 10% were defined as
253 responders (n = 8), subjects with an increase in HOMA-ir larger than 10% were defined as
254 non-responders (n = 12). Subjects with relatively unchanged HOMA-ir (eight subjects) were
255 excluded (Supplemental Figure S1). Analysis of differences in baseline microbiota highlighted
256 *Blautia* spp. as major differentiating factor between responders and non-responders

257 ($p = 0.01$). This finding was also sustained ($p = 0.02$) when we set the responder definition
258 threshold less stringent to 0% (responder = more than 0% reduction and n = 10; non-
259 responder = no reduction or more than 10% increase and n = 18). The *Blautia* spp. median
260 relative abundance was subsequently used to divide the treatment group into high (n = 14)
261 and low (n = 14) baseline abundance groups. This division was further used to analyse
262 changes in static and dynamic glycaemic biomarkers and fasting circulating SCFA in the
263 treatment group.
264

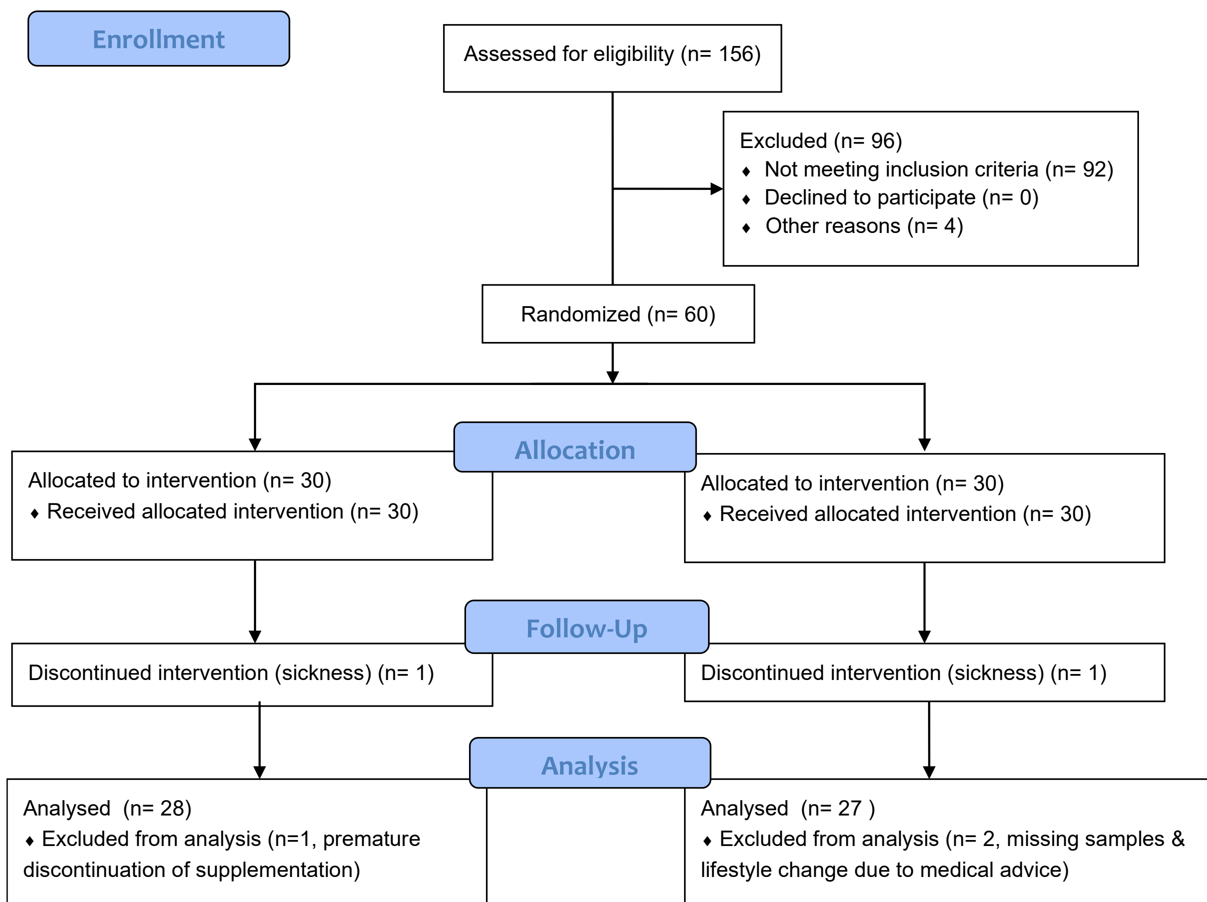


266 **Figure S1 Division of HOMA-responder and non-responders of the treatment group using a 10% cut-off**
267 **(vertical lines) and excluding subjects with relatively unchanged HOMA-ir (n=8).**
268

