International Journal of
Molecular Sciences

MDPI

Article

Key Stratification of Microbiota Taxa and Metabolites in the Host Metabolic Health–Disease Balance

Alfonso Torres-Sánchez [1], Alicia Ruiz-Rodríguez [1,2,3,*], Pilar Ortiz [2] and Margarita Aguilera [1,2,4,*]

[1] Department of Microbiology, Faculty of Pharmacy, Campus of Cartuja, University of Granada, 18071 Granada, Spain
[2] Institute of Nutrition and Food Technology "José Mataix" (INYTA), Centre of Biomedical Research, University of Granada, 18016 Granada, Spain
[3] Department of Biochemistry and Molecular Biology II, Faculty of Pharmacy, Campus of Cartuja, University of Granada, 18071 Granada, Spain
[4] Instituto de Investigación Biosanitaria (IBS), 18012 Granada, Spain
* Correspondence: aliruizrodriguez@ugr.es (A.R.-R.); maguiler@ugr.es (M.A.)

Abstract: Human gut microbiota seems to drive the interaction with host metabolism through microbial metabolites, enzymes, and bioactive compounds. These components determine the host health–disease balance. Recent metabolomics and combined metabolome–microbiome studies have helped to elucidate how these substances could differentially affect the individual host pathophysiology according to several factors and cumulative exposures, such as obesogenic xenobiotics. The present work aims to investigate and interpret newly compiled data from metabolomics and microbiota composition studies, comparing controls with patients suffering from metabolic-related diseases (diabetes, obesity, metabolic syndrome, liver and cardiovascular diseases, etc.). The results showed, first, a differential composition of the most represented genera in healthy individuals compared to patients with metabolic diseases. Second, the analysis of the metabolite counts exhibited a differential composition of bacterial genera in disease compared to health status. Third, qualitative metabolite analysis revealed relevant information about the chemical nature of metabolites related to disease and/or health status. Key microbial genera were commonly considered overrepresented in healthy individuals together with specific metabolites, e.g., *Faecalibacterium* and phosphatidylethanolamine; and the opposite, *Escherichia* and Phosphatidic Acid, which is converted into the intermediate Cytidine Diphosphate Diacylglycerol-diacylglycerol (CDP-DAG), were overrepresented in metabolic-related disease patients. However, it was not possible to associate most specific microbiota taxa and metabolites according to their increased and decreased profiles analyzed with health or disease. Interestingly, positive association of essential amino acids with the genera *Bacteroides* were observed in a cluster related to health, and conversely, benzene derivatives and lipidic metabolites were related to the genera *Clostridium*, *Roseburia*, *Blautia*, and *Oscillibacter* in a disease cluster. More studies are needed to elucidate the microbiota species and their corresponding metabolites that are key in promoting health or disease status. Moreover, we propose that greater attention should be paid to biliary acids and to microbiota–liver cometabolites and its detoxification enzymes and pathways.

Keywords: microbiota; taxa; metabolites; detoxification; pathways

Citation: Torres-Sánchez, A.; Ruiz-Rodríguez, A.; Ortiz, P.; Aguilera, M. Key Stratification of Microbiota Taxa and Metabolites in the Host Metabolic Health–Disease Balance. *Int. J. Mol. Sci.* **2023**, *24*, 4519. https://doi.org/10.3390/ijms24054519

Academic Editor: Ioannis Alexandros Charitos

Received: 31 January 2023
Revised: 21 February 2023
Accepted: 22 February 2023
Published: 24 February 2023

1. Introduction

Gut microbiota is considered a complex ecosystem with a wide array of microorganisms linked to host health. Multiple studies suggested that the structure and composition of the gut microbiota in metabolic-related diseases, such as atherosclerosis, colitis, diabetes, hyperlipidemia, hypertension, metabolic syndrome, non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), obesity, and steatosis, exhibit significant changes compared to healthy individuals and that those changes are related to host physiopathology. In this context, the analysis and description of trends in microbial populations

associated with disease and health status become a key issue to elucidate possible signatures of metabolic-related diseases.

