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Original article

Specific gut microbial, biological, and psychiatric profiling related to binge eating disorders: A cross-sectional study in obese patients

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SUMMARY

Background & aims: Binge eating disorder (BED) is a frequent eating disorder associated with obesity and co-morbidities including psychiatric pathologies, which represent a big health burden on the society. The biological processes related to BED remain unknown. Based on psychological testing, anthropometry, clinical biology, gut microbiota analysis and metabolomic assessment, we aimed to examine the complex biological and psychiatric profile of obese patients with and without BED.

Methods: Psychological and biological characteristics (anthropometry, plasma biology, gut microbiota, blood pressure) of 101 obese subjects from the Food4Gut cohort were analysed to decipher the differences between BED and Non BED patients, classified based on the Questionnaire for Eating Disorder Diagnosis (Q-EDD). Microbial 16S rDNA sequencing and plasma non-targeted metabolomics (liquid chromatography-mass spectrometry) were performed in a subcohort of 91 and 39 patients respectively.

Results: BED subjects exhibited an impaired affect balance, deficits in inhibition and self-regulation together with marked alterations of eating behaviour (increased emotional and external eating). BED subjects displayed a lower blood pressure and hip circumference. A decrease in *Akkermansia* and *Intestimonas* as well as an increase in *Bifidobacterium* and *Anaerostipes* characterized BED subjects. Interestingly, metabolomics analysis revealed that BED subjects displayed a higher level of one food contaminants, Bisphenol A bis(2,3-dihydroxypropyl) ether (BADGE.2H(2)O) and a food derived-metabolite the Isovalerylcarnitine.

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Conclusions: Non-targeted omics approaches allow to select specific microbial genera and two plasma metabolites that characterize BED obese patients. Further studies are needed to confirm their potential role as drivers or biomarkers of binge eating disorder.
Food4gut, clinicaltrial.gov:NCT03852069, https://clinicaltrials.gov/ct2/show/NCT03852069.

1. Introduction

Obesity management is a big health burden on the society and there is a crucial need to better understand the factors related to interindividual difference in terms of food related behaviour to propose adequate therapeutic approaches. Among eating disorders, binge-eating (BED) is characterized by recurrent episodes of over-eating and is often associated with obesity [1]. It affects from 2.2% to 4.6% of the general population and between 10 and 20% of obese people [2,3]. BED patients are prone to experience other psychiatric symptoms with elevated negative affect, food craving, and altered cognitive control [4]. BED is also associated with a significant worsening of well-being and poorer health outcomes [5]. The psychological risk factors for BED include poor impulse control, adverse childhood experiences, parental depression and negative comments about shape [6,7]. While there is an overlap between BED and other addictive disorders, the underlying biological mechanisms characterizing BED – which could be helpful in finding new treatment opportunities-, remain largely unknown [8,9]. Food intake is under the control of a complex and tightly regulated neuroendocrine system [10]. Several factors including inflammation, metabolic disturbances and dietary patterns are likely to modulate feeding behaviour [11–13]. During the last decade, the gut microbiota has been highlighted as a potential modulator of several biological processes including host metabolism, inflammation but also brain function [14,15]. Several environmental factors (e.g., diet, medications) are able to modulate gut microbiota composition and function (metabolites production) with various consequences on host metabolism and behaviour [16]. Despite a lack of certainty, the gut microbiota seems to affect brain function through several pathways, including the modulation of inflammatory mediators, vagus nerve stimulation or its influence on the host's circulating metabolome [17,18]. Indeed, a wide range of biologically active compounds can be produced by the gut microbes from nutrients or xenobiotics, and reach the systemic circulation to act at distance of the gut [14,19–21]. The gut microbiota composition and metabolomics analysis have not been performed yet in the context of BED.

In the present paper, we stratified the obese patients of the Food4GUT cohort at the recruitment phase upon BED profiling based on Q-EED test, and we explored their psychological traits. We also assessed their biological characteristics, taking into account the fecal microbiome and non-targeted plasma metabolomics to unravel new potential targets or biomarkers of BED in obesity.

2. Material and methods

2.1. Participants

Male and female patients were recruited in three university hospitals in Belgium (Hôpital Erasme in Brussels, Centre Hospitalier Universitaire in Liège and Cliniques universitaires Saint-Luc Brussels). The original study (Food4Gut cohort) was a 3-month long, multicentric, single-blind, placebo-controlled trial [22]. In this study, we analyzed the data obtained at baseline in obese participants. The inclusion criteria were: BMI >30 kg/m^2, age 18–65 years, Caucasian ethnicity, presence of at least one metabolic obesity-related disorder (prediabetes/diabetes, dyslipidemia, hypertension, fatty liver disease). The exclusion criteria were: use of antibiotics, pro/prebiotics, dietary fibers or any molecule that modifies intestinal transit time within 6 weeks before starting the study, pregnancy in progress or planned within 6 months, heavy psychiatric problems and/or use of antipsychotics, recent (<6 weeks) or current particular diets (e.g., vegetarian, vegan, high-protein, high-fiber diet), excessive alcohol consumption (more than 3 drinks/day), type 1 diabetes, general dislike for vegetables. The recruitment was conducted from January 2016 to May 2018. Among the 106 patients included in the Food4Gut study, 101 were classified upon their binge eating status. In our paper, we have taken into account the set of 101 patients at baseline, before starting any intervention. Psychological variables were available from 94 patients, microbiome data from 91 patients and metabolomics data from 39 patients (see Supplementary Fig. 1 for more details), the latter being recruited in only one center, namely the Cliniques universitaires Saint-Luc (Brussels). This study was approved by the "Comité d'éthique Hospitalo-facultaire de Saint-Luc". Written informed consents were obtained from all participants before inclusion in the study. The trial was registered at ClinicalTrials.gov under identification number NCT03852069 and the biological data related to the intervention study has been published [22].