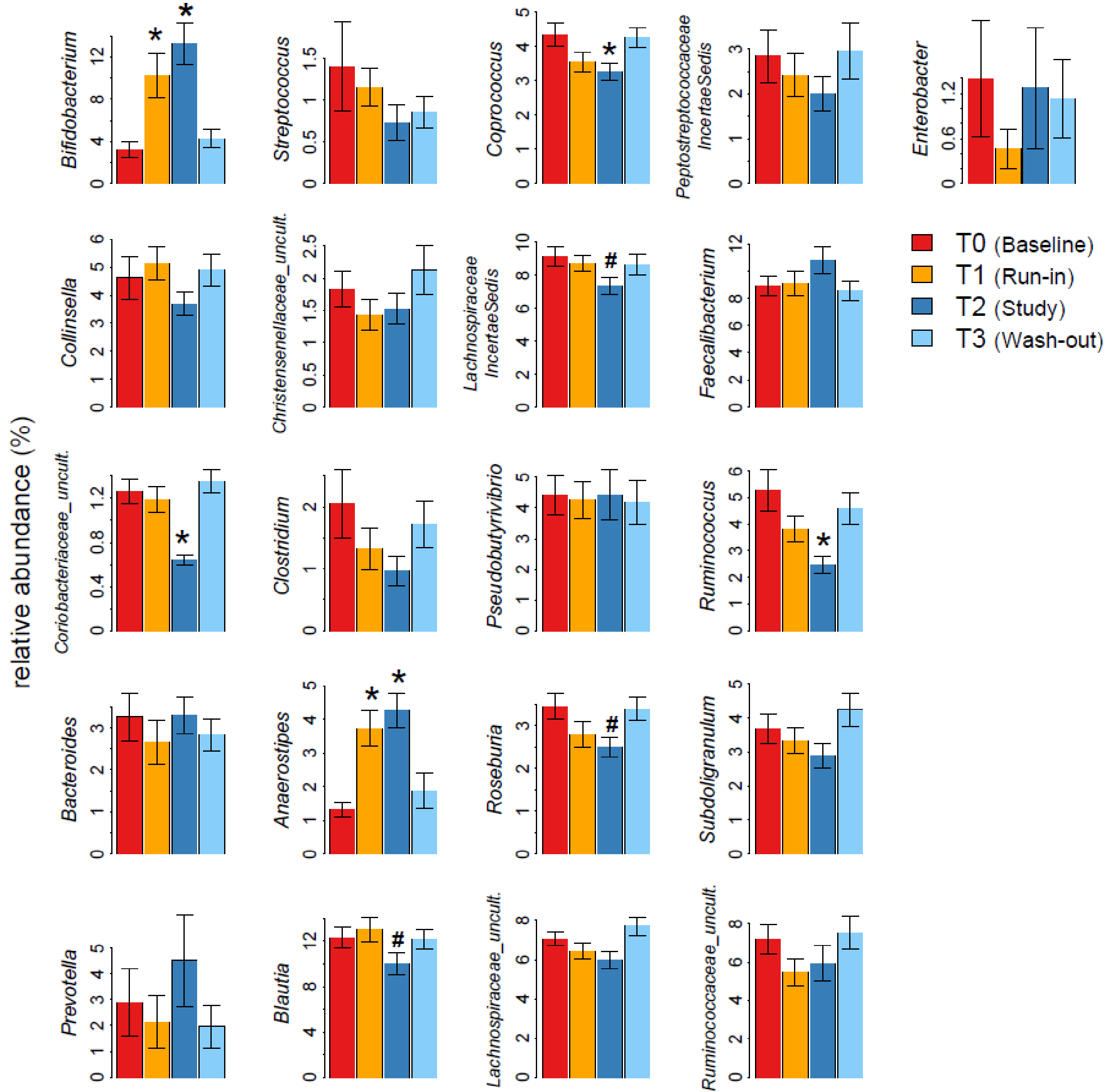
269 ***SUPPLEMENTARY RESULTS***

270 **Participants baseline information**

271 In the Placebo group one participant dropped out during the run-in period due to chest pain, another
272 was excluded from analysis due to missing samples and a third due to medically advised lifestyle
273 changes during the intervention period. In the treatment group one participant dropped out during
274 the run-in period due to an inflammation of the inner ear, another was excluded from analysis due to
275 early discontinuation of the treatment (protocol violation). One participant in the treatment group
276 developed an eczema one week into the study. As the symptoms worsened after the end of the
277 intervention and no earlier allergic reactions to chicory were reported, a possible causal relation with
278 the treatment was excluded.



280 **Figure S2 Consort Statement Flow Diagram**
281



283 **Figure S3 Mean relative abundances of abundant taxa (i.e. mean relative abundance of at least 1% in the**
284 **whole dataset) in the treatment group at Baseline (T0), after two weeks of 15 g/day treatment intake (T1),**
285 **after three weeks of 30 g/day treatment intake (T2) and after two weeks washout (T3).** **** q<0.001, # q < 0.01***
286 ***for differences from baseline (T0)***
287
288

Table S2 Changes in mean relative abundances of abundant taxa[1] in the treatment group from Baseline (T0) to 15 g/day treatment intake for two weeks (T1) to 30 g/day treatment intake for three weeks (T2) and differences in those changes from the placebo group.[2]

