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Fecal *Dysosmobacter* spp. concentration is linked to plasma lipidome in insulin-resistant individuals with overweight, obesity and metabolic syndrome

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Abstract

Background Obesity is reaching epidemic proportions worldwide. This excessive increase of adipose tissue is a risk factor for the development of multiple diseases and premature death. Amongst associated diseases, metabolic syndrome is one of the main comorbidities of obesity. In this context, the gut microbiota has been recognized as both shaping and responding to host energy metabolism. Recently metabolomics has emerged as a powerful tool to capture a snapshot of the metabolites present in a specific tissue, providing new insights into host-microbiota interactions. Integrating metabolomics with gut microbiota studies could help us better understand how specific species impact on host metabolomic profile. *Dysosmobacter welbionis* has been identified as a promising next generation beneficial bacteria with potential effects on fat mass and glucose metabolism in mice, and fecal *Dysosmobacter* spp. concentration was inversely correlated to body mass index fasting glucose and plasmatic HbA1c in humans.

Methods Concentration of *Dysosmobacter* spp. was quantified by qPCR in the stools of insulin resistant overweight/obese participants with a metabolic syndrome and plasma metabolites were analyzed using untargeted metabolomics. Correlations between *Dysosmobacter* spp. fecal abundance and the 1169 identified plasma metabolites were uncovered using Spearman correlations followed by a false discovery rate correction.

Results Interestingly, among the detected metabolites, *Dysosmobacter* spp. was exclusively associated with lipid molecules. Fecal concentration of *Dysosmobacter* spp. was positively associated with plasmatic levels of five phosphatidylcholines, arachidonate, two monoacylglycerols, twelve diacylglycerols, three lysophosphatidylethanolamines, one phosphatidylinositol and three lysophosphatidylinositols, as well as glycerophosphoethanolamines, glycerophosphatidylcholine and PC(P-16:0). The correlation was particularly interesting with acylcholine and lysophosphatidylcholine metabolites as, respectively, 6/8 and 8/10 detected molecules were positively associated with *Dysosmobacter* spp.

Conclusion These results suggest that *Dysosmobacter* spp. plays a specific role in host lipid metabolism. This finding aligns with previous in vivo studies highlighting lipid profile alterations in multiple tissues of mice treated with this

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bacterium. Further studies are needed to elucidate the underlying mechanisms and assess its potential therapeutic applications.

Keywords Lipids, Metabolomics, Microbiota, Metabolic syndrome

Introduction

In its most recent report, the World Health Organization established that 1 in 8 people in the world now live with obesity. This number rises to nearly three billion people when overweight individuals are included. While obesity is not always a direct predictor of metabolic health [1], central obesity (or abdominal) obesity is a key diagnostic criterion for metabolic syndrome.

Metabolic syndrome is defined by meeting at least three of the five following criteria: central obesity, hypertension, hypertriglyceridemia, low levels of HDL cholesterol and elevated glycemia [2]. Consequently, living with a metabolic syndrome significantly increases the risk of developing type 2 diabetes (T2D) and cardiovascular diseases [2]. Obesity and its comorbidities stem from complex and multifactorial causes, prompting significant efforts to understand how they interact and how to tackle this growing epidemic. Over the last decades, the gut microbiota has emerged as a key player in host pathophysiology, influencing the development of metabolic diseases. Recently, several studies have demonstrated the therapeutic potential of specific gut bacteria. For instance, in men with metabolic syndrome, a four-week treatment with *Anaerobutyricum soehngenii* improved glucose metabolism [3]. Similarly, in the Microbes4U[®] cohort, administration of pasteurized *Akkermansia muciniphila* helped mitigate the progression of cardiometabolic disorders associated with overweight and obesity [4].

In 2020, a novel bacterial species, *Dysosmobacter welbionis* J115^T, was isolated. Two years later, this bacterium was associated with beneficial effects on weight and glucose tolerance in a mouse model of obesity [5, 6]. In human, *Dysosmobacter* spp. fecal concentrations were found to be negatively correlated with body mass index (BMI), fasting glucose and plasmatic HbA1c [5] in a cohort of overweight or obese people with a metabolic syndrome and insulin resistance. In a randomized trial (Food4Gut), *Dysosmobacter* spp. fecal concentration was unaffected by prebiotic (inulin) supplementation but obese/diabetic subjects who responded best to the prebiotic intervention had higher baseline *D. welbionis* levels than non-responders, and *D. welbionis* was negatively correlated with fasting glycemia. Interestingly, *D. welbionis* was significantly more abundant in the feces of metformin treated patients [7], although

in vitro experiment did not reveal a direct utilization of metformin by this bacterium.

Metabolomics has become a valuable tool for deciphering metabolic disturbances in both health and disease [8, 9]. By capturing a real-time snapshot of the metabolites within a tissue, it provides critical insights into underlying pathological processes and treatment responses, ultimately contributing to the advancement of personalized medicine. Given the intricate relationship between gut microbiota and host health, more and more studies are exploring how the gut microbiota composition correlates with host metabolomic profiles [10, 11]. Blood metabolites, in particular, hold significant potential as they can be assessed through minimally invasive sampling. Although the origin of many metabolites remains unclear, studies consistently highlight the gut microbiota's influence on blood metabolomic composition [12–17].

As *Dysosmobacter* spp. has been associated with an improved phenotype in people living with overweight/obesity and metabolic syndrome, this study aims to explore its association with plasma metabolites in this population. Identifying a specific metabolomic profile associated with *Dysosmobacter* spp. abundance in overweight humans could enhance our understanding of its role in host metabolic health.

Methods

Data source and study participants

The metabolic parameters, metabolomic profile and fecal concentration of *Dysosmobacter* spp. were obtained from non-diabetic, insulin-resistant and overweight or obese individuals previously recruited in the Microbes4U cohort [4, 5, 18, 19]. Briefly, participants were recruited at the Cliniques Universitaires Saint-Luc located in Brussels, Belgium, between 2015 and 2018. 52 overweight or obese subjects (body mass index >25 kg/m²) newly diagnosed with a metabolic syndrome and with a prediabetes state as well as an insulin sensitivity <75% were included. Metabolic syndrome was diagnosed according to the National Cholesterol Education Program Adult Treatment Panel III definition, that is, at least three of the five following criteria: fasting glycemia >100 mg/dL; blood pressure ≥130/85 mmHg or antihypertensive treatment; fasting triglyceridemia ≥150 mg/dL; high-density lipoprotein (HDL) cholesterol <40 mg/dL for men, <50 mg/dL for women.

dL for women; and/or waist circumference >102 cm for men, >88 cm for women.

Insulin sensitivity and resistance were both analyzed in Depommier et al. 2019 [4] using HOMA. Three blood samples, at 5 min intervals, were taken for each individual. Insulinemia and glycemia were determined for each sample and the mean values were then entered in the HOMA2 calculator (v.2.3.3, available from <http://www.dtu.ox.ac.uk/homacalculator/>) to estimate insulin sensitivity (%) and insulin resistance [20, 21].

Anthropometric measurements and plasma metabolomics were performed in Depommier et al. 2019 [4]. Bodyweight (BW) was measured in kg, BMI in kg.m⁻², and waist and hip circumferences in cm using a flexible tape. After an overnight fasting of 8 h minimum, blood samples were collected in different tubes: sodium fluoride-coated tubes for fasting glycemia and insulinemia; lipopolysaccharide (LPS)-free heparin sulfate coated tubes for LPS measurement (BD Vacutainer, NH sodium heparin, 368,480) measured by Endosafe-MCS (Charles River Laboratories, Lyon, France) in Depommier et al. 2019 [4]; lithium-heparin-coated tubes for enzymatic activities. Fasting glycemia, insulinemia, HbA1c (%), total cholesterol, LDL cholesterol (calculated), HDL cholesterol, triglycerides (TG), gamma-glutamyl transferase (GGT), alanine transaminase (ALT), aspartate transaminase (AST), lactate dehydrogenase (LDH), creatine kinase (CK), creatinine, glomerular filtration rate (GFR), urea, C-reactive protein (hsCRP), alkaline phosphatase (AlkP), and, white blood cell count (WBC) were measured directly at the hospital in the same paper [4]. Plasma non-esterified fatty acids (NEFA) were measured in Depommier et al. 2021 [18], using kits coupling an enzymatic reaction with spectrophotometric detection of the reaction end products (Diasys Diagnostic and Systems, Holzheim, Germany).

Metabolomic analysis

Plasma was isolated by centrifugation at 4200 g for 10 min at 4 °C and stored at −80 °C. 100 µl was aliquoted for metabolomics analyses by Metabolon Inc (North Carolina, USA). Untargeted metabolomics analyses were performed as described in Babu et al. 2019 [22]. It comprised ultra-performance liquid chromatography/mass spectrometry with a heated electrospray ionization source and mass analyzer. Following proper handling, samples were first prepared using the automated MicroLab STAR® system from Hamilton Company. The resulting extract was divided into several fractions, analysed by four ultra-high-performance liquid chromatography-tandem mass spectrometry according to the Metabolon pipeline. Biochemical identification of metabolites contained in one sample was then performed by comparison

to a reference library of purified standards consisting of more than 33,000 metabolites. The comparison was based on retention time/index, mass-to-charge ratio (m/z), and chromatographic data (MS/MS spectral data) using software developed at Metabolon. Further details regarding quality controls, data extraction, curation, quantification, and bioinformatics were previously described [23]. Compounds that have not been confirmed based on a standard, but that are identified by Metabolon Inc with confidence are labelled with an asterisk (*). Structural isomers of another compound in Metabolon Inc spectral library are labelled with the isomer position number in brackets ([#]).

Plasma biomarkers

Plasmatic monocyte chemoattractant protein 1 (MCP-1) was assessed in Depommier et al. 2019 [4] and plasmatic leptin in Depommier et al. 2021 [19]. Plasmatic interferon gamma-induced protein 10 (IP-10), soluble CD40 ligand (sCD40L), eotaxin, growth differentiation factor 15 (GDF-15), soluble vascular cell adhesion molecule-1 (svCAM-1), lipocalin-2, soluble intercellular adhesion molecule-1 (siCAM-1), ADAMTs13, D-Dimer, myoglobin, glucagon, gastric inhibitory polypeptide (GIP) and macrophage-derived chemokine (MDC) were measured using the same MILLIPLEX MAP Human Metabolic Hormone Magnetic Bead Panel technology and measured using Luminex technology (BioPlex; Bio-Rad Laboratories, Hercules, CA, USA) according to the manufacturer's instructions.

Active plasma glucagon-like-peptide-1 (GLP-1) was measured in Depommier et al. 2019 [4] by sandwich ELISA (Merck Millipore). Plasmatic GLP-2, peptide YY (PYY), intestinal fatty-acid binding protein (I-FABP), and interleukin 6 (IL-6) were assessed using the same method, following the manufacturer's instructions. Dipeptidyl peptidase 4 (DDP4) activity was measured previously [4], through the quantification of p-nitroanilide (pNA) production from glycine-proline-pNA (Sigma-Aldrich).