The gut microbiota of patients with metabolic-related diseases shows differences at different taxonomic levels. Many studies showed that *Parabacteroides, Bifidobacterium, Oscillospira,* and *Bacteroides* were decreased in patients with obesity [1–13]. Moreover, *Faecalibacterium* and *Bifidobacterium* were decreased [14–21] and species from Lactobacillaceae family [22] and *Blautia* were increased [7,13,19–27] in diabetic patients. Other metabolic diseases related to intestinal diseases seem to be related to increased *Escherichia* and decreased *Faecalibacterium* [28–37].

Recently, the combination of metagenomics and metabolomics has received extensive attention due to the growing number of studies that establish positive and negative correlations between gut microbiota taxa, metabolites, and health status. Therefore, future studies will contribute to elucidate the essential role of gut microbiota in metabolite synthesis, metabolite modifications, and metabolic pathway regulations.

In this sense, metabolites such as short-chain fatty acids (SCFA), amino acids (AA), or bile acids (BA) can play a crucial role in maintaining metabolic functions or, on the contrary, they might be involved in disease development, such as choline derivatives in the case of cardiovascular diseases [38–41]. Metabolite influences are not restricted to the intestine and distribution to other physiological locations has been described through different axes, such as the gut–liver axis, in which the gut microbiota is related to liver diseases, including NAFLD, NASH, fibrosis, or liver cancer [42]. Gut microbiota partially impacts the host BA profile as it is involved in primary bile acid transformation into secondary free bile acids, such as deoxycholic acid, lithocholic acid, and ursodeoxycholic acid, contributing to the modulation of host total bile acid production [43].

The chemical structure of many endogenous compounds, including gut microbiota metabolites, can be modified, resulting in changes in their bioactivity and half-life [44]. This kind of modifications are related to the development of complex metabolic networks between host and gut microbiota, where final substances could be potentially more toxic than the original ones [45].

Traditional probiotics, mainly consisting of species from Lactobacillaceae and Bifidobacteria and a few from other genera, have been largely applied as a useful strategy in the context of clinical intervention in metabolic-related diseases [46,47]. However, the development of new procedures using Next Generation Probiotics (NGP) opens a new world of possibilities due to the beneficial effects that have already been described in murine models and, to a lesser extent, in humans. In this context, murine models show *Akkermansia muciniphila, Faecalibacterium prausnitzii, Bacteroides uniformis, Bacteroides acidifaciens, Clostridium butyricum,* and *Prevotella copri* as interesting microorganisms with potential applications in obesity [48–53], liver diseases [52,54–59], diabetes [48–53,58,60,61], colitis [62], and hyperlipidemia [53,58].

This work will contribute to finding out microbial and metabolite patterns and their correlation with diseases that have been studied independently or not yet extensively studied. Therefore, the principal aim of this work is to identify and describe the association between human gut microbiota taxa changes in metabolic-related diseases, incorporating the correlations with metabolites, and how they can modulate host health.

2. Results

2.1. Differential Microbiota Taxa Composition and Stratification According to Their Representation in Metabolic Diseases

2.1.1. PRISMA Analysis

Gut microbial taxa differences in diabetes, obesity, metabolic syndrome, and liver and cardiovascular diseases, highlight links between gut microbiota and host health status. In this context, Figure 1 summarizes updated and available information about gut microbial taxa changes in these metabolic-related diseases.