taxon	T0	T1	T2	ΔT1	ΔT2	Fold ΔT1	Fold ΔT2	T1-T0		T2-T0		ΔT1 vs Placebo		ΔT2 vs Placebo	
								p-value	q-value	p-value	q-value	p-value	q-value	p-value	q-value
Bifidobacterium	3.2%	10.1%	13.1%	6.9%	9.9%	3.17	4.09	**<0.001**	**<0.001**	**<0.001**	**<0.001**	0.006	0.050	**<0.001**	**<0.001**
Collinsella	4.4%	5.1%	3.7%	0.7%	-0.7%	1.16	0.83	0.069	0.154	0.365	0.425	0.789	0.876	0.450	0.495
Coriobacteriaceae uncultured	1.2%	1.2%	0.6%	-0.1%	-0.6%	0.93	0.51	0.400	0.514	**<0.001**	**<0.001**	0.825	0.876	-	-
Bacteroides	3.2%	2.7%	3.3%	-0.5%	0.1%	0.83	1.02	-	-	-	-	-	-	0.270	0.393
Prevotella	2.7%	2.1%	3.8%	-0.7%	1.1%	0.76	1.41	0.756	0.756	0.008	0.015	-	-	-	-
Streptococcus	1.1%	1.2%	0.7%	0.1%	-0.3%	1.08	0.68	0.343	0.514	0.377	0.425	0.575	0.876	-	-
Christensenellaceae uncultured	1.8%	1.4%	1.5%	-0.4%	-0.3%	0.79	0.84	0.046	0.118	0.104	0.133	0.941	0.941	0.464	0.495
Clostridium	1.8%	1.3%	1.0%	-0.5%	-0.9%	0.71	0.53	0.170	0.277	0.017	0.026	0.461	0.872	-	-
Anaerostipes	1.3%	3.7%	4.3%	2.4%	3.0%	2.82	3.24	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Blautia	12.3%	13.0%	10.0%	0.7%	-2.3%	1.06	0.81	0.547	0.616	**0.003**	**0.007**	0.573	0.876	0.682	0.682
Coprococcus	4.3%	3.5%	3.3%	-0.8%	-1.0%	0.82	0.76	0.004	0.023	**<0.001**	**<0.001**	0.053	0.226	0.207	0.332
Lachnospiraceae IncertaeSedis	9.1%	8.7%	7.4%	-0.4%	-1.8%	0.95	0.81	0.459	0.550	**<0.001**	**0.001**	0.664	0.876	0.176	0.332
Pseudobutyrivibrio	4.4%	4.3%	4.4%	-0.2%	0.0%	0.96	1.00	0.666	0.705	0.420	0.444	-	-	0.187	0.332
Roseburia	3.4%	2.7%	2.5%	-0.7%	-0.9%	0.80	0.72	0.012	0.043	**0.001**	**0.002**	0.447	0.872	0.340	0.453
Lachnospiraceae uncultured	7.0%	6.4%	6.0%	-0.6%	-1.1%	0.91	0.85	0.141	0.254	0.016	0.026	0.028	0.157	0.140	0.332
Peptostreptococcaceae IncertaeSedis	2.8%	2.4%	2.0%	-0.4%	-0.8%	0.86	0.71	-	-	-	-	0.680	0.876	-	-
Faecalibacterium	8.9%	9.1%	10.8%	0.2%	1.9%	1.02	1.21	-	-	-	-	0.788	0.876	0.463	0.495
Ruminococcus	5.1%	3.8%	2.5%	-1.3%	-2.6%	0.75	0.48	0.027	0.082	**<0.001**	**<0.001**	0.176	0.500	**<0.001**	**<0.001**
Subdoligranulum	3.7%	3.3%	2.8%	-0.4%	-0.8%	0.89	0.78	0.386	0.514	0.020	0.027	0.308	0.749	0.149	0.332
Ruminococcaceae uncultured	7.2%	5.4%	5.9%	-1.7%	-1.3%	0.76	0.81	0.009	0.042	0.012	0.021	0.131	0.445	0.181	0.332
Enterobacter	1.1%	0.5%	0.9%	-0.6%	-0.2%	0.44	0.85	0.141	0.254	0.465	0.465	-	-	0.165	0.332

[1] Abundant taxa represent those with a mean relative abundance of at least 1% in the whole dataset.
[2] Fold ΔT1 = Fold change after 15 g/day treatment; Fold ΔT2 change after 30 g/day of treatment; T1-T0 = comparison between 15 g/day treatment (T1) and baseline (T0) within the treatment group; T2-T0 = comparison between 30 g/day treatment (T2) and baseline (T0) within the treatment group; ΔT1 vs Placebo = comparison of change over baseline after 15 g/day treatment between the treatment group and the placebo group; ΔT2 vs Placebo = comparison of change over baseline after 30 g/day treatment between the treatment group and the placebo group, - represents not calculable estimates and p- and q-values (Korpela, 2016))

Table S3 Mean relative abundances of abundant taxa[1] in the treatment versus placebo group and differences in these taxa between groups at Baseline (T0), after 15 g/day treatment or 8 g/day iso-caloric placebo intake for two weeks (1), after 30 g/day treatment or 16 g/day iso-caloric placebo intake for three weeks (T2) and after washout of two weeks (T3).[2]