Fecal *Dysosmobacter* quantification

The quantity of *Dysosmobacter* spp. per gram of feces for each patient upon recruitment has been measured in Le Roy et al. 2022 [5]. Concisely, genomic DNA was extracted from human stools using the QIAamp DNA Stool Mini Kit (Qiagen, Germany), including a bead-beating step. Using the same DNA extraction protocol than for the stools, quantified standard DNA for *Dysosmobacter* spp. qPCR was obtained by extracting genomic DNA from a *Dysosmobacter welbionis* J115^T culture in exponential growing phase of known concentration in colony forming units (CFU) determined by plating. DNA concentration was determined, and purity (A260/A280)

was checked using a NanoDrop2000 (Thermo Fisher Scientific, USA). Samples were diluted to an end concentration of 10 and 0.1 ng/μl in TE buffer pH 8. Total bacteria qPCR was performed on the 0.1 ng/μl dilution and the *Dysosmobacter* spp. qPCR was performed on the 10 ng/μl dilution. Real-time PCRs were performed with the StepOnePlus real-time PCR system and software (Applied Biosystems, Den Ijssel, The Netherlands) using Mesa Fast qPCR SYBR green mix (Eurogentec, Seraing, Belgium) for detection according to the manufacturer's instructions. A standard curve was included on each plate by diluting genomic DNA from pure culture. *Dysosmobacter* spp. standard curve ranged between 3.2 10³ and 1.0 10⁷ CFU per well for *Dysosmobacter* spp. and between 6.4 10² and 2.0 10⁶ CFU per well for total bacteria (based on *L. acidophilus* DSM20079).

Species	Forward primer (5' → 3')	Reverse primer (5' → 3')
Universal bacteria	ACTCCTACGGGAGGC AGCAG	ATTACCGCGCTGCTGG
<i>Dysosmobacter</i> spp.	ATACCGCATGACGCA TGACC	CCAGCGATAAAATCTTTG ACATGCC

Statistical analysis

Spearman's correlation of *Dysosmobacter* spp. per gram of feces against all metabolites in each dataset was computed on RStudio (RStudio, 2023, Posit team) using the package 'Psych' (version 2.3.6) [24]. A multiple testing correction via false discovery rate (FDR) estimation according to the Benjamini and Hochberg procedure was applied. The metabolites that significantly correlated with *Dysosmobacter* spp. (adjusted *p*-value < 0.05) concentration in the feces after correction were extracted and listed in a table format (Table 1). Correlograms and chord diagrams representing the correlations between *Dysosmobacter* spp. fecal concentration and metabolites subfamilies in which one or multiple metabolites were associated were generated using the R packages 'Corrplot' (version 0.92) [25] and 'Circize' (version 0.4.16) [26]. In these graphs, while selected subfamilies were represented separately for clearer representation, the correlation scores and adjusted *p*-value represented are those obtained during the computation of the correlation between all 453 lipids and *Dysosmobacter* spp.

These metabolites were then used to explore correlation with metabolic and inflammatory parameters (hsCRP, IL-6, WBC, MCP-1, sCD40L, eotaxin, MCD, IP-10, Urea, Creatinine, GFR, ADAMTs13, D-DIMER, GDF-15, Myoglobin, sICAM-1, Lipocalin-2, sVCAM-1, LBP, LPS, insulin sensitivity and resistance score, GIP, leptin, glucagon, BW, waist and hip circumference,

Table 1 Participants characteristics

	Mean ± SEM
Gender (nb (%))	
Women	30 (57.69)
Men	22 (42.30)
Age (years)	51.46 ± 1.096
Height (cm)	1.71 ± 0.013
BMI	37.95 ± 0.681
Waist (cm)	122.59 ± 1.657
Hip (cm)	120.52 ± 1.577
Waist-hip ratio	1.02 ± 0.013
Fat mass (Kg)	46.02 ± 1.59
Lean mass (Kg)	65.79 ± 1.944
Systolic blood pressure (mmHg)	144.09 ± 2.169
Diastolic blood pressure (mmHg)	95.48 ± 2.122
Fasting blood glucose (mg/dl)	102.54 ± 1.512
Glycated hemoglobin A1c (%)	5.7 ± 0.061
Insulinemia (pmol/L)	145.78 ± 9.854
Insulin sensitivity (%)	32.92 ± 2.397
Total Cholesterol (mg/dl)	202.06 ± 5.632
LDL cholesterol (mg/dl)	129.65 ± 4.778
HDL cholesterol (mg/dl)	44.08 ± 1.116
Total cholesterol/HDL ratio	4.67 ± 0.138
AST activity (U/L)	23.52 ± 2.35
ALT activity (U/L)	33.35 ± 3.234
GGT activity (U/L)	40.69 ± 4.747
LDH activity (U/L)	183.58 ± 4.245
CK activity (U/L)	119.18 ± 9.268
TG (mg/dl)	141.65 ± 6.845
Body weight (Kg)	111.14 ± 2.551
DDP4 activity (mU/ml)	15.52 ± 0.489

waist-hip ratio, total cholesterol, LDL, HDL, total cholesterol/HDL ratio, TG, NEFAs, AST, ALT, GGT, AlkP, CK, LDH, iFABP, DDP4 activity, GLP-1, GLP-2, PYY, fasting glycemia, insulinemia, HbA1c proportion, BMI, fat mass, lean mass, diastolic and systolic blood pressure). The significant associations after FDR correction were listed in a table (Table 3).

Abbreviations

In the correlograms and chord diagrams, for readability, the names of some lipid species have been shortened. DAGs, PCs, LysoPCs, PEs, LysoPEs, PIs and LysoPIs names were shortened to only display the acyl chains composition. Myristoyl-linoleoyl-glycerol (14:0/18:2) [1]* = DAG (14:0/18:2) [1]*, palmitoyl-oleoyl-glycerol (16:0/18:1) [1]* = DAG (16:0/18:1) [1]*, palmitoyl-oleoyl-glycerol (16:0/18:1) [2]* = DAG (16:0/18:1) [2]*, palmitoyl-linoleoyl-glycerol (16:0/18:2) [1]* = DAG (16:0/18:2) [1]*, palmitoyl-linoleoyl-glycerol (16:0/18:2)

[2]* = DAG (16:0/18:2) [2]*, palmitoyl-linolenoyl-glycerol (16:0/18:3) [2]* = DAG (16:0/18:3) [2]*, palmitoleoyl-oleoyl-glycerol (16:1/18:1) [1]* = DAG (16:1/18:1) [1]*, palmitoleoyl-linoleoyl-glycerol (16:1/18:2) [1]* = DAG (16:1/18:2) [1]*, palmitoleoyl-linolenoyl-glycerol (16:1/18:2) [2]* = DAG (16:1/18:2) [2]*, palmitoyl-arachidonoyl-glycerol (16:0/20:4) [1]* = DAG (16:0/20:4) [1]*, palmitoyl-arachidonoyl-glycerol (16:0/20:4) [2]* = DAG (16:0/20:4) [2]*, oleoyl-oleoyl-glycerol (18:1/18:1) [1]* = DAG (18:1/18:1) [1]*, oleoyl-oleoyl-glycerol (18:1/18:1) [2]* = DAG (18:1/18:1) [2]*, oleoyl-linoleoyl-glycerol (18:1/18:2) [1] = DAG (18:1/18:2) [1], linoleoyl-linoleoyl-glycerol (18:2/18:2) [1]* = DAG (18:2/18:2) [1]*, oleoyl-linoleoyl-glycerol (18:1/18:2) [2] = DAG (18:1/18:2) [2], oleoyl-linolenoyl-glycerol (18:1/18:3) [2]* = DAG (18:1/18:3) [2]*, linoleoyl-linoleoyl-glycerol (18:2/18:2) [1]* = DAG (18:2/18:2) [1]*, linoleoyl-linoleoyl-glycerol (18:2/18:2) [2]* = DAG (18:2/18:2) [2]*, linoleoyl-linolenoyl-glycerol (18:2/18:3) [1]* = DAG (18:2/18:3) [1]*, linoleoyl-linolenoyl-glycerol (18:2/18:3) [2]* = DAG (18:2/18:3) [2]*, stearoyl-arachidonoyl-glycerol (18:0/20:4) [1]* = DAG (18:0/20:4) [1]*, oleoyl-oleoyl-glycerol (18:1/18:1) [1]* = DAG (18:1/18:1) [1]*, oleoyl-oleoyl-glycerol (18:1/18:1) [2] = DAG (18:1/18:1) [2], stearoyl-arachidonoyl-glycerol (18:0/20:4) [2]* = DAG (18:0/20:4) [2]*, diacylglycerol (14:0/18:1, 16:0/16:1) = DAG (14:0/18:1, 16:0/16:1, oleoyl-arachidonoyl-glycerol (18:1/20:4) [1]* = DAG (18:1/20:4) [1]*, oleoyl-arachidonoyl-glycerol (18:1/20:4) [2]* = DAG (18:1/20:4) [2]*, linoleoyl-arachidonoyl-glycerol (18:2/20:4) [1]* = DAG (18:2/20:4) [1]*, linoleoyl-arachidonoyl-glycerol (18:2/20:4) [2]* = DAG (18:2/20:4) [2]*, linoleoyl-docosahexaenoyl-glycerol (18:2/22:6) [2]* = DAG (18:2/22:6) [2]*, Diacylglycerol (16:1/18:2 [2], 16:0/18:3 [1]) = DAG (16:1/18:2 [2], 16:0/18:3 [1]), 1-myristoyl-2-palmitoyl-GPC (14:0/16:0) = PC (14:0/16:0), 1-myristoyl-2-arachidonoyl-GPC (14:0/20:4)* = PC (14:0/20:4)*, 1,2-dipalmitoyl-GPC (16:0/16:0) = PC (16:0/16:0), 1-palmitoyl-2-palmitoleoyl-GPC (16:0/16:1)* = PC (16:0/16:1)*, 1-palmitoyl-2-stearoyl-GPC (16:0/18:0) = PC (16:0/18:0), 1-palmitoyl-2-oleoyl-GPC (16:0/18:1) = PC (16:0/18:1), 1-palmitoyl-2-linoleoyl-GPC (16:0/18:2) = PC (16:0/18:2), 1-palmitoyl-2- α -linolenoyl-GPC (16:0/18:3n3)* = PC (16:0/18:3n3)*, 1-palmitoyl-2- γ -linolenoyl-GPC (16:0/18:3n6)* = PC (16:0/18:3n6)*, 1-palmitoyl-2-dihomo-linolenoyl-GPC (16:0/20:3n3 or 6)* = PC (16:0/20:3n3 or 6)*, 1-palmitoyl-2-arachidonoyl-GPC (16:0/20:4n6) = PC (16:0/20:4n6), 1-palmitoyl-2-docosahexaenoyl-GPC (16:0/22:6) = PC (16:0/22:6), 1-palmitoleoyl-2-linoleoyl-GPC (16:1/18:2)* = PC (16:1/18:2)*, 1-palmitoleoyl-2-linolenoyl-GPC (16:1/18:3)* = PC (16:1/18:3)*, 1,2-distearoyl-GPC (18:0/18:0) = PC (18:0/18:0), 1-stearoyl-2-oleoyl-GPC