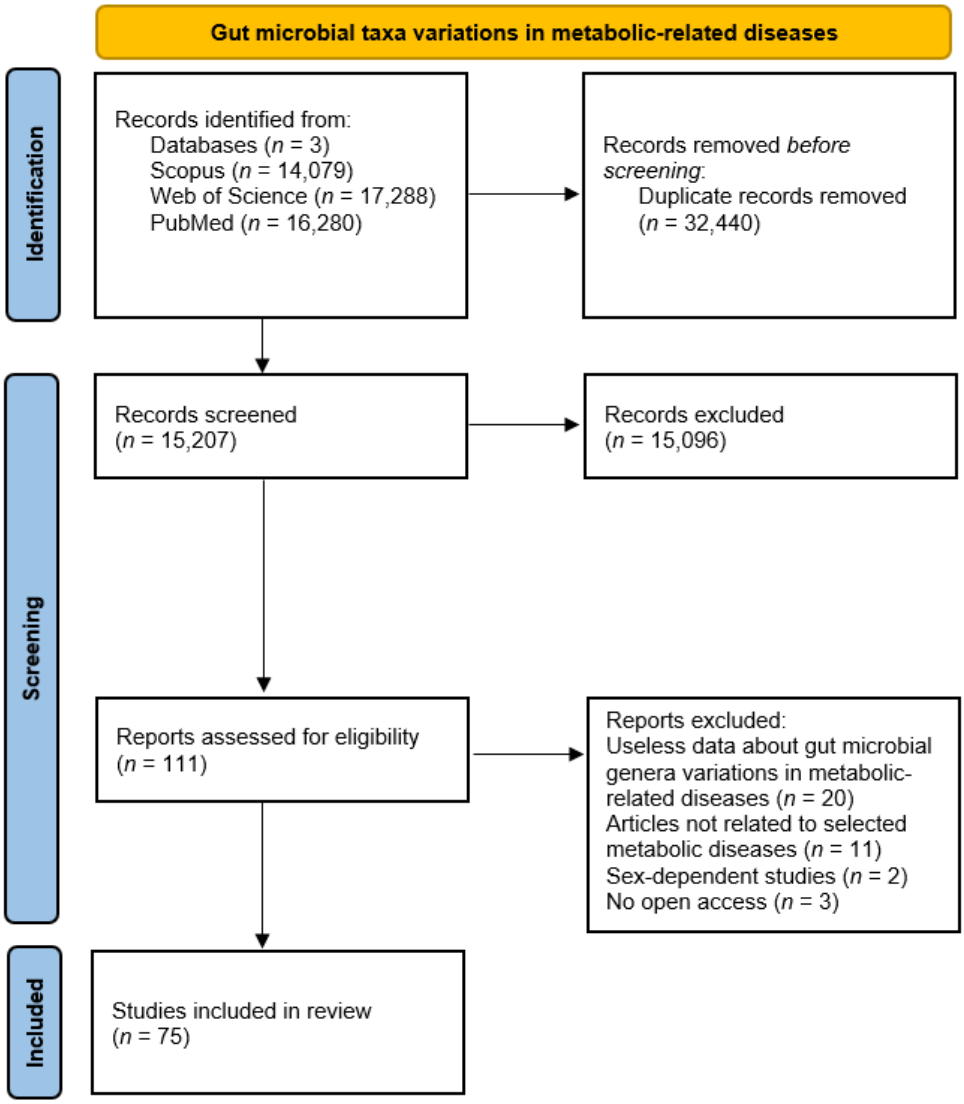

Figure 1. PRISMA diagram for gut microbial taxa changes in metabolic diseases.

2.1.2. Microbial Taxa Decreased in Patients Suffering from Metabolic-Related Diseases

Increased and decreased trends in gut microbiota taxa were assessed through an extensive literature search including information about metabolic diseases investigated by different authors. In this context, the approach we followed offered some drivers of specific changes in gut microbiota composition that could be related to host health.

The analysis of 75 studies involving changes of the main taxa altered in patients suffering metabolic-related diseases disclosed 121 differentially abundant microbial genera (complete data are available in Supplementary Material S1). Figure 2 shows representative genera count value comparison obtained in metabolic diseases after microbial taxa variation analysis.