	T0					**T1**					**T2**					**T3**				
taxon	**P**	**T**	**FoldΔ T-P**	**p-value**	**q-value**	**P**	**T**	**FoldΔ T-P**	**p-value**	**q-value**	**P**	**T**	**FoldΔ T-P**	**p-value**	**q-value**	**P**	**T**	**FoldΔ T-P**	**p-value**	**q-value**
Bifidobacterium	4.8%	3.1%	0.65	0.190	0.792	5.5%	10.0%	1.82	0.059	0.615	4.5%	13.0%	2.88	**<0.001**	**0.001**	5.4%	4.3%	0.79	0.447	0.948
Collinsella	4.1%	4.5%	1.09	0.729	0.942	4.6%	5.1%	1.11	0.696	0.858	3.2%	3.7%	1.14	0.468	0.655	4.6%	4.9%	1.07	0.722	0.948
Coriobacteriaceae uncultured	1.5%	1.3%	0.86	0.282	0.821	1.5%	1.2%	0.81	0.126	0.660	1.4%	0.6%	0.47	**<0.001**	**<0.001**	1.7%	1.4%	0.80	0.123	0.835
Bacteroides	3.4%	3.3%	0.96	0.942	0.942	2.1%	2.6%	1.25	0.646	0.858	4.2%	3.3%	0.77	0.879	0.885	3.1%	2.8%	0.92	0.690	0.948
Prevotella	3.4%	2.6%	0.77	0.647	0.942	3.4%	1.9%	0.58	0.277	0.836	4.3%	4.2%	0.97	0.614	0.806	2.2%	1.8%	0.83	0.701	0.948
Streptococcus	1.2%	1.2%	0.96	0.313	0.821	1.3%	1.2%	0.91	0.748	0.858	1.7%	0.7%	0.44	0.015	0.062	1.3%	0.9%	0.67	0.234	0.835
Christensenellaceae uncultured	2.0%	1.8%	0.92	0.693	0.942	1.5%	1.4%	0.95	0.824	0.865	1.8%	1.5%	0.83	0.421	0.655	1.8%	2.1%	1.18	0.651	0.948
Clostridium	1.8%	1.9%	1.08	0.842	0.942	1.6%	1.3%	0.82	0.562	0.858	2.1%	1.0%	0.47	0.075	0.261	1.4%	1.7%	1.23	0.526	0.948
Anaerostipes	1.3%	1.3%	1.02	0.932	0.942	1.6%	3.7%	2.23	**<0.001**	**<0.001**	1.4%	4.3%	3.08	**<0.001**	**<0.001**	1.8%	1.7%	0.91	0.704	0.948
Blautia	12.1%	12.3%	1.02	0.865	0.942	13.7%	13.0%	0.95	0.660	0.858	10.4%	9.9%	0.96	0.726	0.847	11.8%	12.1%	1.02	0.824	0.948
Coprococcus	3.4%	4.3%	1.27	0.035	0.728	3.8%	3.5%	0.93	0.506	0.858	3.3%	3.3%	0.98	0.885	0.885	3.7%	4.3%	1.15	0.170	0.835
IncertaeSedis	7.7%	9.1%	1.19	0.073	0.769	8.3%	8.7%	1.05	0.531	0.858	7.5%	7.4%	0.98	0.840	0.885	8.8%	8.6%	0.98	0.883	0.948
Pseudobutyrivibrio	3.6%	4.4%	1.23	0.426	0.942	4.2%	4.3%	1.02	0.949	0.949	2.7%	4.4%	1.63	0.140	0.327	3.0%	4.2%	1.38	0.278	0.835
Roseburia	3.6%	3.4%	0.96	0.805	0.942	3.1%	2.8%	0.88	0.347	0.836	2.8%	2.5%	0.88	0.363	0.635	2.9%	3.4%	1.18	0.261	0.835
Lachnospiraceae uncultured	6.4%	7.0%	1.10	0.226	0.792	7.2%	6.4%	0.90	0.216	0.836	6.6%	6.0%	0.91	0.345	0.635	6.9%	7.7%	1.11	0.259	0.835
Peptostreptococcaceae IncertaeSedis	3.2%	2.8%	0.88	0.689	0.942	2.9%	2.4%	0.83	0.594	0.858	3.4%	2.0%	0.59	0.109	0.285	3.1%	3.0%	0.95	0.903	0.948
Faecalibacterium	8.6%	8.9%	1.04	0.845	0.942	8.7%	9.1%	1.05	0.777	0.858	9.7%	10.8%	1.12	0.441	0.655	8.9%	8.5%	0.96	0.798	0.948
Ruminococcus	5.0%	5.2%	1.03	0.881	0.942	4.6%	3.8%	0.83	0.358	0.836	5.0%	2.5%	0.50	**<0.001**	**0.002**	5.1%	4.6%	0.90	0.627	0.948
Subdoligranulum	3.5%	3.7%	1.03	0.832	0.942	3.7%	3.3%	0.89	0.494	0.858	3.5%	2.9%	0.82	0.292	0.612	3.4%	4.2%	1.24	0.256	0.835
Ruminococcaceae uncultured	8.7%	7.2%	0.83	0.150	0.785	7.0%	5.4%	0.77	0.097	0.660	7.9%	5.9%	0.75	0.098	0.285	7.5%	7.5%	1.00	0.977	0.977
Enterobacter	0.4%	1.0%	2.80	0.118	0.785	0.9%	0.5%	0.52	0.325	0.836	1.3%	1.0%	0.76	0.691	0.847	0.9%	1.0%	1.10	0.888	0.948

[1] Abundant taxa represent those with a mean relative abundance of at least 1% in the whole dataset.

[2] T=treatment, P=placebo, Fold Δ_{T-P}=fold difference in mean relative abundances between treatment and placebo, - represents not calculable estimates and p- and q-values (Korpela, 2016))

303 **Table S4 Changes in abundant taxa[1] in the placebo group from baseline (T0) to 8 g/day placebo intake for two weeks (T1) to 16 g/day placebo intake for three weeks**
304 **(T2). Intake of 8 g/day placebo and 16 g/day placebo product are iso-calorically corresponding amounts of 15 g/day and 30 g/day treatment product, respectively.[2]**
305