(18:0/18:1) = PC (18:0/18:1), 1-stearoyl-2-linoleoyl-GPC (18:0/18:2)* = PC (18:0/18:2)*, 1-stearoyl-2-arachidonoyl-GPC (18:0/20:4) = PC (18:0/20:4), 1-stearoyl-2-docosahexaenoyl-GPC (18:0/22:6) = PC (18:0/22:6), 1-oleoyl-2-linoleoyl-GPC (18:1/18:2)* = PC (18:1/18:2)*, 1-oleoyl-2-docosahexaenoyl-GPC (18:1/22:6)* = PC (18:1/22:6)*, 1,2-dilinoyleoyl-GPC (18:2/18:2) = PC (18:2/18:2), 1-linoleoyl-2-linolenoyl-GPC (18:2/18:3)* = PC (18:2/18:3)*, 1-linoleoyl-2-arachidonoyl-GPC (18:2/20:4n6)* = PC (18:2/20:4n6)*, 1-palmitoyl-GPC (16:0) = PC (16:0) [1], 2-palmitoyl-GPC* (16:0)* = PC* (16:0)* [2], 1-palmitoleoyl-GPC* (16:1)* = PC* (16:1)* [1], 2-palmitoleoyl-GPC* (16:1)* = PC* (16:1)* [2], 1-oleoyl-GPC (18:1) = PC (18:1), 1-stearoyl-GPC (18:0) = PC (18:0), 1-linoleoyl-GPC (18:2) = PC (18:2), 1-linolenoyl-GPC (18:3)* = PC (18:3)*, 1-linoleoyl-GPC (18:3)* = PC (18:3)*, 1-arachidonoyl-GPC* (20:4)* = PC* (20:4)*, 1-lignoceroyl-GPC (24:0) = PC (24:0), 1-palmitoyl-2-oleoyl-GPE (16:0/18:1) = PE (16:0/18:1), 1-palmitoyl-2-linoleoyl-GPE (16:0/18:2) = PE (16:0/18:2), 1-palmitoyl-2-arachidonoyl-GPE (16:0/20:4)* = PE (16:0/20:4)*, 1-palmitoyl-2-docosahexaenoyl-GPE (16:0/22:6)* = PE (16:0/22:6)*, 1-stearoyl-2-oleoyl-GPE (18:0/18:1) = PE (18:0/18:1), 1-stearoyl-2-linoleoyl-GPE (18:0/18:2)* = PE (18:0/18:2)*, 1-stearoyl-2-arachidonoyl-GPE (18:0/20:4) = PE (18:0/20:4), 1-stearoyl-2-docosahexaenoyl-GPE (18:0/22:6)* = PE (18:0/22:6)*, 1-oleoyl-2-linoleoyl-GPE (18:1/18:2)* = PE (18:1/18:2)*, 1-oleoyl-2-arachidonoyl-GPE (18:1/20:4)* = PE (18:1/20:4)*, 1-oleoyl-2-docosahexaenoyl-GPE (18:1/22:6)* = PE (18:1/22:6)*, 1,2-dilinoyleoyl-GPE (18:2/18:2)* = PE (18:2/18:2)*, 1-palmitoyl-GPE (16:0) = PE (16:0), 1-stearoyl-GPE (18:0) = PE (18:0) [1], 2-stearoyl-GPE (18:0)* [2] = PE (18:0)*, 1-oleoyl-GPE (18:1) = PE (18:1), 1-linoleoyl-GPE (18:2)* = PE (18:2)*, 1-palmitoyl-2-oleoyl-GPI (16:0/18:1)* = PI (16:0/18:1)*, 1-palmitoyl-2-linoleoyl-GPI (16:0/18:2) = PI (16:0/18:2), 1-palmitoyl-2-arachidonoyl-GPI (16:0/20:4)* = PI (16:0/20:4)*, 1-stearoyl-2-oleoyl-GPI (18:0/18:1)* = PI (18:0/18:1)*, 1-stearoyl-2-linoleoyl-GPI (18:0/18:2) = PI (18:0/18:2), 1-stearoyl-2-arachidonoyl-GPI (18:0/20:4) = PI (18:0/20:4), 1-palmitoyl-GPI* (16:0) = PI* (16:0), 1-stearoyl-GPI (18:0) = PI (18:0), 1-oleoyl-GPI (18:1) = PI (18:1), 1-linoleoyl-GPI* (18:2)* = PI* (18:2)*, 1-arachidonoyl-GPI* (20:4)* = PI* (20:4)*.

Results

In a previous study in mice, supplementation with *D. welbionis* J115^T under high-fat diet (60%, HFD) altered the lipid profile in the plasma, the brown adipose tissue (BAT) and the colon. Using a targeted lipidomics approach focused on a small subset of lipids (65 targeted), we observed that in plasma, six lipids (PGD2, 17-HDoHE,

C18-3OH, C14-3OH, C18-2OH and 12-HETE) were restored to levels comparable to the control group, while two lipids (15-dPGJ2, C16-3OH) were decreased. Additionally, 14,15-EET was elevated compared to normal diet (ND), 9oxoODE was decreased compared to HFD, and three lipids (13-oxoODE, 9-HODE and 10-HODE) were decreased compared to both ND and untreated HFD groups [27].

Building on these findings, we extended our investigation to humans by analyzing the association of *Dysosmobacter* spp. with plasmatic lipid metabolites in the Microbes4U cohort. This study included 30 women and 22 men who were overweight or obese based on BMI and had a metabolic syndrome and insulin resistance (Table 1). Metabolomic profiling detected a total of 1169 compounds, 935 of which were of known identity, while 234 were of unknown identity (X-number) or partially characterized. Because of a very weak detection rate, metabolites related to drugs (i.e. analgesic, neurological, respiratory, antibiotic, psychoactive) and tobacco were not considered in the analysis, which gave us a final dataset of 862 metabolites. Based on Metabolon's super-pathway classification, the metabolites were split into two datasets. The first one containing the 453 metabolites referred as belonging to the "Lipid" super-pathway, and the second one, "non-lipid", encompassing the remaining 405 metabolites (Supplementary table).

No correlation was found between *Dysosmobacter* spp. fecal concentration and plasma non-lipid metabolites. Interestingly in the lipid metabolites dataset, 46 molecules showed positive correlations with *Dysosmobacter* spp. fecal levels (Table 2). These metabolites had an average correlation coefficient (*r*-score) of 0.456, ranging from a minimum correlation of 0.387 for 1-palmitoyl-GPE (16:0) to a maximum of 0.544 for 1-palmitoyl-GPC (16:0).

Since this study focused on plasmatic metabolites, all lipids detected were either free fatty acid derived from triglycerides lipolysis, circulating primarily bound to albumin, or from chylomicrons lysed during the sample preparation [28].

***Dysosmobacter* spp. partially correlates with DAGs and MAGs**

Among the 28 measured diacylglycerols (DAGs), 12 showed a positive correlation with *Dysosmobacter* spp. fecal concentrations, all of which contained at least one mono- or polyunsaturated acyl chain (Fig. 1 and supplementary Fig. 1). These included: diacylglycerol (14:0/18:1, 16:0/16:1) [1]*, myristoyl-linoleoyl-glycerol (14:0/18:2) [1]*, linoleoyl-linolenoyl-glycerol(18:2/18:3) [2]*, palmitoyl-linoleoyl-glycerol (16:0/18:2) [2]*, two isomers of palmitoyl-arachidonoyl-glycerol (16:0/20:4), two

isomers of stearoyl-arachidonoyl-glycerol (18:0/20:4), two isomers of oleoyl-arachidonoyl-glycerol (18:1/20:4), and two isomers of linoleoyl-arachidonoyl-glycerol (18:2/20:4) (Table 2).

Notably, several of these DAGs were negatively correlated with GLP-1, an incretin involved in energy metabolism [29]. Specifically, linoleoyl-arachidonoyl-glycerol (18:2/20:4) [1]*, palmitoyl-arachidonoyl-glycerol (16:0/20:4) [2]*, linoleoyl-linolenoyl-glycerol (18:2/18:3) [2]*, and stearoyl-arachidonoyl-glycerol (18:0/20:4) [1]*. Furthermore, Palmitoyl-arachidonoyl-glycerol (16:0/20:4) [1]* was negatively associated with plasma LPS concentration and Stearoyl-arachidonoyl-glycerol (18:0/20:4) [2]* was positively associated with GDF-15 (Table 3).

In general, several plasmatic DAGs have been positively linked to insulin resistance, T2D progression, and related markers in various cohorts, including non-diabetic overweight/obese individuals [30], non-diabetic individuals with high risk of cardiovascular disease (CVD), and those with T2D [31]. However, in our cohort of insulin resistant but non-diabetic participants, DAGs showed no correlation with key glucose metabolism parameters, including fasting glycemia, HbA1c, insulin sensitivity and, insulin resistance scores.

One possible explanation for these discrepancies is the variation in how DAG species are reported across studies. Like for many lipid families, many studies aggregate DAGs as a total lipid class or sum the carbon and double-bound content of their acyl chains, rendering direct comparison between studies difficult. The specific composition and localization of DAG species may influence their metabolic effects, and these differences should be considered in future investigations.

Among the monoacylglycerols (MAGs), 1-palmitoleoylglycerol (16:1)* and 1-arachidonoylglycerol (20:4) (1-AG) were both positively correlated with *Dysosmobacter* spp. fecal concentration ($r = 0.392$, adjusted p -value = 0.045; and $r = 0.431$, adjusted p -value = 0.021 respectively) (Table 1 Fig. 1 and supplementary Fig. 2). MAGs are typically produced from DAGs via diacylglycerol lipases, with 2-monoacylglycerols (2-MAGs) capable of non-enzymatic isomerization into 1/3-MAGs, which are thermodynamically more stable [32]. This may occur in vivo or during the analytical process. The analytical method used in this study does not distinguish between 1- and 3-MAG isomers, so these molecules are collectively labeled as 1-MAGs.