2.2. Anthropometric characteristics

Weight, height, waist and hip circumference, blood pressure and body composition were measured at baseline and after three months of intervention. Body composition was assessed by bio-impedance devices (BIA 101, Akern, Italy; Biocorpus, Medi Cal, Germany; Tanita BC-418 MA, Tanita, UK). Resistance measurement was used to calculate fat-free mass and total body fat. Subcutaneous and visceral fat areas were obtained by CT-scan, and Fibroscan was used to quantify liver stiffness (elasticity) and controlled attenuation parameter.

2.3. Blood parameters

Fasting glycaemia, HbA1c, liver enzymes, and lipids were measured in the hospital laboratory. The remaining plasma was centrifuged at 2000×*g* for 10 min at 4 °C and frozen at −80 °C. Insulin levels were measured by ELISA (Mercodia, Uppsala, Sweden). Dipeptidyl-peptidase IV (DPP-IV) activity was assessed as previously described [23]. C-reactive protein (CRP) levels were measured using the quantikine ELISA (R&D Systems, Minneapolis, USA).

2.4. Dietary anamnesis

The dietary assessment was done by a trained dietician at baseline using a 24-h recall. Energy and nutrient intakes were evaluated using the Nubel Pro program (Nubel asbl, Belgium).

2.5. Gut microbiota composition

Stool samples were collected at baseline and stored at room temperature with a DNA stabilizer (Stratecbiomolecular, Berlin, Germany) for maximum three days, then transferred to −80 °C. Genomic DNA was extracted using a PSP® spin stool DNA kit (Stratecbiomolecular). Sequencing and subsequent bioinformatics were performed as previously described [24], with dataset-specific details reported in supplemental methods. For the gut microbiota analysis, raw sequences can be accessed in Sequence Read Archive database (SRA accession numbers PRJNA595949).

2.6. Non-targeted metabolomics

We conducted a metabolomics analysis on a subset of subjects (n = 39, 15 BED and 24 Non BED, from the St Luc Hospital). The analysis pipeline has been described in detail before [25]. Frozen plasma samples were randomized. For metabolite extraction, cold acetonitrile was added in a ratio of 400 μl per 100 μl of plasma. The samples were then vortexed for 15 s, sonicated for 5 min, and centrifuged for 5 min at 4 °C and 13 000 rpm. The samples were kept in ice between the steps. The supernatants were filtered (Acrodisc 4 mm with 0.45 μm membrane) and inserted into HPLC vials for analysis. The QC sample was prepared by collecting 10 μl from each sample vial and combining the material in another vial.

The samples were analyzed by liquid chromatography–mass spectrometry, consisting of a 1290 Infinity Binary UPLC coupled with a 6540 UHD Accurate-Mass Q-TOF (Agilent Technologies). A Zorbax Eclipse XDB-C18 column (2.1 × 100 mm, 1.8 μm; Agilent Technologies) was used for the reversed-phase (RP) separation and an Aqcuity UPLC BEH amide column (Waters) for the HILIC separation. After each chromatographic run, the ionization was carried out using jet stream electrospray ionization (ESI) in the positive and negative mode, yielding four data files per sample. The collision energies for the MS/MS analysis were selected as 10, 20 and 40 V, for compatibility with spectral databases.

Peak detection and alignment was performed in MS-DIAL ver. 3.96 [26]. For the peak collection, *m*/*z* values up to 1500 and all retention times were considered. The amplitude of minimum peak height was set at 2000. The peaks were detected using the linear weighted moving average algorithm. For the alignment of the peaks across samples, the retention time tolerance was 0.05 min and the *m*/*z* tolerance was 0.015 Da. Drift correction and removal of low quality signals was done as described in Klåvus et al. (2020).

The chromatographic and mass spectrometric characteristics (retention time, exact mass, and MS/MS spectra) of the significantly differential molecular features were compared with entries in an in-house standard library and publicly available databases, such as METLIN and HMDB, as well as with published literature. The annotation of each metabolite and the level of identification was given based on the recommendations published by the Chemical Analysis Working Group (CAWG) Metabolomics Standards Initiative (MSI) [27]: 1 = identified based on a reference standard, 2 = putatively annotated based on MS/MS spectra or physicochemical properties, 3 = putatively annotated to a compound group (e.g. phosphatidylcholine), and 4 = unknown.

2.7. Psychological measures

Participants were tested using questionnaires and cognitive tests at baseline. The binge-eating classification was made using questionnaire for Eating Disorder Diagnosis (Q-EDD) [28] and a semi-structured interview conducted by a trained psychologist. Based on the outcome of these two steps we have defined our two groups.

Participants were asked to answer to questions regarding their background information and lifestyle, fill out self-reported questionnaires, and perform cognitive tasks on a computer. The short version of the Dutch Eating Behavior Questionnaire (DEBQ) was use to assessment of restrained, emotional, and external eating behaviour [29]. The following self-reported questionnaires were used to measure actual and general mood, and emotion regulation abilities: Positive and Negative Affect Schedule (PANAS; NA and PA, negative and positive affect respectively), the Scale of Positive and Negative Experience (SPANE, NE and PE, negative and positive emotion respectively; BE, Balance emotion), and the Profile of Emotional Competences (PEC. TOT, total, INTRA, intrapersonal; INTER, interpersonal, Self Reg, emotional self-regulation) [30–32].