Gut microbiota genera such as *Oscillibacter*, *Butyricicoccus*, *Odoribacter*, and *Paraprevotella* were exclusively decreased in individuals affected by metabolic diseases. On the other hand, *Faecalibacterium*, *Bifidobacterium*, *Ruminococcus*, *Parabacteroides*, *Roseburia*, *Akkermansia*, *Alistipes*, *Coprococcus*, and *Oscillospira* were both decreased and increased in metabolic-related diseases. However, overall, these microbial genera showed a negative association with the metabolic diseases studied here.

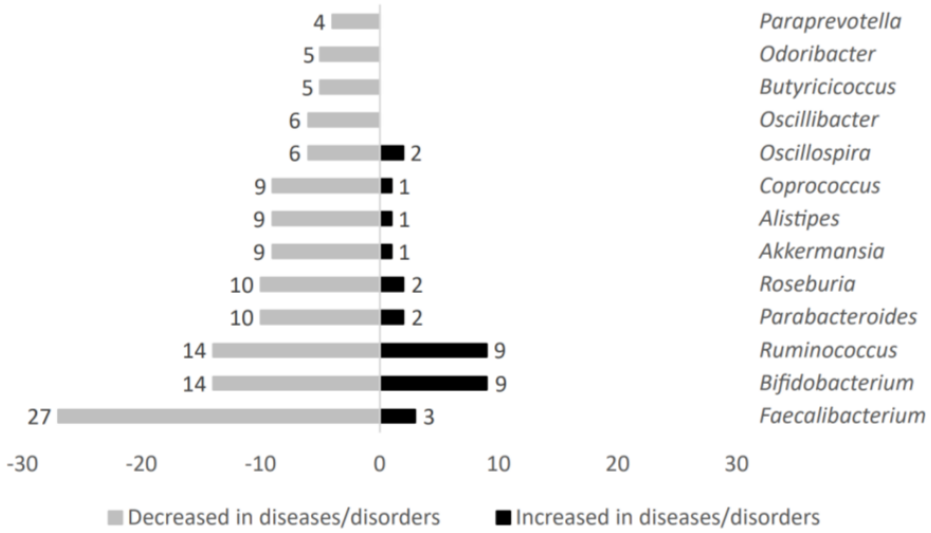

Figure 2. Analysis of main taxa stratified according to high representativeness in patients without metabolic-related diseases.

2.1.3. Microbial Taxa Increased in Patients Suffering Metabolic-Related Diseases

Microbial genera such as *Klebsiella*, *Collinsella*, and *Enterococcus* were exclusively present in those cases in which individuals were affected by metabolic diseases. However, taxa belonging to *Escherichia*, Lactobacillaceae, *Blautia*, *Streptococcus*, and *Dorea* were also identified in patients without metabolic-related diseases. These microbial genera showed an upward trend in metabolic-related diseases studied here. Figure 3 shows the distribution of representative microbial taxa linked to metabolic-related diseases.