Very few studies have reported the detection of plasmatic 1-palmitoleoylglycerol and 1-AG in human cohorts focused on metabolic diseases. In a Finnish male cohort, plasma 1-palmitoleoylglycerol was positively associated with T2D incidence over a seven-year follow-up

Table 2 Plasma lipids correlated with *Dysosmobacter* spp. fecal concentration

	<i>r</i> -score	<i>p</i> -value	Adjusted <i>p</i> -value
Diacylglycerol			
Diacylglycerol (14:0/18:1, 16:0/16:1) [1]*	0.39310	0.00394	0.04488
Linoleoyl-arachidonoyl-glycerol (18:2/20:4) [1]*	0.41945	0.00197	0.02739
Linoleoyl-arachidonoyl-glycerol (18:2/20:4) [2]*	0.51567	0.00009	0.00265
Linoleoyl-linolenoyl-glycerol (18:2/18:3) [2]*	0.46911	0.00045	0.00917
Myristoyl-linoleoyl-glycerol (14:0/18:2) [1]*	0.45500	0.00070	0.01282
Oleoyl-arachidonoyl-glycerol (18:1/20:4) [1]*	0.48877	0.00024	0.00558
Oleoyl-arachidonoyl-glycerol (18:1/20:4) [2]*	0.50423	0.00014	0.00367
Palmitoyl-arachidonoyl-glycerol (16:0/20:4) [1]*	0.43149	0.00140	0.02143
Palmitoyl-arachidonoyl-glycerol (16:0/20:4) [2]*	0.53916	0.00004	0.00130
Palmitoyl-linoleoyl-glycerol (16:0/18:2) [2]*	0.39042	0.00422	0.04701
Stearoyl-arachidonoyl-glycerol (18:0/20:4) [1]*	0.52275	0.00007	0.00215
Stearoyl-arachidonoyl-glycerol (18:0/20:4) [2]*	0.53663	0.00004	0.00141
Monoacylglycerol			
1-arachidonoylglycerol (20:4)	0.43166	0.00140	0.02136
1-palmitoleoylglycerol (16:1)*	0.39231	0.00402	0.04547
Acylcholines			
Arachidonoylcholine	0.40630	0.00280	0.03524
Eicosapentaenoylcholine	0.40596	0.00283	0.03549
Oleoylcholine	0.41168	0.00243	0.03182
Palmitoleoylcholine	0.45420	0.00072	0.01305
Palmitoylcholine	0.40195	0.00314	0.03829
Stearoylcholine*	0.40451	0.00294	0.03647
Long Chain Polyunsaturated Fatty Acids			
Arachidonate (20:4n6)	0.40203	0.00313	0.03823
Phosphatidylcholine			
1-linoleoyl-2-arachidonoyl-GPC (18:2/20:4n6)*	0.45121	0.00079	0.01395
1-myristoyl-2-arachidonoyl-GPC (14:0/20:4)*	0.43618	0.00123	0.01942
1-palmitoyl-2-gamma-linolenoyl-GPC (16:0/18:3n6)*	0.46779	0.00047	0.00948
1-palmitoyl-2-oleoyl-GPC (16:0/18:1)	0.44404	0.00098	0.01636
1-stearoyl-2-oleoyl-GPC (18:0/18:1)	0.42679	0.00160	0.02361
Lysophosphatidylcholine			
1-lignoceroyl-GPC (24:0)	0.40357	0.00301	0.03715
1-linolenoyl-GPC (18:3)*	0.50645	0.00013	0.00344
1-oleoyl-GPC (18:1)	0.48596	0.00026	0.00600
1-palmitoleoyl-GPC* (16:1)*	0.53436	0.00004	0.00151
1-palmitoyl-GPC (16:0)	0.54418	0.00003	0.00110
1-stearoyl-GPC (18:0)	0.47887	0.00033	0.00721
2-palmitoleoyl-GPC* (16:1)*	0.49142	0.00022	0.00521
2-palmitoyl-GPC* (16:0)*	0.51900	0.00008	0.00241
Lysophosphatidylethanolamine			
1-palmitoyl-GPE (16:0)	0.38709	0.00458	0.04988
1-stearoyl-GPE (18:0)	0.49244	0.00021	0.00507
2-stearoyl-GPE (18:0)*	0.48707	0.00025	0.00583
Phosphatidylinositol			
1-stearoyl-2-arachidonoyl-GPI (18:0/20:4)	0.44574	0.00093	0.01573
Lysophosphatidylinositol			
1-arachidonoyl-GPI* (20:4)*	0.39076	0.00418	0.04671
1-palmitoyl-GPI* (16:0)	0.46991	0.00044	0.00899

Table 2 (continued)

	r-score	p-value	Adjusted p-value
1-stearoyl-GPI (18:0)	0.40348	0.00302	0.03722
Lysoplasmalogen			
PC(P-16:0)	0.42995	0.00147	0.02211
Phospholipid Metabolism			
Glycerophosphoethanolamine	0.49825	0.00017	0.00433
Glycerophosphorylcholine (GPC)	0.46376	0.00053	0.01042
Ceramides			
Ceramide (d18:1/20:0, d16:1/22:0, d20:1/18:0)*	0.51225	0.00010	0.00291
Sterol			
Cholesterol	0.45087	0.00080	0.01406

* Indicates a compound that has not been confirmed based on a standard, but that is identified by Metabolon with confidence
[#] Indicates a compound that is a structural isomer of another compound in the Metabolon spectral library

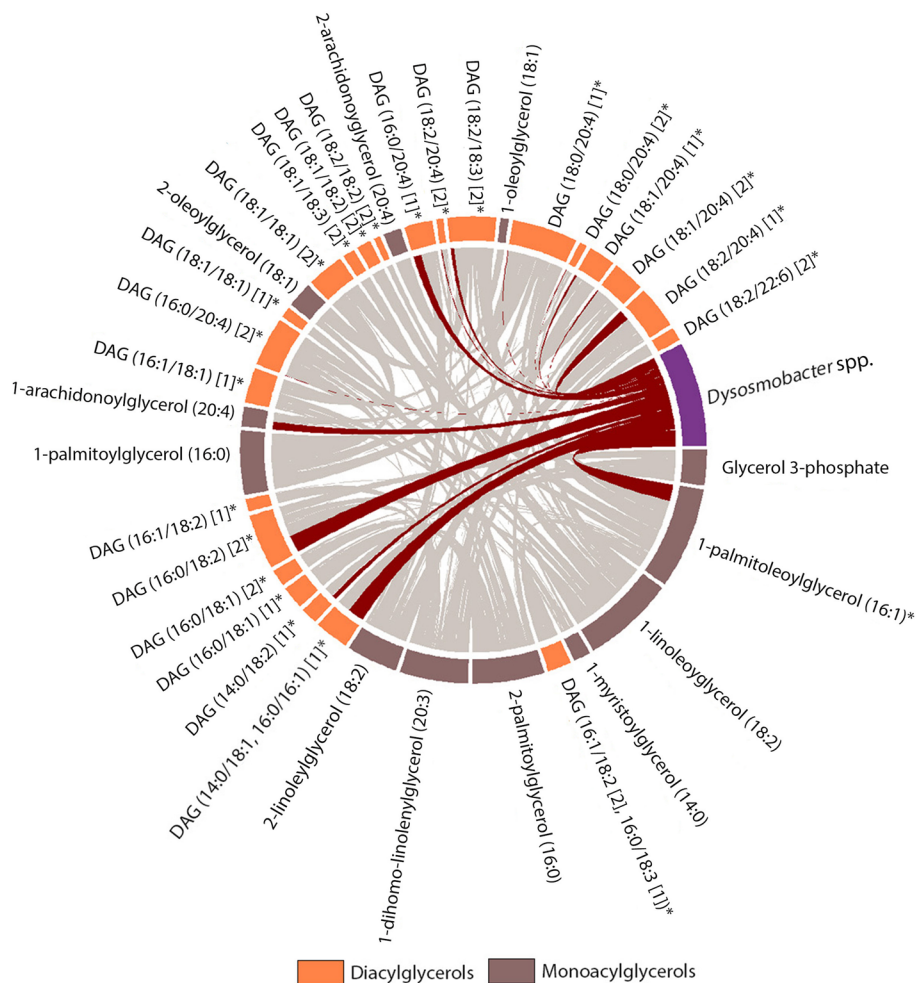


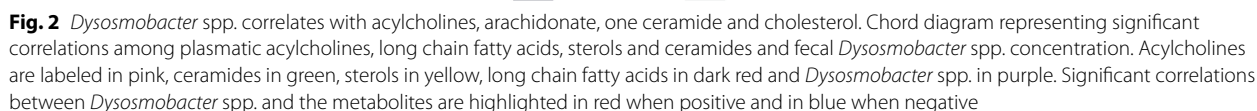
Fig. 1 *Dysosmobacter* spp. partially correlates with DAGs and MAGs. Chord diagram representing significant correlations among plasmatic DAGs and MAGs and fecal *Dysosmobacter* spp. concentration. DAGs are labeled in orange, MAGs in brown and *Dysosmobacter* spp. in purple. Significant correlations between *Dysosmobacter* spp. and metabolites are highlighted in red when positive and in blue when negative

Table 3 Identified lipids correlate with metabolic & inflammatory plasmatic parameters

	<i>r</i> -score	<i>p</i> -value	Adjusted <i>p</i> -value
GLP-1			
1-arachidonoyl-GPI ^a * (20:4)*	− 0.37585	0.00715	0.03729
Arachidonoylcholine	− 0.41330	0.00285	0.01724
Glycerophosphoethanolamine	− 0.38343	0.00598	0.03213
Glycerophosphorylcholine (GPC)	− 0.36874	0.00841	0.04289
Linoleoyl-arachidonoyl-glycerol (18:2/20:4) [1]*	− 0.41263	0.00290	0.01752
Linoleoyl-linolenoyl-glycerol (18:2/18:3) [2]*	− 0.41532	0.00271	0.01651
Oleoylcholine	− 0.36749	0.00865	0.04403
Palmitoleoylcholine	− 0.40860	0.00322	0.01900
Palmitoyl-arachidonoyl-glycerol (16:0/20:4) [2]*	− 0.36913	0.00834	0.04255
Palmitoylcholine	− 0.36634	0.00888	0.04482
Stearoyl-arachidonoyl-glycerol (18:0/20:4) [1]*	− 0.40994	0.00311	0.01852
Stearoylcholine*	− 0.46689	0.00063	0.00475
LPS			
1-arachidonoyl-GPI* (20:4)*	− 0.37742	0.00581	0.03144
1-palmitoyl-GPI* (16:0)	− 0.44878	0.00085	0.00614
1-stearoyl-GPI (18:0)	− 0.39604	0.00366	0.02125
Palmitoyl-arachidonoyl-glycerol (16:0/20:4) [1]*	− 0.38971	0.00429	0.02434
GDF-15			
1-lignoceroyl-GPC (24:0)	0.35976	0.00880	0.04453
Stearoyl-arachidonoyl-glycerol (18:0/20:4) [2]*	0.37574	0.00605	0.03238
IL-6			
1-linolenoyl-GPC (18:3)*	− 0.42002	0.00239	0.01484
MCP-1			
1-oleoyl-GPC (18:1)	0.36948	0.00702	0.03676
1-palmitoleoyl-GPC* (16:1)*	0.35812	0.00914	0.04592
1-stearoyl-2-arachidonoyl-GPI (18:0/20:4)	0.37217	0.00659	0.03489
1-stearoyl-2-oleoyl-GPC (18:0/18:1)	0.42442	0.00171	0.01109
1-stearoyl-GPC (18:0)	0.37708	0.00586	0.03159
LBP			
1-palmitoleoyl-GPC* (16:1)*	0.37096	0.00678	0.03568
1-palmitoyl-2-oleoyl-GPC (16:0/18:1)	0.43960	0.00111	0.00765
1-stearoyl-2-oleoyl-GPC (18:0/18:1)	0.43319	0.00134	0.00893
2-palmitoleoyl-GPC* (16:1)*	0.38043	0.00540	0.02957
AlkP			
1-palmitoyl-GPC (16:0)	0.37648	0.00647	0.03433
1-stearoyl-GPE (18:0)	0.38848	0.00485	0.02711
Waist-hip ratio			
1-stearoyl-2-arachidonoyl-GPI (18:0/20:4)	0.4108	0.00228	0.01422
HbA1c			
2-palmitoleoyl-GPC* (16:1)*	− 0.35592	0.00961	0.04814
Urea			
Arachidonate (20:4n6)	− 0.36366	0.00805	0.04128
ADAMTs13			
PC(P-16:0)	0.46398	0.00053	0.00410