taxon	T0	T1	T2	ΔT1	Δ T2	FoldΔ T1	FoldΔ T2	T1-T0		T2-T0	
								p-value	q-value	p-value	q-value
Bifidobacterium	4.8%	5.3%	4.5%	0.5%	-0.3%	1.11	0.95	0.646	0.794	0.355	0.632
Collinsella	4.0%	4.6%	3.2%	0.6%	-0.8%	1.15	0.81	-	-	-	-
Coriobacteriaceae uncultured	1.5%	1.5%	1.4%	0.0%	-0.1%	1.00	0.96	0.827	0.917	0.290	0.632
Bacteroides	3.4%	2.3%	4.2%	-1.1%	0.8%	0.67	1.25	0.041	0.218	0.106	0.565
Prevotella	3.4%	3.4%	4.3%	0.0%	0.9%	0.99	1.26	0.599	0.794	0.335	0.632
Streptococcus	1.2%	1.3%	1.6%	0.1%	0.4%	1.08	1.36	0.917	0.917	0.711	0.812
Christensenellaceae uncultured	2.0%	1.6%	1.9%	-0.5%	-0.2%	0.77	0.92	0.058	0.232	0.552	0.747
Clostridium	1.8%	1.6%	2.1%	-0.2%	0.3%	0.90	1.16	0.570	0.794	0.315	0.632
Anaerostipes	1.3%	1.6%	1.3%	0.4%	0.0%	1.30	1.02	-	-	-	-
Blautia	12.1%	13.7%	10.4%	1.6%	-1.7%	1.13	0.86	0.137	0.365	0.079	0.565
Coprococcus	3.4%	3.8%	3.3%	0.4%	-0.1%	1.12	0.98	0.097	0.312	0.859	0.916
Lachnospiraceae IncertaeSedis	7.7%	8.3%	7.5%	0.6%	-0.2%	1.08	0.98	-	-	-	-
Pseudobutyrivibrio	3.6%	4.2%	2.7%	0.6%	-0.9%	1.18	0.76	0.867	0.917	0.254	0.632
Roseburia	3.6%	3.1%	2.9%	-0.4%	-0.7%	0.88	0.81	0.536	0.794	0.105	0.565
Lachnospiraceae uncultured	6.4%	7.2%	6.6%	0.8%	0.2%	1.12	1.03	0.014	0.114	0.581	0.747
Peptostreptococcaceae IncertaeSedis	3.2%	2.9%	3.4%	-0.3%	0.2%	0.91	1.06	0.334	0.679	0.974	0.974
Faecalibacterium	8.6%	8.7%	9.7%	0.1%	1.1%	1.01	1.12	0.487	0.794	0.607	0.747
Ruminococcus	5.0%	4.6%	5.0%	-0.4%	0.0%	0.91	1.00	0.340	0.679	0.591	0.747
Subdoligranulum	3.5%	3.7%	3.5%	0.1%	-0.1%	1.03	0.98	-	-	-	-
Ruminococcaceae uncultured	8.7%	7.0%	7.8%	-1.6%	-0.8%	0.81	0.91	0.009	0.114	0.207	0.632
Enterobacter	0.4%	0.9%	1.1%	0.6%	0.7%	2.63	2.95	-	-	-	-

306 [1] Abundant taxa represent those with a mean relative abundance of at least 1% in the whole dataset.
307 [2] Fold ΔT1 = Fold change after 8 g/day placebo intake; Fold ΔT2 change after 16 g/day placebo; T1-T0 = comparison between 8 g/day placebo (T1) and baseline (T0) within
308 the placebo group; T2-T0 = comparison between 16 g/day placebo (T2) and baseline (T0) within the placebo group; - represents not calculable estimates and p- and q-
309 values (Korpela, 2016))

310 **Fold-changes in the treatment group subjects with low or high baseline *Bifidobacterium***
311 **spp. and *Anaerostipes* spp. relative abundances.**
312
313 **Table S5 Differences in fold-change between subjects of the treatment group with high or low baseline**
314 **relative abundance (5) of *Bifidobacterium* and *Anaerostipes* spp. based on baseline median division.**[1]
315

Group		Relative abundance (%) T0	Relative abundance (%) T2	Fold-change T2
Bifidobacterium spp.	High (n=14)	5.67 ± 1.21	18.67 ± 2.98	4.23
	Low (n=14)	0.72 ± 0.18	7.84 ± 1.72	11.55
Anaerostipes spp	High (n=14)	2.04 ± 0.32	5.31 ± 0.78	2.74
	Low (n=14)	0.60 ± 0.05	3.24 ± 0.55	6.12

316 [1] Data is presented as mean with SEM in parentheses. T0 = baseline; T2 = 30 g/day treatment; Fold-change T2 =
317 fold change after 30 g/day treatment over baseline.
318

319 **Table S6 Estimated model fixed effects of Linear Mixed Model analysis of changes in faecal short-chain fatty**
320 **acids (SCFA) between the intervention groups (treatment versus placebo) over the intervention periods from**
321 **baseline to run-in (15 g/day treatment or 8 g/day iso-caloric placebo), study (30 g/day treatment or 16 g/day**
322 **iso-caloric placebo) and washout (no product intake).**

Effect		Estimate	Std. error	df	t-value	p-value
Total faecal SCFA (mmol/kg)						
Intercept		56.50	5.66	135.28	9.98	<2e-16
Intervention group	treatment	-5.86	7.94	135.28	-0.738	0.462
	placebo	0	-	-	-	-
Period	run-in	2.57	6.14	153.20	0.419	0.676
	study	-6.51	6.07	152.65	-1.073	0.285
	washout	-4.87	6.14	153.20	-0.793	0.429
	baseline	0	-	-	-	-
*Intervention*Period*	treatment*run-in	6.99	8.55	152.93	0.818	0.415
	treatment*study	19.53	8.50	152.65	2.297	0.023
	treatment*washout	3.532	8.83	154.36	0.4	0.69
Faecal acetate (mmol/kg)						
Intercept		37.49	3.87	140.59	9.689	<2e-16
Intervention group	treatment	-4.82	5.42	140.59	-0.888	0.3759
	placebo	0	-	-	-	-
Period	run-in	2.04	4.28	153.24	0.477	0.634
	study	-4.44	4.23	152.66	-1.049	0.2959
	washout	-3.57	4.28	153.24	-0.834	0.4058
	baseline	0	-	-	-	-
*Intervention*Period*	treatment*run-in	3.63	5.97	152.96	0.608	0.5443
	treatment*study	13.69	5.93	152.66	2.309	0.0223
	treatment*washout	2.91	6.16	154.47	0.472	0.6374
Faecal propionate (mmol/kg)						
Intercept		9.28	0.96	117.67	9.661	<2e-16
Intervention group	treatment	-0.21	1.35	117.67	-0.157	0.8751
	placebo	0	-	-	-	-
Period	run-in	0.80	0.96	153.01	0.833	0.4063
	study	-0.45	0.95	152.58	-0.476	0.6351
	washout	-0.11	0.96	153.01	-0.113	0.9099
	baseline	0	-	-	-	-
*Intervention*Period*	treatment*run-in	0.80	1.34	152.80	0.595	0.5527
	treatment*study	2.47	1.33	152.58	1.858	0.0651
	treatment*washout	-0.08	1.38	153.93	-0.056	0.9553
Faecal butyrate (mmol/kg)						
Intercept		9.74	1.17	128.61	8.297	1.25e-13
Intervention group	treatment	-0.83	1.65	128.61	-0.502	0.6163
	placebo	0	-	-	-	-
Period	run-in	-0.27	1.24	152.71	-0.217	0.8286
	study	-1.62	1.23	152.20	-1.321	0.1886
	washout	-1.18	1.24	152.71	-0.95	0.3438
	baseline					
*Intervention*Period*	treatment*run-in	2.56	1.73	152.47	1.484	0.1398
	treatment*study	3.36	1.72	152.20	1.959	0.0519
	treatment*washout	0.65	1.78	153.79	0.364	0.716