Cognitive tasks were developed based on Miyake's model, and used to test flexibility, working memory and inhibition [33]. Testing order was the same for all participants and lasted 2–3 h. A well-trained scientist conducted each session in French. The detailed procedures to collect personal information and assess mood, emotional competences and cognition are presented in supplementary methods.

2.8. Statistical analyses

R Software (version 3.5.1, MixOmics package), JMP Pro 14, MetaboAnalyst platform and Graphpad Prism 8.0 were used for analyses. In the present work, we used the data at baseline to characterize the profile of obese patients with binge-eating “BED” compared to without Binge-eating “Non BED”. Group differences were assessed using χ_2-tests for categorical variables and parametric t-tests applicable or Mann–Whitney–Wilcoxon test for quantitative variables based on distribution. Logistic regressions were used to confirm the robustness of the observations by taking into account major potential confounding factors for each variable. All analyses were adjusted for age, gender and center. For psychological variables (Table 1), additional adjustments were made for classical confounders, educational level and antidepressant medication. Biological variables corrected for were BMI, energy intake and antihypertensive drugs (Table 2). For microbial variables (Table 3) we adjusted for BMI, antihypertensive drugs and nutritional pattern scores. The latter was determined using a PCA approach. Using macronutrients (carbohydrates, lipids, protein), fiber and energy intake we obtained a score for the component 1 (61.8%) and the component 2 (20.4%) which were used to perform adjusted linear regression. For metabolomics data (Table 4), adjustments were made for BMI, energy and fiber intake. As metagenomics and metabolomics data were characterized by a large number of variables we conducted partial least square discriminant analysis (PLS-DA) to select the ones accounting for the difference between BED and Non BED. To do so, we took advantage of the MetaboAnalyst platform [34]. The selection was made based on the VIP scores of bacterial genera (>1,5) and metabolites (>1,8). Data are expressed as mean ± SD. Odds ratios were estimated for the logistic regression and the p-value was considered as statistically significant when $p < 0,05$.

3. Results

3.1. BED vs non BED characterization

The Q-EDD score distinguishes between no BED, subthreshold BED (sub-clinical) and clinical BED. We defined two groups of patients, one without BED (n = 59), and another with BED (n = 42; sub-clinical and clinical). There were no statistically significant differences in sociodemographic characteristics nor medications in BED vs Non BED subjects (Supplementary Table 1).

Table 1
Psychological parameters in Binge-eaters and non Binge-eaters.

	Non Binge-eaters	Binge-eaters	*P*	Model 1		Model 2	
	Mean ± SD	Mean ± SD		*OR*	*p*	*OR*	*p*
Mood							
PANAS PA	32,6 ± 7,03	30,8 ± 7,57	0,29	0,97	0,31	0,96	0,17
PANAS NA	15,4 ± 7,33	16,0 ± 7,13	0,64	1,01	0,71	1,03	0,35
PANAS PA-NA	17,2 ± 9,85	14,8 ± 12,1	0,46	0,98	0,36	0,97	0,12
PEC TOT	3,27 ± 0,42	3,33 ± 0,54	0,64	1,18	0,71	1,21	0,70
PEC INTRA	3,27 ± 0,48	3,21 ± 0,62	0,74	0,71	0,41	0,69	0,39
PEC INTER	3,22 ± 0,44	3,41 ± 0,57	0,13	2,13	0,09	2,23	0,09
PEC Reg Self	3,21 ± 0,78	2,85 ± 0,92	0,07	0,53	**0,02**	0,51	**0,02**
SPANE.PE	18,9 ± 3,53	17,5 ± 4,15	0,09	0,92	0,06	0,87	**0,02**
SPANE.NE	11,9 ± 3,47	12,8 ± 4,25	0,52	1,08	0,19	1,11	0,09
SPANE.BE	6,98 ± 6,19	4,73 ± 7,55	0,18	0,95	0,06	0,93	**0,02**
Eating Behaviour							
Emotional eating	3,05 ± 1,05	3,76 ± 0,82	**0,001**	2,46	**<0,001**	2,35	**<0,001**
External eating	2,82 ± 0,79	3,60 ± 0,68	**<0,001**	4,30	**<0,001**	4,82	**<0,001**
Restrained eating	2,96 ± 0,70	2,93 ± 0,75	0,85	0,95	0,89	0,84	0,62
Cognition							
Flexibility RT, ms	2251 ± 974	2187 ± 714	0,85	1,00	0,95	1,00	0,94
Flexibility errors	9,04 ± 12,5	3,43 ± 7,11	**0,02**	0,93	**0,005**	0,94	**0,01**
Working memory RT, ms	4911 ± 2266	4408 ± 1786	0,26	1,00	0,19	1,00	0,13
Working memory errors	8,06 ± 4,67	6,39 ± 4,01	0,09	0,89	0,06	0,92	0,19
Inhibition RT, ms	748 ± 103	784 ± 75,8	0,15	1,01	**0,01**	1,01	**0,02**
Inhibition errors	61,3 ± 26,2	66,2 ± 33,1	0,70	1,01	0,32	1,01	0,24

Unpaired t-test or Mann–Whitney test were used to compare the two groups. Model 1: Logistic regression adjusted for age, gender and center; Model 2: Logistic regression adjusted for age, gender, center, educational level and antidepressant medication. PANAS, Positive and Negative Affect Schedule; PEC, Profile of Emotional Competences; SPANE, Scale of Positive and Negative Experience; PA, positive affect; NA, negative affect INTRA, intra-personal; INTER, inter-personal; REG SELF, Self regulation; TOT, total, RT, reaction time.