* Indicates a compound that has not been confirmed based on a standard, but that is identified by Metabolon with confidence

[#] Indicates a compound that is a structural isomer of another compound in the Metabolon spectral library



Despite the typical association of DAGs and MAGs with metabolic dysfunction, 14 of these were associated with *Dysosmobacter* spp. fecal concentration in our study. Given that *Dysosmobacter* spp. has been linked to beneficial metabolic outcomes, this unexpected finding raises important questions about its role in lipid metabolism. Future studies are needed to elucidate whether these correlations reflect a protective mechanism, a compensatory response, or an unrelated phenomenon.

***Dysosmobacter* spp. correlates with acylcholines**

Fecal *Dysosmobacter* spp. concentration positively correlated with six of the nine plasma acylcholines detected: palmitoylcholine, oleoylcholine, palmitoleoylcholine, stearoylcholine*, arachidonoylcholine and eicosapentaenoylcholine (Table 2 Fig. 2 and supplementary Fig. 2). Notably, all identified acylcholines -except eicosapentaenoylcholine- were negatively associated with plasma GLP-1 plasmatic levels (Table 1), suggesting a potential metabolic interaction.

Despite their presence in circulation, the role of plasma acylcholines in metabolic syndrome remains largely unexplored. In a 2023 Qatari cohort of individuals with T2D treated with metformin, palmitoylcholine and arachidonoylcholine were associated with a better treatment response [37]. This is particularly intriguing given that a previous study from our lab demonstrated an increased abundance of *Dysosmobacter* spp. in metformin-treated diabetic individuals. However, in an experiment in which mice were co-treated with both metformin and *D. welbiensis* J115^T no synergistic effect was observed.

Beyond metabolic syndrome, plasmatic acylcholines variations show inconsistent associations across different pathological contexts. They have been positively linked to endometrial cancer [38], pulmonary embolism risk [39] and atherosclerotic plaques [40], while negatively associated with chronic thromboembolic pulmonary hypertension [41] and myalgic encephalomyelitis/chronic fatigue syndrome [42]. Additionally, in clinical trials where prebiotic interventions aimed to modulate gut microbiota, plasmatic acylcholine profile were altered [43–46], highlighting a potential microbiota-mediated influence on acylcholine metabolism. However, these changes were highly variable and dependent on cohort composition and the type of prebiotic used.

First described in 1911, long-chain acylcholines were initially studied for their pressor effect, conferring them a role in blood pressure regulation [47]. Research on their biological activity declined after the 1950's, resulting in limited data [42, 47], but recent studies have reignited interest. In vitro experiments have shown that arachidonoylcholine, oleoylcholine, and linoleoylcholine, act as inhibitors of nicotinic acetylcholine receptors (nAChR), while arachidonoylcholine can also modestly inhibit acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) at higher concentrations [48]. While we don't know the pathophysiological concentration range of these molecules in various tissues, these findings suggest that acylcholines may play a role in endogenous acetylcholine signaling.

BChE (previously pseudocholinesterase), a nonspecific cholinesterase enzyme synthesized in the liver and released into the plasma either in free form or bound

to LDLs, has been implicated in metabolic disorders. Increased plasma BChE activity has been described in patients with hyperlipidemia [49], and correlates with metabolic syndrome markers in diabetic and non-diabetic individuals [50, 51]. BChE also plays a role in the hydrolysis of octanoyl-ghrelin, an orexigenic hormone, converting it to its inactive form [52]. However, the resulting des-acyl ghrelin may have cell-proliferative effects, potentially stimulating adipogenesis and cardiovascular alterations. This suggests a functional role for BChE in the development and progression of both obesity and coronary artery disease [51]. The complexity of BChE's role in energy metabolism is further underscored by mouse knockout models, where BChE deficiency led to increased obesity under a high-fat diet, indicating that the role of BChE in energy metabolism is still far from being understood.

While the gut microbiota appears to influence plasma acylcholine regulation, the underlying mechanisms remain poorly characterized. The observed link between *Dysosmobacter* spp., acylcholines, and metformin response warrants further exploration to clarify this association and its metabolic implications.

Plasmatic arachidonate correlates with *Dysosmobacter* spp.

Plasma levels of arachidonate (20:4n6), showed a positive correlation with *Dysosmobacter* spp. fecal concentration ($r = 0.402$, adjusted p -value = 0.038) (Table 2 Fig. 2 and supplementary Fig. 4). Arachidonate is the second most mobilized fatty acid during fasting [53] and plays a central role in numerous physiological and pathological processes. However, its precise impact on metabolic diseases remains unclear [54, 55].

In this cohort, plasma arachidonate levels were negatively correlated with urea (Table 3), although urea levels remained within the physiological range for all participants based on Belgian clinical guidelines [56].

The role of arachidonate in metabolic disorders is complex and context dependent. In T2D, increased free arachidonate has been linked to oxidative stress, a key driver of insulin resistance in adipocytes and muscle tissue, as well as impaired insulin secretion [54, 55]. Conversely, other studies suggest an inverse correlation with T2D and a protective role. In a very limited cohort of fasting women, arachidonate was inversely correlated with glycemia, and in another T2D cohort, individuals with lower circulatory arachidonate levels exhibited more pronounced diabetic characteristics, which were attenuated upon arachidonic acid supplementation [54, 57].

These discrepancies may stem from differences in arachidonate metabolism. While arachidonate itself has been shown to stimulate insulin secretion, its downstream metabolites exert divergent effects. For example,

PGE2 contributes to pancreatic beta-cell dysfunction, whereas metabolites such as epoxyeicosatrienoic acids (EETs) and 20-hydroxyeicosatetraenoic acid (20-HETE) from the cytochrome P450 (CYP450) pathway, or lipoxin A4 (LXA4) from the lipoxygenase (LOX) pathway, have opposing, potentially beneficial effects [55, 58, 59].

Arachidonate is best known for its role in inflammation, a key component of the metabolic syndrome. However, as described above, its impact depends on its enzymatic conversion. Arachidonate can be processed by cyclooxygenases (COX), LOX or CYP450, producing a wide variety of metabolites that are either pro-inflammatory (e.g. PGE2, Leukotrienes, HETEs) or anti-inflammatory (e.g. LXA4) properties [54, 60].

Since our study did not include a complete profiling of arachidonate-derived metabolites, we cannot determine whether *Dysosmobacter* spp. is associated with reduced arachidonate metabolism – potentially leading to a pro-inflammatory state—or whether it promotes a metabolic shift toward either pro- or anti-inflammatory lipid mediators. Further investigations are needed to clarify the implications of *Dysosmobacter* spp. in arachidonate metabolism and its potential role in metabolic health.

Association between *Dysosmobacter* spp. and ceramides

A ceramide species (d18:1/20:0, d16:1/22:0, d20:1/18:0)* was positively correlated with *Dysosmobacter* spp. fecal concentration (r -score = 0.512, adjusted p -value = 0.002) (Table 2 Fig. 2 and supplementary Fig. 5). Ceramides are sphingolipids composed of a sphingoid base linked to a fatty acid via an amide bond and serve as precursors for more complex sphingolipids such as sphingomyelins and hexosylceramides. In plasma, ceramides are primarily transported by LDL and VLDL, suggesting a predominant hepatic origin, with a minor contribution from dietary sources [61].

In most studies ceramides are classified using the notation Cer(C:n) where “C” refers to the number of carbon in the fatty acid chain and “n” denotes the number of unsaturation. However, this convention often overlooks potential variations in the sphingoid base, which may influence the biological effects of these molecules.

As a lipid class, ceramides (Cer), have been implicated in insulin resistance in animal models, though their role in human metabolism is still debated [30]. They are frequently described as lipotoxic bioactive lipids that accumulate in the plasma of obese and insulin resistant individuals [62–66]. In various cohorts across different countries, plasma levels of Cer16:0, Cer18:0, Cer20:0 and Cer22:0 have been linked to insulin resistance, HOMA-IR, β -cell function (HOMA-%S), incident diabetes and Matsuda index, and pro-inflammatory cytokines in individuals with CVD, as well as increased CVD incidence

[67–75]. Unexpectedly, a 2018 study by Razquin et al. reported an inverse correlation between ceramides and T2D in two different cohorts [76, 77]. This contradictory finding may be explained by differences in lipid transport, with a sub-phenotype of patients exhibiting triglyceride-loaded LDL particles instead of ceramide-enriched LDL [76].

In our study, the analytical method did not provide sufficient resolution to differentiate between the three ceramide species grouped under the name *Ceramide* (d18:1/20:0, d16:1/22:0, d20:1/18:0). However, these species likely correspond to Cer20:0, Cer22:0 and Cer18:0, which have previously been associated with T2D, obesity and CVD markers. While we cannot determine the exact ceramide species linked to *Dysosmobacter* spp., all three potential molecules have been reported in association with adverse metabolic phenotypes, warranting further investigation into their role in host metabolism.

Plasmatic cholesterol levels correlate with *Dysosmobacter* spp.

Plasma total cholesterol levels positively correlated with *Dysosmobacter* spp. fecal concentrations, (r -score = 0.450; adjusted p -value = 0.014) (Table 2, Fig. 2 and supplementary Fig. 6). While elevated total cholesterol is not a defining characteristic of metabolic syndrome, it is associated with an increased risk of CVD [78], particularly when levels exceed 200 mg/dl. In this cohort, total cholesterol ranged from 102 to 312 mg/dl, with some participants exceeding this threshold. The link between cholesterol and *Dysosmobacter welbionis*, is supported by a recent 2024 study by Li et al., which identified this bacterium as a cholesterol-metabolizing species. How this metabolic activity translates to plasma cholesterol levels, however, remains unclear [79].

Phospholipids, lysophospholipids & lysoplasmalogens correlations with *Dysosmobacter* spp.