323
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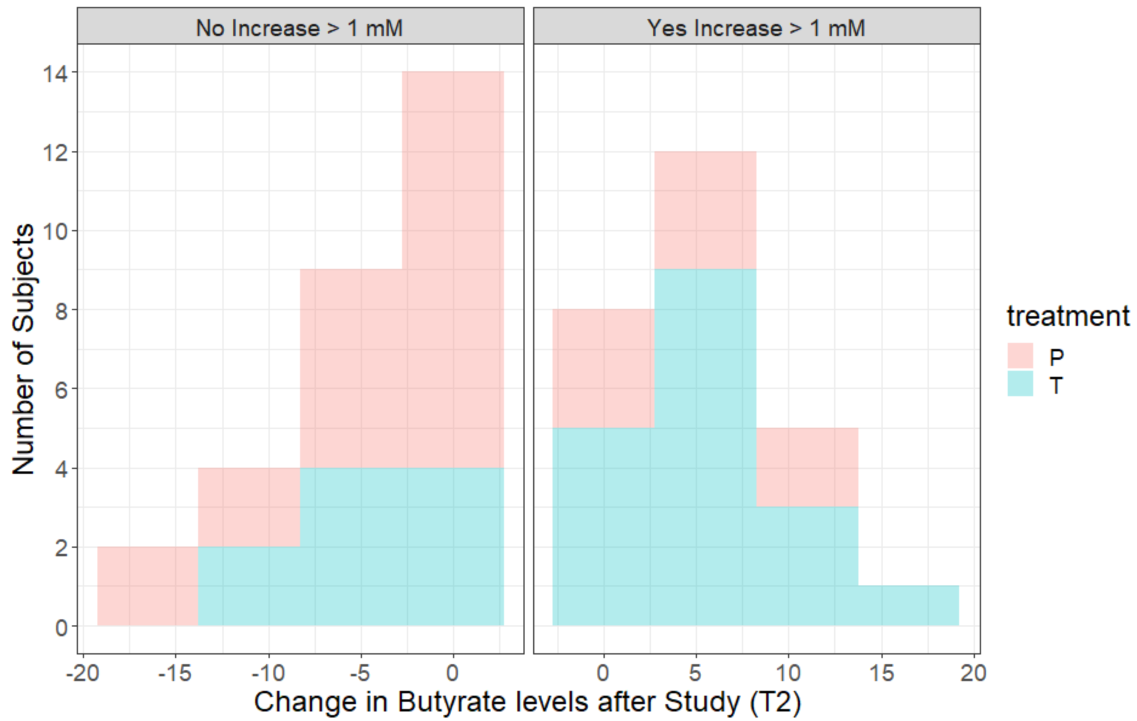


325
326 **Figure S4 Differences between treatment (T) and placebo (P) in the proportion of subjects increasing in**
327 **butyrate after three weeks of 30 g/day treatment or iso-caloric placebo intake (T2); with >1 mM being the**
328 **minimal increase observed in the treatment group. In the treatment 64.3% (n = 18) increased, while 35.7% (n**
329 **= 10) showed no increase versus 29.6% (n = 8) increase in the placebo and 70.3% (n = 19) showing no**
330 **increase (Fisher's exact test p = 0.015).**

Post-intervention differences at only T2 between groups

Table S7 Post-intervention differences corrected for baseline between the treatment (T) and the placebo (P) after the intervention period (T2) of three weeks intake of 30g/day treatment or 16 g/day iso-caloric placebo product. Adjusted means and mean differences assessed by analysis of covariance (ANCOVA with baseline as covariate). No ANCOVA was done for bowel function measurements due to model violation. [1]

		Treatment	**Placebo**		
	adjusted mean T0	**Adjusted mean T2**	**adjusted mean T2**	**Adjusted mean difference T2 T vs P**	***p-value adjusted mean difference T2 T vs P***
Faecal SCFA					
Total SCFA (mmol/kg)	53.50	64.60 (5.04)	49.10 (5.14)	+ 15.50 (7.22)	***0.036***
Acetate (mmol/kg)	35.00	42.50 (3.44)	32.40 (3.50)	+ 10.10 (4.93)	***0.045***
Propionate (mmol/kg)	9.17	11.10 (0.82)	8.77 (0.84)	+2.38 (1.17)	***0.048***
Butyrate (mmol/kg)	9.32	10.80 (0.99)	7.94 (1.01)	+ 2.89 (1.42)	***0.047***
Circulating fasting SCFA					
Total SCFA (µM)	50.50	57.40 (3.48)	48.90 (3.54)	+ 8.56 (4.97)	*0.091*
Acetate (µM)	44.90	51.60 (3.39)	44.10 (3.46)	+ 7.47 (4.85)	*0.129*
Propionate (µM)	5.31	5.61 (0.53)	4.76 (0.54)	+ 0.85 (0.76)	*0.266*
Butyrate (µM)	0.25	0.15 (0.06)	0.08 (0.6)	+ 0.06 (0.08)	*0.451*
Glucose Homeostasis					
HOMA-ir	1.31	1.26 (0.07)	1.31 (0.07)	-0.05 (0.09)	*0.570*
Fasting insulin (µU/mL)	8.31	8.05 (0.42)	8.36 (0.43)	-0.32 (0.60)	*0.597*
Fasting Glucose (mmol/L)	6.01	5.92 (0.08)	5.93 (0.08)	-0.02 (0.12)	*0.877*