Table 2
Biological and nutritional parameters in Binge-eaters and non Binge-eaters.

	Non Binge-eaters	Binge-eaters	*p*	Model 1		Model 2	
	Mean ± SD	Mean ± SD		*OR*	*p*	*OR*	*p*
Anthropometry							
BMI, kg/m^2	36,8 ± 5,78	35,3 ± 3,52	0,43	0,92	0,09	0,92	0,07[c]
Fat mass, kg	41,7 ± 11,5	39,2 ± 8,67	0,43	0,97	0,12	0,96	0,09[c]
Waist, cm	115 ± 16,4	112 ± 8,94	0,55	0,97	0,10	0,96	0,05[c]
Hip, cm	122 ± 13,8	116 ± 9,85	**0,03**	0,94	**0,009**	0,94	**0,005** [c]
Waist/hip ratio	0,94 ± 0,10	0,97 ± 0,08	0,24	159	0,17	97	0,23[c]
Visceral fat, cm^2	232 ± 107	241 ± 101	0,69	1,00	0,08	1,00	0,44[c]
Subc. fat, cm^2	374 ± 130	339 ± 129	0,18	1,00	0,45	1,00	0,39[c]
Biological parameters							
Diastolic BP, mm Hg	87,4 ± 10,7	82,4 ± 12,3	**0,04**	0,95	**0,02**	0,96	**0,022**[b]
Systolic BP, mm Hg	140 ± 15,7	133 ± 14,3	**0,04**	0,97	**0,02**	0,96	**0,012**[b]
Cholesterol	195 ± 48,2	186 ± 44,6	0,41	1,00	0,33	1,00	0,44[a]
HDL	48,1 ± 9,57	45,0 ± 12,7	0,09	0,99	0,24	0,98	0,39[a]
LDL	120 ± 44,5	108 ± 38,9	0,33	0,97	0,12	0,99	0,13[a]
Triglycerides	165 ± 131	171 ± 97,1	0,45	1,00	0,98	1,00	0,97[a]
Elasticity	6,87 ± 4,30	6,73 ± 3,56	0,80	1,03	0,73	1,13	0,06[a]
AST, U/l	26,8 ± 15,2	26,4 ± 10,9	0,84	1,00	0,78	1,00	0,82[a]
ALT, U/l	37,8 ± 27,6	36,0 ± 19,9	0,63	1,00	0,58	1,00	0,78[a]
γGT, U/l	43,3 ± 41,7	45,3 ± 33,3	0,39	1,00	0,92	1,00	0,52[a]
APO-A1	1,48 ± 0,21	1,41 ± 0,26	0,18	0,28	0,23	0,33	0,31[a]
DPP-IV, mUI/ml	17,6 ± 6,82	18,7 ± 6,26	0,24	1,02	0,48	1,03	0,43[a]
CRP, mg/l	4,32 ± 4,85	3,80 ± 4,21	0,46	1,00	0,58	1,00	0,33[a]
HbA1c, %	6,15 ± 1,37	6,12 ± 1,00	0,64	0,96	0,84	0,98	0,90[a]
Glycemia, mg/dl	113 ± 38,5	115 ± 41,3	0,80	1,00	0,16	1,00	0,77[a]
Insulin, mU/L	15,9 ± 11,0	17,0 ± 10,9	0,49	1,00	0,79	1,01	0,59[a]
C-peptide, pM	1034 ± 411	1115 ± 552	0,81	1,00	0,56	1,00	0,34[a]
HOMA (IR)	4,56 ± 4,51	5,17 ± 4,48	0,28	1,04	0,45	1,04	0,45[a]
Dietary anamnesis							
Energy, kcal/d	2005 ± 554	2109 ± 566	0,32	1,00	0,61	–	–
Protein, g/d	87,5 ± 21,2	88,2 ± 19,3	0,96	1,00	0,24	0,99	0,36[c]
Lipid, g/d	80,0 ± 32,5	91,4 ± 41,8	0,07	1,00	0,23	1,02	0,08[c]
Carbohydrates, g/d	215 ± 65,7	216 ± 52,7	0,83	1,00	0,73	0,99	0,22[c]
Dietary fiber, g/d	21,6 ± 8,65	23,3 ± 8,67	0,40	1,03	0,26	1,03	0,30[c]

Unpaired t-test or Mann–Whitney test were used to compare the two groups. Model 1: Logistic regression adjusted for age, gender and center; Model 2: Logistic regression adjusted for age, gender, center, BMI (for biological parameters)[a] or anti-hypertensive medication (for blood pressure)[b] or energy intake (for anthropometric and nutritional variables)[c]. BMI: body mass index; HDL, LDL: high and low-density lipoprotein; APO-A1: Apolipoprotein-A1; W/H ratio: waist to hip ratio.

Table 3
Microbial parameters in Binge-eaters and non Binge-eaters.