Phospholipids (PL) are amphipathic molecules that serve as the main structural components of cell membranes. They are composed of a glycerol backbone, a polar head group (e.g. choline, serine, inositol, ethanolamine, or glycerol), and two acyl chains. Hydrolysis of one acyl chains results in lysophospholipids (LysoPL). If one of the fatty acid chains is attached to the backbone via a vinyl-ether bond instead of an ester bond, the PL classifies as a plasmenylphospholipids (also called a plasmalogen), while a LysoPL becomes a lysoplasmenylphospholipid (lysoplasmalogen). These molecules are further categorized based on their polar head group and acyl chain composition.

Phosphocholines (PC) and lysophosphocholines (LysoPC)

Fecal *Dysosmobacter* spp. concentrations correlated with five phosphocholines (PC), and eight lysophosphocholines (LysoPC) (Table 2, Fig. 3 and supplementary Fig. 7). Notably, all five PC molecules contained at least one mono or poly-unsaturated acyl chain, which might be functionally relevant. Among them, 1-stearoyl-2-oleoyl-GPC (18:0/18:1) was positively associated with plasmatic monocyte chemoattractant protein-1 (MCP-1, CCL-2 in humans) (r -score = 0.424; adjusted p -value = 0.011), a marker of immune cell recruitment. This molecule, along with 1-palmitoyl-2-oleoyl-GPC (16:0/18:1) also correlated positively with lipopolysaccharide-binding protein (LBP) (Table 3), a marker of systemic endotoxemia.

Previous studies have shown that the associations between circulating PC and metabolic syndrome vary widely and potentially depend on the differences in acyl chains length and saturation. A 2022 study carried out on Qatari cohort with and without T2D found that certain PC species correlated with BMI and dyslipidemia, but not with T2D or diabetic retinopathy [34]. For example, PC (16:0/16:1) was positively associated with BMI and PC (16:0/18:0) was positively associated with LDL, triglycerides, LDL/HDL ratio and dyslipidemia, whereas PC (18:2/18:2) and PC (18:2/18:3) were negatively associated with BMI [34]. In another cohort PC (16:0/20:4) was the only PC disrupted in prediabetic and diabetic patients, with elevated plasma levels [80]. However, many studies reporting PC levels in metabolic disorders have lacked

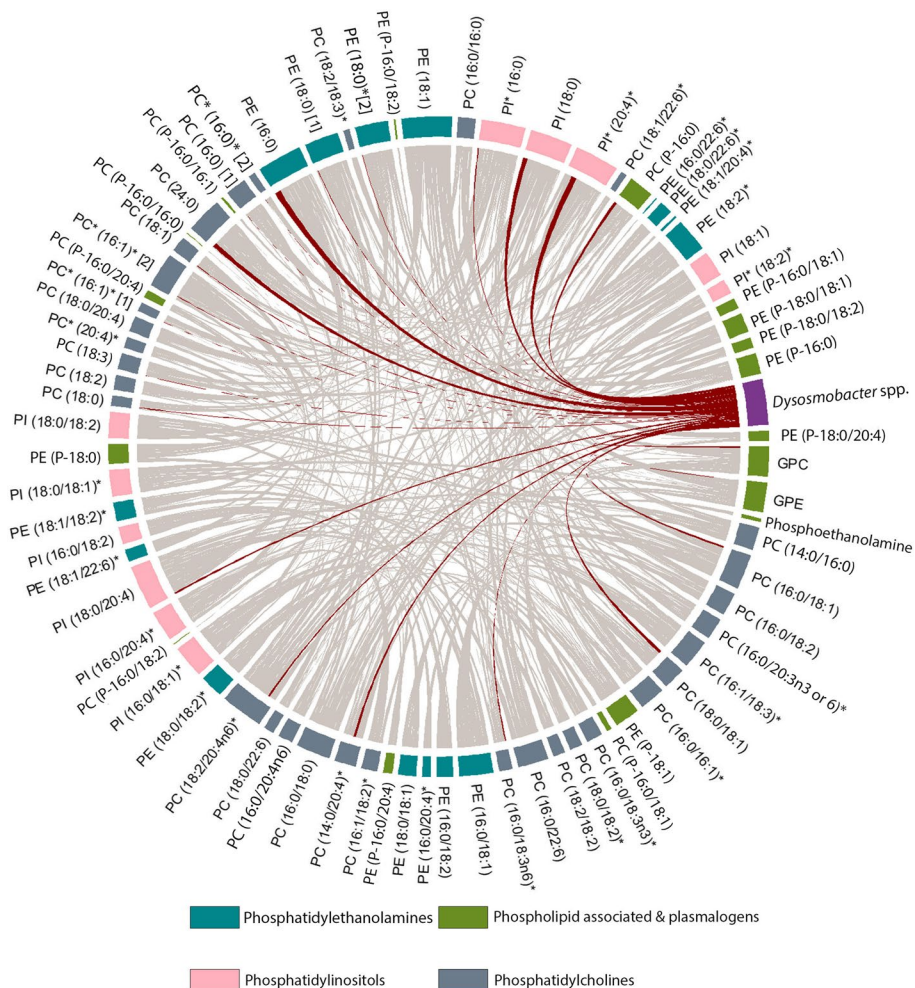


Fig. 3 *Dysosmobacter* spp. correlations with phospholipids and associated molecules. Chord diagram representing significant correlations among plasmatic PCs, PEs, PIs, LysoPCs, LysoPEs, LysoPIs, plasmalogens and PL metabolism associated molecules and fecal *Dysosmobacter* spp. concentration. PEs and LysoPEs are labeled in blue, PL metabolism associated molecules and plasmalogens in green, PIs and LysoPIs in pink, PCs and LysoPCs in dark gray and *Dysosmobacter* spp. in purple. Significant correlations between *Dysosmobacter* spp. and the metabolites are highlighted in red when positive and in blue when negative

the analytical sensitivity to resolve individual molecular species, instead reporting summed acyl chain compositions, complicating cross-study comparisons [81–84].

Among the 10 detected LysoPCs, eight were positively correlated with *Dysosmobacter* spp. fecal concentration (Table 2, Fig. 3 and supplementary Fig. 7). Though present in lower quantities in cell membranes compared to their phospholipid counterparts [85–87], LysoPCs are abundant in human plasma, where their concentration range from 100 and 300 μ M in physiological state, with approximately 80% in the non-lipoprotein fraction, bound to albumin [30, 88]. LysoPCs are signaling molecules that exhibit a wide range of activities with receptors present in various tissues and have been implicated in the etiology of numerous disorders such as metabolic diseases, inflammation and cancer [87, 89].

In this study, 1-palmitoleoyl-GPC* (16:1)*, 1-oleoyl-GPC (18:1) and 1-stearoyl-GPC (18:0) were positively correlated positively with MCP-1 while 1-linolenoyl-GPC (18:3)* was negatively correlated with plasmatic IL-6. Both MCP-1 and IL-6 are markers of systemic inflammation and are often increased in obesity [90–95]. 1-palmitoyl-GPC (16:0) correlated with plasmatic alkaline phosphatase (AlkP), a marker linked to hepatobiliary disorders and cardiometabolic risks [96, 97]. 1-lignoceroyl GPC (24:0) positively correlated with plasmatic growth differentiation factor-15 (GDF-15), a member of the TGF-beta superfamily with complex effects on metabolism [98]. Finally, both isomers of palmitoleoyl-GPC* (16:1)* were positively associated with plasma LBP levels, while one isomer was negatively associated with HbA1c, a marker reflecting long-term glycemic control (Table 1).

The relationship between LysoPCs and obesity appears to be highly dependent on acyl chain composition. Most human studies conducted have reported that plasma LysoPC (14:0) and LysoPC (16:1) are positively associated with obesity [81, 99, 100], whereas other LysoPCs tend to be negatively associated [67, 88, 100–103] with a few exceptions [80, 104, 105]. In this study, LysoPCs containing 16:0, 16:1, 18:0, 18:1, 18:3, and 24:0, were positively correlated with *Dysosmobacter* spp. but none correlated with weight parameters (BW, BMI, hip circumference, waist circumference) measured in our cohort.

Previous studies investigating the relationship between LysoPCs and T2D, like in obesity, have predominantly reported an inverse correlation between plasma LysoPCs levels and various T2D-related parameters. In particular, LysoPCs species containing polyunsaturated fatty acids (PUFAs) tend to decrease with increasing insulin resistance (IR) and HOMA-IR scores [30, 76, 82, 106]. Additionally, in two independent cohorts, baseline plasma LysoPCs concentrations were found to predict worsening

glucose tolerance and progression toward T2D [107, 108].

Despite these associations, the mechanisms underlying the potential beneficial effects of LysoPCs on glucose metabolism remain unclear. While in vitro studies suggest that LysoPCs can stimulate insulin secretion in pancreatic beta-cell lines further research is needed to fully understand this interaction [109].

In our study, none of the LysoPCs correlated with *Dysosmobacter* spp. fecal concentrations showed associations with glucose metabolism markers, including glucagon, insulin sensitivity, insulin resistance score, GLP-1 and leptin, excepted for the negative correlation between 2-palmitoleoyl-GPC* (16:1)* and HbA1c. When considering obesity and T2D comorbidities, research on LysoPCs remains limited and often yields conflicting results. Some studies have reported negative associations between LysoPCs levels hepatic fat accumulation, CVD risks, and cancer [30, 110–112], whereas findings on atherosclerosis and inflammation suggest both protective and detrimental roles depending on the context [89].

Phosphatidylethanolamines (PE)

and lysophosphatidylethanolamines (LysoPE)

No correlations were found between *Dysosmobacter* spp. fecal concentrations and total phosphatidylethanolamines (PE). However, three saturated LysoPE species—2-stearoyl-GPE (18:0)* ($r = 0.487$, adjusted p -value = 0.005), 1-stearoyl-GPE (18:0) ($r = 0.492$, adjusted p -value = 0.005), and 1-palmitoyl-GPE (16:0) ($r = 0.387$, adjusted p -value = 0.049)—were positively correlated (Table 2, Fig. 3 and supplementary Fig. 8). These molecules have previously been identified as negatively associated with HOMA-IR in Chinese non-diabetic, non-obese individuals [82]. While plasma PE levels are generally elevated in insulin-resistant individuals [80], LysoPEs are often reduced in overweight/obese participants [30, 105, 113], T2D patients, and inversely correlated with T2D and CVD risks [76, 112], and BMI [99]. In this study, 1-stearoyl-GPE (18:0) was positively correlated with plasma AlkP (Table 1).