[1] Data is presented as mean with SEM in parentheses

339 **Changes in static glycaemic markers**

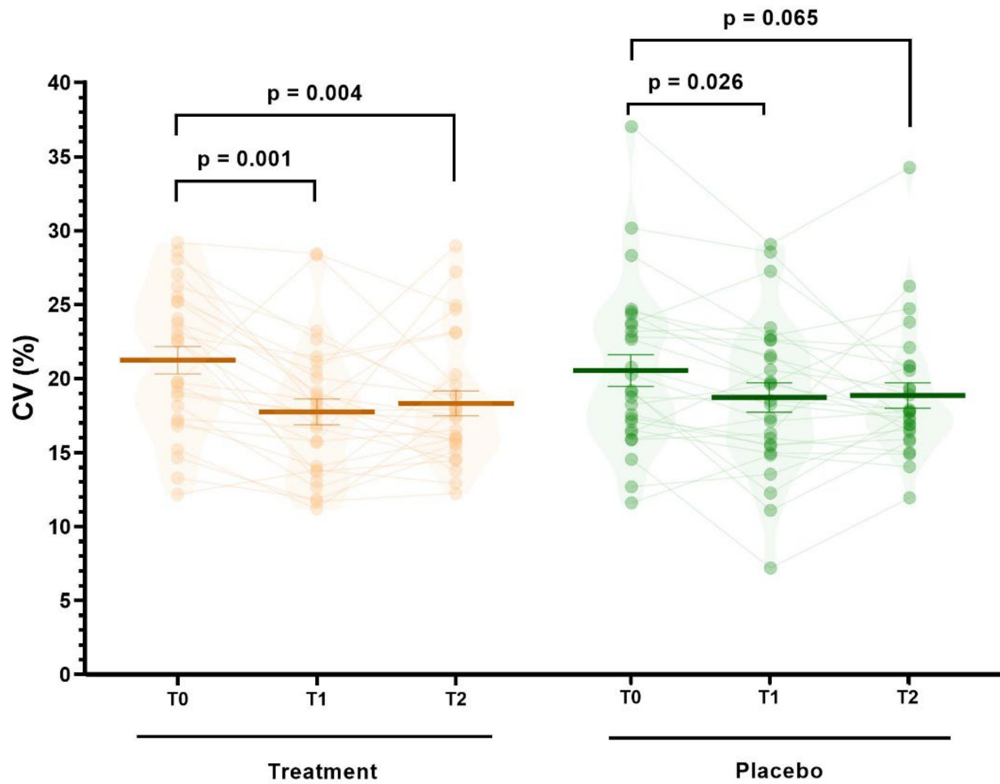
340

341 **Table S8 Changes in HOMA-ir and fasting glucose and insulin levels after the intervention period consisting of three weeks intake of 30g/day treatment or 16 g/day iso-**
342 **caloric placebo product.** [1]
343

	Treatment (n=28)				**Placebo (n=27)**				***p-value*** Δ_T - Δ_P
	T0	**T2**	Δ_T	***p-value***	**T0**	**T2**	Δ_P	***p-value***	
HOMA-ir†	1.28 ± 0.12	1.24 ± 0.09	-0.04 ± 0.08	0.566	1.34 ± 0.12	1.34 ± 0.12	0.00 ± 0.07	0.790	0.877
Fasting glucose, *mmol/L*	6.11 ± 0.11	5.98 ± 0.11	-0.29 ± 0.04	0.142	5.91 ± 0.11	5.87 ± 0.11	-0.04 ± 0.09	0.637	0.519
Fasting insulin, *µU/mL*	8.05 ± 0.73	7.87 ± 0.58	-0.19 ± 0.50	0.713	8.57 ± 0.77	8.55 ± 0.77	-0.02 ± 0.43	0.966	0.802

344 [1] Data is presented as mean with SEM in parentheses.† represents analysed using non-parametric testing
345

346 **Glycaemic variability assessed by coefficient or variation from continuous glucose**
347 **monitoring**
348