	Non Binge-eaters	Binge-eaters	*p*	Model 1		Model 2	
	Mean ± SD	Mean ± SD		*OR*	*p*	*OR*	*p*
Roseburia	2,48 ± 2,00	3,72 ± 3,32	0,09	1,20	**0,03**	1,18	0,07
Akkermansia	1,96 ± 4,44	0,51 ± 1,03	0,59	0,79	**0,03**	0,76	**0,01**
Sutterella	2,69 ± 2,79	1,56 ± 2,74	**0,03**	0,82	**0,03**	0,86	0,10
Desulfovibrio	0,50 ± 1,11	0,14 ± 0,34	0,18	0,35	**0,02**	0,40	**0,04**
Bilophila	0,36 ± 0,31	0,53 ± 0,58	0,29	2,88	0,05	3,06	0,05
Bifidobacterium	0,72 ± 0,99	1,39 ± 2,43	0,26	1,27	0,08	1,29	0,08
Fusicatenibacter	0,30 ± 0,29	0,45 ± 0,56	0,40	2,43	0,09	1,85	0,30
Anaerostipes	0,12 ± 0,18	0,20 ± 0,23	**0,04**	6,31	0,09	14,3	**0,03**
Flavonifractor	0,02 ± 0,05	0,05 ± 0,12	0,63	213	0,07	175	0,12
Intestinimonas	0,04 ± 0,09	0,01 ± 0,02	0,29	4,4e-6	**0,05**	1,50e-5	**0,04**
Lactobacillus	0,10 ± 0,35	0,01 ± 0,04	0,64	0,05	0,06	0,08	0,21

The genus presented here were the ones with the higher contribution (VIP score >1.5) for the segregation between Binge-eaters and Non Binge-eaters. 1Unpaired t-test or Mann−Whitney test were used to compare the two groups; Model 1: Logistic regression adjusted for age, gender and center; Model 2: Logistic regression adjusted for age, gender, center and nutritional pattern 1 and 2.

Table 4
Circulating metabolites in Binge-eaters and non Binge-eaters.

	Non Binge-eaters	Binge-eaters	*P*	Model 1		Model 2	
	Mean ± SD	Mean ± SD		*OR*	*p*	*OR*	*p*
BADGE.2H(2)O *	2,04 ± 1,90	4,65 ± 3,96	**0,017**	1,40	**0,015**	1,50	**0,011**
AC 5:0	9,08 ± 3,16	12,2 ± 4,08	**0,011**	1,37	**0,016**	1,60	**0,006**
Cadaverine	47,2 ± 7,57	52,7 ± 9,71	0,07	1,09	0,06	1,09	0,18
FA 18:1 (oleic acid)	53,7 ± 19,3	42,8 ± 11,9	0,05	0,96	0,08	0,97	0,21
SM d34:2	86,8 ± 19,5	75,5 ± 14,1	0,06	0,96	0,12	0,96	0,15
FA 18:2 (Linoleic acid)	27,5 ± 9,40	22,1 ± 7,16	0,06	0,93	0,11	0,94	0,20
Isoleucine	155 ± 26,6	174 ± 34,7	0,06	1,03	0,07	1,00	0,10
CDCA*	4,77 ± 3,40	6,57 ± 4,56	0,19	1,12	0,07	1,11	0,09
GUDC*	8,73 ± 6,22	11,9 ± 8,36	0,25	1,06	0,08	1,06	0,09
FA 20:4 (Arachidonic acid)	21,5 ± 8,66	17,03 ± 5,16	0,12	0,91	0,07	0,92	0,14
Dodecyl sulfate	2,04 ± 6,51	8,63 ± 16,2	0,12	1,05	0,010	1,06	0,09
LysoPC 18:2	841 ± 275	996 ± 246	0,06	1,00	0,13	1,00	0,15
FA 16:1 (Palmitoleic acid)	7,67 ± 4,98	5,13 ± 3,03	0,06	0,85	0,11	0,90	0,27
LysoPC 18:3	12,7 ± 5,82	16,4 ± 7,39	0,09	1,08	0,13	1,09	0,14

Unit is "Signal counts x 10^4. The 14 metabolites presented here were the ones with the higher contribution (VIP score >1,8) for the segregation between Binge-eaters and Non Binge-eaters. Unpaired t-test or Mann−Whitney test were used to compare the two groups; Model 1: Logistic regression adjusted for age and gender; Model 2: Logistic regression adjusted for age, gender, BMI, energy intake.

* Complete names: BADGE.2H(2)O: Bisphenol A bis(2,3-dihydroxypropyl) ether; Cadaverine: 1,5 Pentanediamine; CDCA: Chenodeoxycholic acid glycine conjugate; GUDC: Glycoursodeoxycholic acid.

3.2. Binge eaters display a distinct psychological profile

Unidimensional analysis revealed that BED group displayed an increased emotional and external eating and a decreased number of errors during the flexibility task (Table 1, $p < 0.05$). Logistic regression (adjusted for age, gender and center) confirmed these results and further revealed that BED subjects had a lower self-regulation score (PEC scale) and a longer reaction time for the correct responses during an inhibition task (Table 1, $p < 0.05$). The second model, adjusted for age, gender, center, educational level and antidepressant medication, confirmed these results and showed that BED subjects had elevated mood disturbances: decreased SPANE PE and BE score (Table 1, $p < 0.05$). Overall, these psychological assessments revealed that BED subjects display psychological disturbances including decreased of positive emotion, self-regulation and inhibition abilities while they did not exhibit other cognitive disturbances as they had even better score in flexibility test.

3.3. Binge eaters display few specific clinical features

Unidimensional analysis revealed that among 30 anthropometric and biological parameters, BED participants only displayed lower hip circumference, systolic and diastolic blood pressure (Table 2, $p < 0.05$). Logistic regression (adjusted for age, gender and center, model 1) confirmed these results. To further test the robustness of the results we used a third model in which we used three types of adjustments depending on the type of variables. The model −2 confirmed the findings on blood pressure (after adjustment for age, gender, center and anti-hypertensive medication) and hip's circumference (after adjustment for age, gender, center and energy intake). Overall, BED subjects exhibited a minor set of differences in clinical parameters as compared to Non BED subjects.