Phosphatidylinositols (PI) and lysophosphatidylinositols (LysoPI)

For phosphatidylinositols (PI) and lysophosphatidylinositols (LysoPI), *Dysosmobacter* spp. fecal concentrations correlated positively with plasma 1-stearoyl-2-arachidonoyl-GPI (18:0/20:4) (r -score = 0.445, adjusted p -value = 0.015), 1-palmitoyl-GPI* (16:0) (r -score = 0.469, adjusted p -value = 0.008), 1-stearoyl-GPI (18:0) (r -score = 0.403, adjusted p -value = 0.037), and 1-arachidonoyl-GPI* (20:4)* (r -score = 0.390, adjusted p -value = 0.046) (Table 2, Fig. 3 and supplementary Fig. 9). Among these,

1-arachidonoyl-GPI* (20:4)*, 1-palmitoyl-GPI* (16:0) and 1-stearoyl-GPI (18:0) were negatively associated with plasma LPS concentrations. In addition, 1-arachidonoyl-GPI* (20:4)* was negatively correlated with GLP-1, while 1-stearoyl-2-arachidonoyl-GPI (18:0/20:4) was positively associated with MCP-1 and waist-to-hip ratio, suggesting a potential link to visceral fat distribution (Table 3).

PI accounts for ~1% of total plasma lipids in humans [114] but their relationship with metabolic disorders is largely understudied. In 2019, a study in overweight and obese children reported reduced PI levels, suggesting a potential association with metabolic health [115]. However, further research is needed to clarify these relationships.

Lysoplasmalogens, phospholipids associated molecules and their potential role in metabolic health

In our study, fecal *Dysosmobacter* spp. concentration was positively associated with PC (P-16:0) a lysoplasmalogen molecule. However, literature on the role of lysoplasmalogens in obesity, T2D and metabolic syndrome is scarce, making it difficult to draw definitive conclusions or propose clear hypotheses about their metabolic impact.

Additionally, glycerophosphorylcholine (GPC) and glycerophosphorylethanolamine (GPE) were also positively correlated with *Dysosmobacter* spp. (Table 2, Fig. 3 and supplementary Fig. 10). These molecules are degradation products of (lyso)phospholipids, with GPC serving as a major circulating precursor of choline [116]. However, few information regarding GPC & GPE association with metabolic disorders has been published. In this study, GPC and GPE were negatively correlated with plasma GLP-1, while PC (P-16:0) was positively associated with plasma ADAMTS13, a metalloprotease involved in platelet aggregation regulation [117] (Table 3).

Although the limited available studies on the subject suggest that plasma PL, LysoPL and lysoplasmalogens are altered in metabolic disorders, however, whether these changes are causative or consequential remain unclear and the mechanisms involved remain unknown. Variability between studies likely stems from differences in analytical methods, lipid subclass resolution, and cohort characteristics. Identifying consistent patterns in PL metabolism across studies is particularly challenging due to several factors. First, PLs represent a highly diverse family of molecules, and no single analytical method can comprehensively capture their full spectrum. Second, the sensitivity and resolution of lipidomic methods vary across research groups, limiting the ability to precisely characterize the acyl chain composition of detected phospholipids. These methodological inconsistencies

complicate direct comparisons between studies and hinder a deeper understanding of PL dynamics in metabolic disorders.

Discussion

Interestingly, among the 862 identified metabolites covering multiple molecular families, only those belonging to the lipid super-pathway correlated significantly with *Dysosmobacter* spp. fecal concentration. This finding aligns with a previous mouse study, where *Dysosmobacter welbionis* J115^T supplementation altered the lipid profiles in brown adipose tissue, colon and plasma under a high-fat diet [27]. Within the lipid super-pathway, only 9-HODE, previously identified in the mouse study, was detected. However, due to the detection method's limited resolution, it was annotated as 9-HODE/13-HODE, as the two isomers could not be distinguished. No significant correlation was observed between this lipid and *Dysosmobacter* spp. fecal concentration. Here, six of nine detected acylcholines and eight of ten lysophosphatidylcholines (LysoPC) showed positive correlations with fecal *Dysosmobacter* levels, highlighting a potentially privileged relationship between this bacterium and host lipid metabolism. How *Dysosmobacter* spp. modifies the lipid profile of various tissues, either directly or indirectly, remains unknown and requires further investigations.

Although *Dysosmobacter* spp. itself was not directly associating with GLP-1 levels in this study, twelve lipid metabolites positively associated with *Dysosmobacter* spp. fecal concentration were negatively correlated with GLP-1 plasma levels. GLP-1 is an incretin secreted by enteroendocrine cells in the intestine that plays a central role in glucose and energy homeostasis [29]. Reduced circulating levels of this satiety-inducing hormone have been reported in obese and T2D patients, although findings are not consistent across all studies [118]. Our previous research demonstrated that *D. welbionis* J115^T directly stimulated the dose-dependent secretion of GLP-1 in entero-endocrine cell in vitro [7]. However, following in vivo studies did not find elevated portal GLP-1 levels after *Dysosmobacter welbionis* J115^T supplementation, suggesting the involvement of complex mechanisms and potential indirect pathways linking this bacterium with host metabolism.

Overall, the results obtained in this human cohort support further exploration of *Dysosmobacter* spp. and its potential influence on host lipid pathways, clarifying whether observed correlations represent causal mechanisms or indirect associations.

Limitations of this study

Although our findings highlight previously undescribed links between *Dysosmobacter* spp. and the host lipidome,

several limitations must be considered. Firstly, the study remains descriptive because participants were not specifically supplemented with *Dysosmobacter* spp. to assess its effects. The human cohort was relatively small, included one timepoint and lacked a lean control group, restricting definitive causal interpretations. Moreover, this cohort is made of 57.7% of females and 42.3% of males participants and no correction has been applied for this confounding factor which could impact plasmatic metabolomics.

Secondly, the metabolomics analysis provided only relative quantification of metabolites, without absolute reference values or a control group, limiting our ability to determine whether metabolite levels fall within physiological or pathological ranges and preventing direct comparisons to healthy populations.

Thirdly, due to methodological limitations, we could not clearly resolve all lipid species at the molecular level (e.g., certain ceramide species were grouped), hindering precise comparisons with existing literature.

Moreover, we cannot determine whether the observed lipids originated directly from host metabolism or from microbial metabolism. Gut bacteria can synthesize, accumulate and metabolize a wide variety of lipids, some identical to mammalian lipids and others unique, such as odd-chain fatty acids typically absent in those of mammal origin [119–121]. Current knowledge regarding bacterial lipid composition remains limited, largely restricted to studies of model organisms such as *Escherichia coli*, and does not encompass the full diversity of the gut microbiota [122]. Although certain bacterial lipids, including phospholipids with ethanolamine, choline, or inositol head groups, have been documented in various gut microbiota species [120, 122–125], there is very little known about the microbial production of MAGs, DAGs, ceramides, or acylcholines [123, 125–127]. How much of these lipids interact with the host is still unclear, as we don't know which subclasses can be absorbed by the host to integrate its own metabolism. Notably, recent evidence demonstrates that odd-chain bacterial lipids, including sphingolipids produced by *Bacteroides thetaiotaomicron*, can be detected in the gut epithelium and portal vein, although not in the liver, suggesting active absorption and subsequent metabolism by host tissues [128]. While in the referenced study the lipids were administered to the mice via gavage as purified solution rather than produced in situ by bacteria, it remains plausible that similar microbial lipids could be naturally synthesized and absorbed within the gut. Additionally, gut bacteria might also influence the host lipid profile indirectly through modulation of host metabolic pathways [122, 129–136]. Therefore, *Dysosmobacter* spp. could influence host metabolism either directly, through microbial lipid production and absorption, or indirectly, by shaping

overall microbial community dynamics that subsequently impact host lipid profiles. These limitations highlight the necessity of future studies that investigate both the direct lipidomic profiles of gut bacteria and the causal relationships between specific bacterial taxa, host lipid metabolism, and metabolic health outcomes.

Conclusion

Dysosmobacter welbionis is a recently discovered gut bacterium strongly linked to beneficial metabolic effects, positioning it as an attractive “next-generation” probiotic candidate for addressing obesity and diabetes. To effectively translate these promising findings, however, it remains crucial to understand how this bacterium interacts with host metabolism. The present study advances this goal by providing novel and valuable insights by demonstrating that *Dysosmobacter* spp. correlates with distinct circulating metabolites in humans. This highlights a previously unexplored microbial-host interaction and offers a foundation for exploring potential underlying mechanisms.

Abbreviations

20-HETE	20-hydroxyeicosatetraenoic acid
AChE	Acetylcholinesterase
AlkP	Alkaline phosphatase
ALT	Alanine transaminase
AST	Aspartate transaminase
BChE	Butyrylcholinesterase
BMI	Body Mass Index
BW	Bodyweight
CB1	Cannabinoid receptor-1
Cer	Ceramide
CK	Creatinine kinase
COX	Cyclooxygenase
CVD	Cardiovascular diseases
CYP450	Cytochrome P450
DAG (14:0/18:1, 16:0/16:1)	Diacylglycerol (14:0/18:1, 16:0/16:1)
DAG (16:0/18:1) [2]*	Palmitoyl-oleoyl-glycerol (16:0/18:1) [2]*
DAG (16:0/18:2) [2]*	Palmitoyl-linoleoyl-glycerol (16:0/18:2) [2]*
DAG (16:0/20:4) [1]*	Palmitoyl-arachidonoyl-glycerol (16:0/20:4) [1]*
DAG (16:1/18:1) [1]*	Palmitoleoyl-oleoyl-glycerol (16:1/18:1) [1]*
DAG (16:1/18:2 [2], 16:0/18:3 [1])	Diacylglycerol (16:1/18:2 [2], 16:0/18:3 [1])
DAG (16:1/18:2) [1]*	Palmitoleoyl-linoleoyl-glycerol (16:1/18:2) [1]*
DAG (16:1/18:2) [2]*	Palmitoleoyl-linoleoyl-glycerol (16:1/18:2) [2]*
DAG (18:0/20:4) [1]*	Stearoyl-arachidonoyl-glycerol (18:0/20:4) [1]*
DAG (18:0/20:4) [2]*	Stearoyl-arachidonoyl-glycerol (18:0/20:4) [2]*
DAG (18:1/18:1) [1]*	Oleoyl-oleoyl-glycerol (18:1/18:1) [1]*
DAG (18:1/18:1) [2]	Oleoyl-oleoyl-glycerol (18:1/18:1) [2]
DAG (18:1/18:2) [1]	Oleoyl-linoleoyl-glycerol (18:1/18:2) [1]
DAG (18:1/18:2) [2]	Oleoyl-linoleoyl-glycerol (18:1/18:2) [2]
DAG (18:1/18:3) [2]*	Oleoyl-linolenoyl-glycerol (18:1/18:3) [2]*
DAG (18:1/20:4) [1]*	Oleoyl-arachidonoyl-glycerol (18:1/20:4) [1]*
DAG (18:1/20:4) [2]*	Oleoyl-arachidonoyl-glycerol (18:1/20:4) [2]*
DAG (18:2/18:2) [1]	Linoleoyl-linoleoyl-glycerol (18:2/18:2) [1]*
DAG (18:2/18:2) [1]*	Linoleoyl-linoleoyl-glycerol (18:2/18:2) [1]*
DAG (18:2/18:2) [2]*	Linoleoyl-linoleoyl-glycerol (18:2/18:2) [2]*