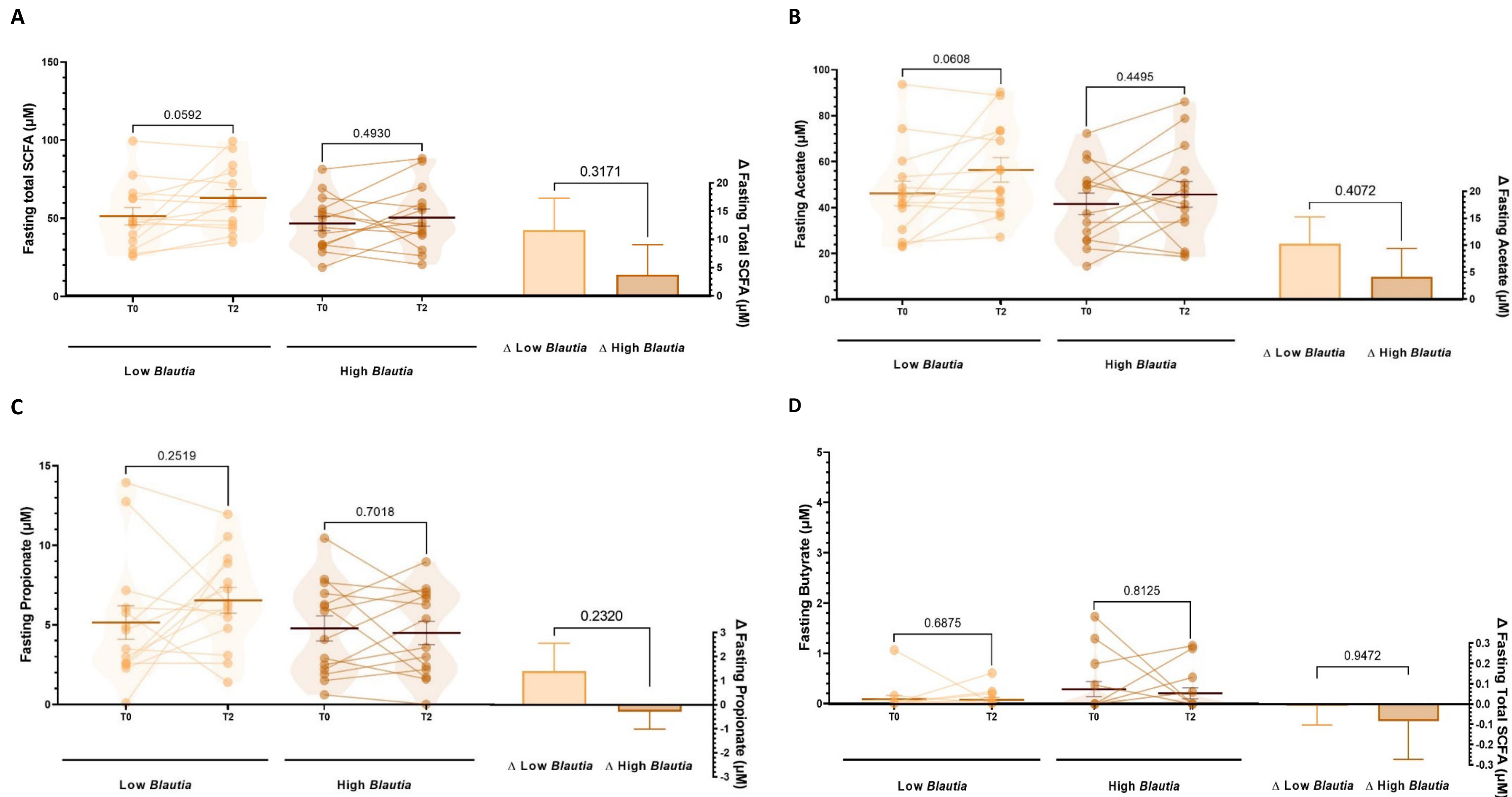
349
350 **Figure S5 Coefficient of variation (CV%) as a measure of glycaemic control assessed in the treatment group**
351 **(n=27) and the placebo group (n=27) using continuous glucose measurement on three same consecutive**
352 **weekdays during baseline (T0), the run-in period (T1) with 15 g/day treatment or 8 g/day iso-caloric placebo,**
353 **and during the study period (T2) with 30 g/day treatment or 16 g/day isocaloric placebo (repeated measures**
354 **ANOVA with main effect of period p<0.001, post-hoc tests with FDR-adjustment). No difference between**
355 **groups in baseline CV was observed before (p = 0.55) and after sensitivity analysis (p = 0.25).**

356 **Changes in static glycaemic markers in subject with high or low baseline *Blautia* spp. relative abundance**
357
358 **Table S9 Changes in HOMA-ir and fasting glucose and insulin levels in the treatment group in subjects with either low or high baseline relative abundance of *Blautia* spp.**
359 **after the intervention period consisting of three weeks of 30 g/day treatment.**[1]
360

	Low *Blautia* spp. (n=14)				**High *Blautia* spp. (n=14)**				
	T0	**T2**	Δ_T	***p-value***	**T0**	**T2**	Δ_P	***p-value***	***p-value*** $\Delta_L - \Delta_H$
HOMA-ir†	1.30 ± 0.18	1.16 ± 0.15	-0.14 ± 0.10	0.289	1.25 ± 0.15	1.32 ± 0.10	0.07 ± 0.12	0.055	0.045
Fasting glucose, *mmol/L*	6.06 ± 0.13	5.75 ± 0.11	-0.31 ± 0.11	0.013	6.15 ± 0.17	6.21 ± 0.16	0.06 ± 0.10	0.546	0.019
Fasting insulin, *µU/mL*	8.23 ± 1.17	7.46 ± 0.99	-0.82 ± 0.65	0.229	7.83 ± 0.91	8.28 ± 0.63	0.45 ± 0.75	0.556	0.210

361 [1] Data is presented as mean with SEM in parentheses. † represents analysed using non-parametric testing

362 **Fasting circulating short-chain fatty acid levels in subject with high or low baseline *Blautia* spp. relative abundance**



363 **Figure S6 Effect of *Blautia* baseline abundance on changes in fasting circulating short-chain fatty acids (SCFA) after 30 g/day treatment in subjects of the treatment**
364 **group with either low (n=14) or high (n=14) baseline *Blautia* spp. relative abundance. Butyrate levels were analysed using nonparametric testing. A: fasting circulating**
365 **total SCFA, B: fasting circulating acetate levels, C: fasting circulating propionate levels, D: fasting circulating butyrate levels.**

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