3.4. Binge eaters have specific differences in the composition of their microbiome

First, we selected the bacterial genera accounting for the difference between BED and Non BED subjects by using a PLS-DA analysis of the genus relative abundance (Fig. 1 A-B). It revealed no major clustering of the overall gut microbiota between BED and Non BED subjects (Fig. 1A). Nevertheless, the PLS-DA allowed to select 11 important genera that explain the difference between both groups (Fig. 1B, VIP score >1.5).

Unidimensional analysis revealed that BED subjects had higher level of *Anaerostipes* and less *Sutterella* than Non BED (Table 3). A logistic regression adjusted for age, gender and center (Model 1) confirmed that *Sutterella* was decreased in BED subjects (OR: 0.82).

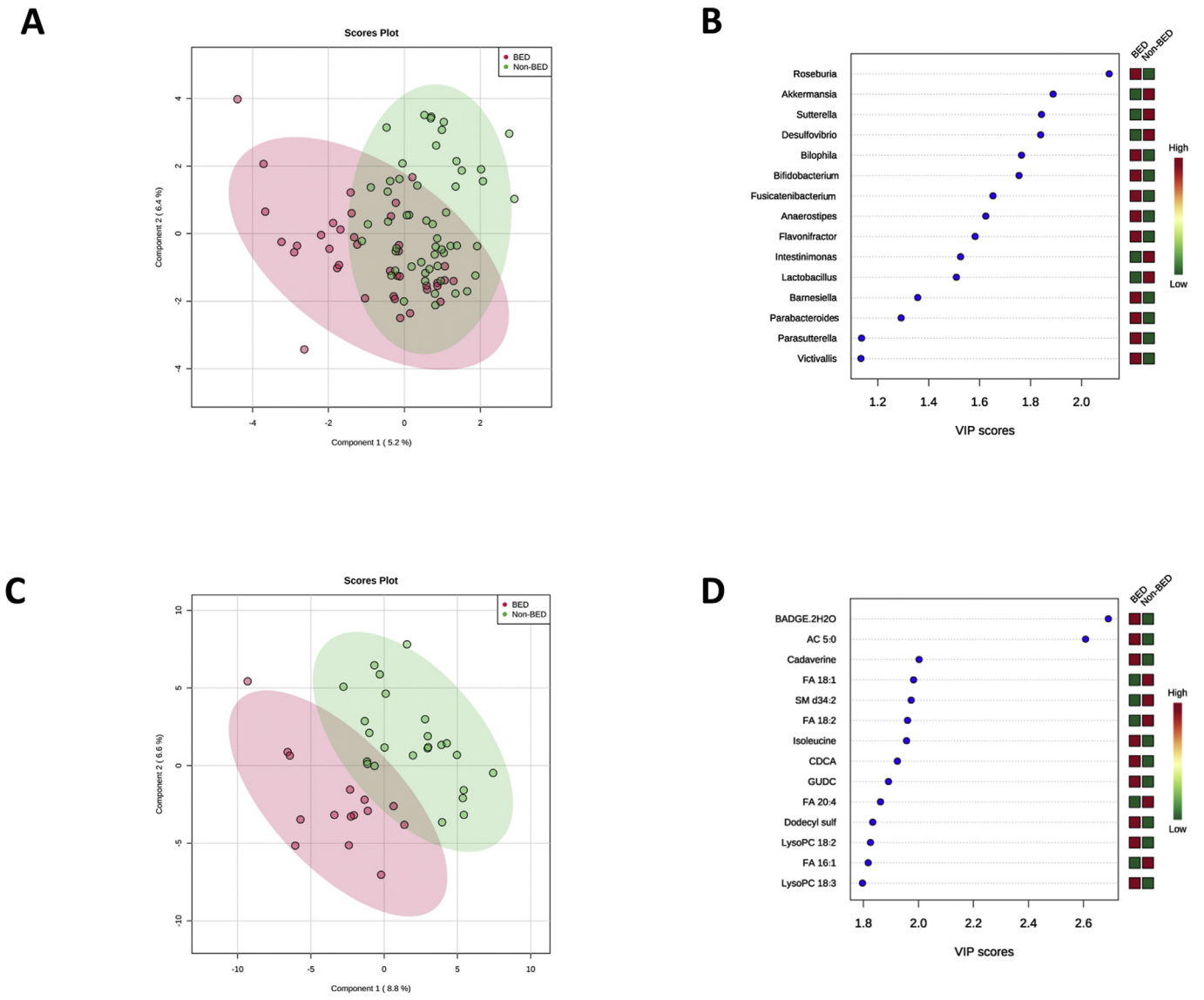

Fig. 1. Partial least square discriminant analysis (PLS-DA) to highlight variables responsible for the segregation between BED and Non-BED subjects for gut microbiota composition (A–B) and metabolome (C–D). On the left, the PLS-DA score plots were presented for each type of variables: gut microbiota composition (A) and metabolome (C). On the right, the graphs present the "variable importance in projection" or VIP score for each the two analysis. * Complete names: BADGE.2H(2)O: Bisphenol A bis(2,3-dihydroxypropyl) ether; Cadaverine: 1,5 Pentanediamine; CDCA: Chenodeoxycholic acid glycine conjugate; GUDC: Glycoursodeoxycholic acid.