DAG (18:2/18:3) [1]*	Linoleoyl-linolenoyl-glycerol (18:2/18:3) [1]*	PC (16:0/22:6)	(16:0/20:4n6)
DAG (18:2/18:3) [2]*	Linoleoyl-linolenoyl-glycerol (18:2/18:3) [2]*	PC (16:1/18:2)*	1-palmitoyl-2-docosahexaenoyl-GPC (16:0/22:6)
DAG (18:2/20:4) [1]*	Linoleoyl-arachidonoyl-glycerol (18:2/20:4) [1]*	PC (16:1/18:3)*	1-palmitoleoyl-2-linoleoyl-GPC (16:1/18:2)*
DAG (18:2/20:4) [2]*	Linoleoyl-arachidonoyl-glycerol (18:2/20:4) [2]*	PC (18:0)	1-palmitoleoyl-2-linolenoyl-GPC (16:1/18:3)*
DAG (18:2/22:6) [2]*	Linoleoyl-docosahexaenoyl-glycerol (18:2/22:6) [2]*	PC (18:0/18:0)	1-stearoyl-GPC (18:0)
DAG(14:0/18:2) [1]*	Myristoyl-linoleoyl-glycerol (14:0/18:2) [1]*	PC (18:0/18:1)	1,2-distearoyl-GPC (18:0/18:0)
DAG(16:0/18:1) [1]*	Palmitoyl-oleoyl-glycerol (16:0/18:1) [1]*	PC (18:0/18:2)*	1-stearoyl-2-oleoyl-GPC (18:0/18:1)
DAG(16:0/18:2) [1]*	Palmitoyl-linoleoyl-glycerol (16:0/18:2) [1]*	PC (18:0/20:4)	1-stearoyl-2-linoleoyl-GPC (18:0/18:2)*
DAG(16:0/18:3) [2]*	Palmitoyl-linolenoyl-glycerol (16:0/18:3) [2]*	PC (18:0/22:6)	1-stearoyl-2-arachidonoyl-GPC (18:0/20:4)
DAG(16:0/20:4) [2]*	Palmitoyl-arachidonoyl-glycerol (16:0/20:4) [2]*	PC (18:1)	1-stearoyl-2-docosahexaenoyl-GPC (18:0/22:6)
DAG(18:1/18:1) [2]*:	Oleoyl-oleoyl-glycerol (18:1/18:1) [2]*	PC (18:1/18:2)*	1-oleoyl-GPC (18:1)
DAG(18:1/18:1) [1]*	Oleoyl-oleoyl-glycerol (18:1/18:1) [1]*	PC (18:1/22:6)*	1-oleoyl-2-linoleoyl-GPC (18:1/18:2)*
DAG	Diacylglycerol	PC (18:2/18:2)	1-oleoyl-2-docosahexaenoyl-GPC (18:1/22:6)*
DDP-4	Dipeptidyl peptidase 4	PC (18:2/20:4n6)*	1-linoleoyl-GPC (18:2)
EET	Epoxycosatrienoic acids	PC (18:3)*	1,2-dilinoeloyl-GPC (18:2/18:2)
FDR	False discovery rate	PC (18:3)*	1-linoleoyl-2-linolenoyl-GPC (18:2/18:3)*
GDF-15	Growth differentiation factor 15	PC (24:0)	1-linoleoyl-2-arachidonoyl-GPC (18:2/20:4n6)*
GFR	Glomerular filtration rate	PC (16:0)[1]	1-linolenoyl-GPC (18:3)*
GGT	Gamma-glutamyl transferase	PC* (16:1)* [1]	1-linoleoyl-GPC (18:3)*
GIP	Gastric inhibitory polypeptide	PC* (16:1)* [2]	1-lignoceryl-GPC (24:0)
GLP-1	Glucagon-like-peptide-1	PC* (20:4)*	1-palmitoyl-GPC (16:0)
GPC	Glycerophosphorylcholine	PC	1-palmitoleoyl-GPC* (16:1)*
GPE	Glycerophosphorylethanolamine	PE (16:0)	2-palmitoleoyl-GPC* (16:1)*
HDL	High density lipoprotein	PE (16:0/18:1)	1-arachidonoyl-GPC* (20:4)*
HFD	High-fat diet	PE (16:0/18:2)	Phosphocholine
hsCRP	C-reactive protein	PE (16:0/20:4)*	1-palmitoyl-GPE (16:0)
IFABP	Intestinal fatty-acid binding protein	PE (16:0/22:6)*	1-palmitoyl-2-oleoyl-GPE (16:0/18:1)
IL-6	Interleukin-6	PE (18:0) [1]	1-palmitoyl-2-linoleoyl-GPE (16:0/18:2)
IP-10	Interferon gamma-induced protein 10	PE (18:0)* [2]	1-palmitoyl-2-arachidonoyl-GPE (16:0/20:4)*
IR	Insulin resistance	PE (18:0/18:1)	1-palmitoyl-2-docosahexaenoyl-GPE (16:0/22:6)*
LBP	Lipopolysaccharide binding protein	PE (18:0/18:2)*	1-stearoyl-GPE (18:0) [1]
LDH	Lactate dehydrogenase	PE (18:0/20:4)	2-stearoyl-GPE (18:0)* [2]
LOX	Lipoxygenase	PE (18:0/22:6)*	1-stearoyl-2-oleoyl-GPE (18:0/18:1)
LPS	Lipopolysaccharide	PE (18:1/18:2)*	1-stearoyl-2-linoleoyl-GPE (18:0/18:2)*
LXA4	Lipoxin A4	PE (18:1/20:4)*	1-stearoyl-2-arachidonoyl-GPE (18:0/20:4)
LysoPC	Lysophosphocholine	PE (18:1/22:6)*	1-stearoyl-2-docosahexaenoyl-GPE (18:0/22:6)*
LysoPE	Lysophosphatidylethanolamine	PE (18:1)	1-oleoyl-GPE (18:1)
LysoPI	Lysophosphatidylinositol	PE (18:1/18:2)*	1-oleoyl-2-linoleoyl-GPE (18:1/18:2)*
LysoPL	Lysophospholipid	PE (18:1/20:4)*	1-oleoyl-2-arachidonoyl-GPE (18:1/20:4)*
MAG	Monoacylglycerol	PE (18:1/22:6)*	1-oleoyl-2-docosahexaenoyl-GPE (18:1/22:6)*
MCP-1	Plasmatic monocyte chemoattractant protein-1	PE (18:2)*	1-linoleoyl-GPE (18:2)*
MDC	Macrophage derived chemokine	PE (18:2/18:2)*	1,2-dilinoeloyl-GPE (18:2/18:2)*
nAChR	Nicotinic acetylcholine receptor	PE	Phosphatidylethanolamine
ND	Normal diet	PI (16:0/18:1)*	1-palmitoyl-2-oleoyl-GPI (16:0/18:1)*
NEFA	Plasma non-esterified fatty acids	PI (16:0/18:2)	1-palmitoyl-2-linoleoyl-GPI (16:0/18:2)
PC (14:0/16:0)	1-myristoyl-2-palmitoyl-GPC (14:0/16:0)	PI (16:0/20:4)*	1-palmitoyl-2-arachidonoyl-GPI (16:0/20:4)*
PC (14:0/20:4)*	1-myristoyl-2-arachidonoyl-GPC (14:0/20:4)*	PI (18:0)	1-stearoyl-GPI (18:0)
PC* (16:0)* [2]	2-palmitoyl-GPC* (16:0)*	PI (18:0/18:1)*	1-stearoyl-2-oleoyl-GPI (18:0/18:1)*
PC (16:0) [1]	palmitoyl-GPC1 (16:0)	PI (18:0/18:2)	1-stearoyl-2-linoleoyl-GPI (18:0/18:2)
PC (16:0/16:0)	1,2-dipalmitoyl-GPC (16:0/16:0)	PI (18:0/20:4)	1-stearoyl-2-arachidonoyl-GPI (18:0/20:4)
PC (16:0/16:1)*	1-palmitoyl-2-palmitoleoyl-GPC (16:0/16:1)*	PI (18:1)	1-oleoyl-GPI (18:1)
PC (16:0/18:0)	1-palmitoyl-2-stearoyl-GPC (16:0/18:0)	PI* (16:0)	1-palmitoyl-GPI* (16:0)
PC (16:0/18:1)	1-palmitoyl-2-oleoyl-GPC (16:0/18:1)	PI* (18:2)*	1-linoleoyl-GPI* (18:2)*
PC (16:0/18:2)	1-palmitoyl-2-linoleoyl-GPC (16:0/18:2)	PI* (20:4)*	1-arachidonoyl-GPI* (20:4)*
PC (16:0/18:3n3)*	1-palmitoyl-2-alpha-linolenoyl-GPC (16:0/18:3n3)*	PI	Phosphatidylinositol
PC (16:0/18:3n6)*	1-palmitoyl-2-gamma-linolenoyl-GPC (16:0/18:3n6)*	PL	Phospholipid
PC (16:0/20:3n3 or 6)*	1-palmitoyl-2-dihomo-linolenoyl-GPC (16:0/20:3n3 or 6)*	pNA	p-nitroanilide
PC (16:0/20:4n6)	1-palmitoyl-2-arachidonoyl-GPC	PUFA	Polyunsaturated fatty acid
		PYY	Peptide YY
		sCD40L	Soluble CD40 ligand
		siCAM-1	Soluble intercellular adhesion molecule-1

svCAM-1
T2D
TG
WBC

Soluble vascular cell adhesion molecule-1
Type 2 diabetes
Triglyceride
White blood cell count

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Supplementary Material 1.

Supplementary Material 2.

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Authors' contributions

Conceptualization: CP, MVH, PDC; Data curation: CP, CD; Formal analysis: CP; Funding acquisition: PDC; Investigation: CP, CD, AE; Methodology: CP, CD, AE, MVH, PDC; Project administration: MVH, PDC; Resources: PDC and NMD; Supervision: MVH, PDC; Validation: MVH, PDC; Visualization: CP; Writing original draft: CP; Writing – review & editing: CP, AE, MVH, PDC; all authors agreed with the final submitted manuscript.

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Data availability

The datasets used and/or analyzed during the current study are available as supplementary data and from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Ethics Committee Commission d'Éthique Biomédicale Hospitalo-facultaire of the Université catholique de Louvain (Brussel, Belgium). The study was registered at <https://clinicaltrials.gov> as trial no. NCT02637115 (protocol code: 2015/02 JUL/369, approved on the 13 July 2015). Informed consent was obtained from all subjects involved in the study.

Consent for publication

Not applicable.

Competing interests

PDC and AE are inventors on patent applications dealing with the use bacteria on metabolic disorders. PDC was co-founders of The Akkermansia company SA and Enterosys. A. E. and P.D.C. are inventors on patent applications dealing with gut microbes in food reward dysregulations. A.E. is inventor on patent applications dealing with the use of bacteria metabolites in the prevention or treatment of respiratory viral infections.

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