This model also revealed that BED have an increased level of *Roseburia* (OR: 1.20) and a decreased levels of *Akkermansia* (OR: 0.79), *Desulfovibrio* (OR: 0.35) and *Intestinimonas* (OR: 4.4e-6) (Table 3). Additional adjustments for BMI, anti-hypertensive medication and nutritional patterns (Model 2) confirmed the differences in BED and Non BED subjects for *Akkermansia*, *Desulfovibrio*, *Anaerostipes* and *Intestinimonas* (Table 3). Of note, we observed trend for elevated levels of *Roseburia* (OR: 1.18; p = 0.07), *Bilophila* (OR: 3.06; p = 0.05) and *Bifidobacterium* (OR: 1.29; p = 0.05) (Table 3). Overall, BED patients displayed very specific changes in their gut microbiota composition with an increased level of *Anaerostipes* while *Akkermansia*, *Desulfovibrio* and *Intestinimonas* were decreased.

3.5. Binge eaters displayed selective differences in plasma metabolomic profile

We conducted a PLS-DA to select the most discriminant metabolites (Fig. 1C). 14 metabolites segregated BED and Non BED subjects (Fig. 1D, VIP score > 1,8). Surprisingly, unidimensional analysis revealed that BED displayed significant elevated levels of BADGE.2H(2)O and Isovalerylcarnitine in plasma (Table 4, p < 0,05) while there was a trend for eight other metabolites (Table 4). Logistic regression adjusted for age and gender (Model 1) and age, gender, BMI, energy intake (Model 2) confirmed the robustness of the increased BADGE.2H(2)O (OR: 1.40, p = 0.02 and OR: 1.50, p = 0.01 respectively) and isovalerylcarnitine (OR: 1.37, p = 0.02 and OR: 1.60, p = 0.006 respectively) in BED.

4. Discussion

This study reveals that obese patients suffering from binge eating display several differences compared to obese individuals without BED. Regarding the psychological profile, BED subjects exhibited more negative mood, poorer inhibition performance and weaker self-regulation capacity together with marked alterations of eating behaviour (increased emotional and external eating). They

had a lower blood pressure and hip circumference while their gut microbiota displayed shifts in selected bacteria, consisting in a lower abundance of *Akkermansia* and *Intestimonas* as well as a higher level of *Bifidobacterium* and *Anaerostipes*. Finally, BED subjects were characterized by elevated plasma levels of one food contaminant- BADGE.2H(2)O- and a food-derived metabolite (isovalerylcarnitine).

Concerning psychosocial parameters, we observed typical hallmarks of the BED with an impaired affect balance, a decreased inhibition and self-regulation, as previously shown [35,36]. In line with previous studies, we found that increased emotional eating (overeating tendency as a response to negative emotions) and external eating (a tendency to overeating in the presence of food stimuli) can differentiate between the profile of obese patients with or without BED which confirm the robustness of the classification based on the Q-EED score [37–39]. BED patients scored higher both on emotional and external eating even after correcting for socio-economic variables and antidepressant use. Regarding the performance on executive function tasks, in contrary to previous findings, our BED group performed significantly poorer only on the inhibition task, whilst they had a significantly better performance on the flexibility task compared to non-BED group [40,41]. Thus, our findings confirm the importance of inhibition problem in BED but do not reveal an alteration of the whole executive functions in binge eating.

Clinical variables measured in BED subjects revealed that they did not display worse anthropometric characteristics or metabolic disorders than Non-BED obese patients. Surprisingly, they even exhibited a lower blood pressure and hip circumference. To our knowledge, none of these observations has been reported so far. The regulation of blood pressure and body fat deposition are under the control of several neuroendocrine pathways including the sympathetic nervous system [42]. Other eating disorders including anorexia and *bulimia nervosa* (AS and BS respectively) have been associated with disturbances of the sympathico-vagal control of heart rate variability [43]. Lisdexamfetamine dimesylate, the sole drug approved for BED treatment, leads to an increased blood pressure despite weight loss [44,45]. It would be interesting to test in a specifically designed study if the sympathetic nervous system is specifically affected in BED.

To our knowledge, our study is the first to assess gut microbiota composition in BED subjects compared to Non-BED obese subjects. We did not observe profound differences of gut microbiota composition as evidenced by the lack of marked segregation in the PLS-DA analysis. However, we observed very specific differences in some bacterial genera. We found a decreased *Akkermansia* in subjects with BED. *Akkermansia* has been shown to produce short chain fatty acids such as propionate and acetate, which are known to contribute to the regulation of immunity, inflammation but also gut peptides involved in food intake behavior [46,47]. Usually a decreased level of *Akkermansia* is associated with a worse metabolic profile and its administration reinforces the gut barrier function, reduces low-grade inflammation, improves insulin-sensitivity and decreases adiposity both in preclinical and clinical settings without changing food intake [48–50]. In our study, decreased *Akkermansia* is not associated with a worse metabolic profile but with changes in eating behaviour. The metabolic protection in BED subjects could be related to the trend toward an increase of bacteria such as *Bifidobacterium* and *Roseburia*. Indeed, these two genera have been proposed as beneficial regarding cardiometabolic health [51,52]. For example, blood pressure is inversely associated with *Bifidobacterium* levels in patients with hypertension while in a preclinical model of atherogenesis *Roseburia* exerts beneficial effects [53,54]. The increase of *Anaerostipes* in BED subjects is coherent with a drop in this bacteria in subjects with *anorexia nervosa* [55]. Moreover, in psychiatric diseases like depression, *Anaerostipes* is increased suggesting that this genus can play a role in the modulation of human behaviour [56]. *Intestinimonas* was decreased in BED. This decrease could be considered as potentially harmful, since this genus has been shown to produce SCFA (butyrate and acetate) from lysine, those metabolites being generally considered as key players for the maintenance of gut function. Moreover, *Intestinimonas* can degrade Amadori products, which are toxic metabolites issued from processed foods containing amino acid and carbohydrates [57]. Of note, the very low abundance of *Intestinimonas* in our cohort did not allow to calculate a representative odd-ratio. It would be interesting to assess whether *Intestinimonas* activity protects from some pathological processes associated with BED. Overall, beneficial bacteria (*Bifidobacterium* and *Roseburia*) tend to be higher in patients with BED, which is intriguing. Based on the results obtained after adjustments for nutritional patterns, differences between BED and non-BED subjects regarding *Bifidobacterium*, *Roseburia* and *Akkermansia* levels do not seem to be driven by dietary habits since odd-ratios were not modified. These results highlight the need to improve the knowledge in the relationship between co-existing bacteria.

Another option is to study directly the function of the gut microbiota by assessing the production of bioactive compounds that will in turn affects host physiology. For this purpose, we analyzed the plasma available for a subcohort of patients to perform a wide metabolomics analysis. It revealed that, among hundreds of metabolites recorded, none related to the gut microbiota were associated with BED. However, two compounds were significantly elevated in BED subjects, namely BADGE.2H(2)O and isovalerylcarnitine. As bisphenol A, BADGE.2H(2)O, is a compound used in the food packaging industry and can be released in food [58,59]. A study showed that BADGE can affect lipid metabolism and disrupt endocrine function [60]. Another recent work showed that BADGE.2H(2)O disrupts testicular function by increasing Nur77 expression [61]. It is noteworthy that Nur77 have been shown to influence profoundly dopaminergic transmission as well as to control appetite and leptin sensitivity [62,63]. To our knowledge, no studies assessed potential long-term harmful effect of BADGE.2H(2)O on the brain. Our observational findings cannot rule out the fact that the elevated level of BADGE.2H(2)O were due to modified dietary habits in BED subjects rather than a driver of binge eating. Specific studies need to address the potential detrimental effect of BADGE compounds on obesity and food-related disorders, and to address which type of food - including packaging-are involved in this environmental component of food related behaviour.

Isovalerylcarnitine is produced from isovalerate and carnitine by carnitine acetyltransferase and is involved in several biological processes [64]. Isovalerylcarnitine has been shown to be elevated in obesity and cardiovascular diseases [65–67]. In our study, BED subjects displayed an elevated level of this metabolite despite a lower hip circumference. Isovalerylcarnitine is also inversely associated with the consumption of fruits and vegetables by autistic children [59]. In our cohort, BED subjects do not display significant differences in their nutritional intake and the elevated levels of isovalerylcarnitine remained significant even after adjustment for these factors. Acyl-carnitine molecules have been proposed as possible biomarker of several psychiatric disorders including depression, schizophrenia and autism [68–72]. However, little is known about the potential neurological effects of isovalerylcarnitine itself. One genetic disorder, isovaleric acidemia, is characterized by elevated levels of isovalerylcarnitine due to the accumulation of isovaleric acid resulting from the absence of the isovaleryl-coa dehydrogenase [73]. Isovalerate, which is produced by fermentation of amino acids (leucine), is detrimental for brain

function at high doses (isovaleric acidemia) and is elevated in feces of depressive patients [73,74]. A preclinical study demonstrated that isovalerate stimulates the production of GABA in the brain [75]. This molecule has been elegantly shown to stimulate enterochromaffin cells leading to the activation of the nervous system [76]. The potential impact of isovalerylcarnitine on energy balance and behaviour remains to be determined but this compound represents an interesting target regarding its importance for mitochondrial function as alterations in the cellular bioenergetics seems to play a role in several neurological and psychiatric conditions [77–80].

Overall, in this study we discovered that BED is characterized by some specific changes in biological markers, bacteria and metabolites. The lack of longitudinal follow-up does not allow any assumption on causality. Thus, further studies are needed to understand whether specific microbes (*Akkermansia*, *Roseburia*, *Bifidobacterium, Anaerostipes* and *Intestimonas*), a toxic (BADGE.2H(2)O) or some metabolites issued from amino-acid metabolism (isovalerylcarnitine, cadaverin) contribute to behavioural disturbances observed in BED and other psychiatric diseases. The availability of a large set of data (i.e., biology, psychology, medications, food habits, microbiota) for each participant in our study allowed us to control for several potential confounding factors. However, we cannot rule out the possibility that a more detailed nutritional survey (types of lipids, amino acids, number of meals, fasting period) would have revealed some modulating factors of the gut microbiota composition or the circulating metabolites profile.

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Author contributions

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Writing – review & editing: QL, RC, OK, OL, MDM, AMN, SL, MAG, MC, NP, NL, PDC, LBB, NMD.
All authors read and approved the final manuscript.

Conflict of Interest

Dr. Cani reports being the co-founder of A-Mansia biotech SA and is inventor on patent applications about the therapeutic use of *Akkermansia muciniphila* and its components. Dr. Karkkainen and Hanhineva disclosed being founders of Afekta Technologies Ltd., a company providing metabolomics services. QL, RC, MDGHM, GZ, SH, MAG, JR, DP, CA, SL, LB, AMN, NL, PT, NP, MC, JPT, OK, OL, NMD reported no biomedical financial interests or potential conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2020.09.025.

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