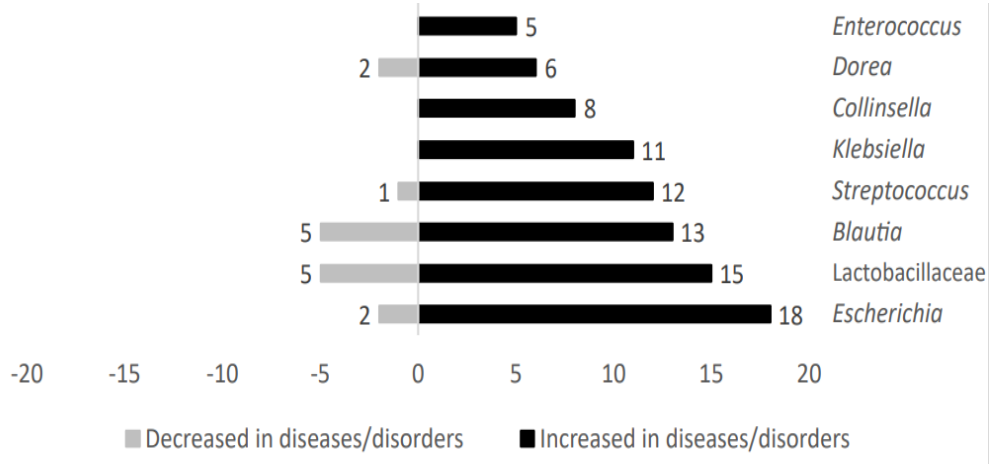

Figure 3. Analysis of main taxa stratified according to high representativeness in metabolic−related diseases patients.

In a previous study exploring next generation probiotics for metabolic and microbiota dysbiosis linked to xenobiotic exposure [63], we tried the first approach to describe changes in gut microbial taxa associated to metabolic-related disease. As a result, potential associations between bacterial genera and metabolic diseases were described despite the lesser number of analyzed studies. In this case, Table 1 shows an expansion of the current knowledge available in this field, including the relevant information identified in the previous study.

Table 1. Changes in the main microbiota taxa found in patients suffering metabolic-related diseases.

Ref.	Sample Size and Clinical Traits	Gut Microbiota Taxa Modification
[1]	*n* = 42; HC *n* = 21; OB *n* = 21	↑ *Prevotella*, *Megamonas*, *Blautia*, and *Fusobacterium*, ↓ *Alistipes*, *Faecalibacterium*, *Oscillibacter*, *Clostridium IV*, *XIVa*, *Barnesiella*, *Gemmiger*, *Parabacteroides*, *Coprococcus*, *Ruminococcus*, and *Bifidobacterium* in OB
[2]	*n* = 51; HC *n* = 30; OB/OW *n* = 21	↑ *Lactobacillus* *, ↓ *Bifidobacterium* in OB/OW
[3]	*n* = 51; HC *n* = 23; OB/OW *n* = 28	↑ *Faecalibacterium*, *Phascolarctobacterium*, *Lachnospira*, *Megamonas*, and *Haemophilus*, ↓ *Oscillospira*, and *Dialister* in OB
[4]	*n* = 192; HC *n* = 25; OW *n* = 22; OB *n* = 145	↑ *Escherichia coli*, *Pseudomonas*, *Fusobacterium*, ↓ *Bifidobacterium* in OW/OB
[5]	*n* = 143; HC *n* = 56; OB *n* = 87	↑ *Enterococcus*, *Blautia*, *Sutterella*, *Klebsiella*, and *Collinsella*, ↓ *Bacteroides*, *Parabacteroides*, *Anaerotruncus*, and *Coprobacillus* in OB
[6]	*n* = 78; HC *n* = 36; OB *n* = 42	↓ *Bacteroides* in OB
[23]	*n* = 66; HC *n* = 27; OB *n* = 17; OBT2D *n* = 22	↑ *Staphylococcus* in OB; ↑ *Lactobacillus* * and *Escherichia* in T2D
[7]	OW *n* = 34; OB *n* = 23; AbOB *n* = 53; Dys *n* = 78; IFG *n* = 21; IGT *n* = 3; T2D *n* = 21; HT *n* = 34	↑ *Serratia* and *Prevotella*, ↓ *Oscillospira* in OW, OB, AbOB group; ↑ *Blautia* in T2D; ↑ *Prevotella* in HT
[8]	*n* = 58; HC *n* = 15; OB *n* = 18; OB NAFLD *n* = 25	↑ *Phascolarctobacterium*, *Phascolarctobacterium succinatutens*, *Klebsiella*, *Klebsiella pneumoniae*, *Kluyvera*, and *Kluyvera ascorbata*, ↓ *Lactobacillus* *, *Oscillibacter*, *Ruminiclostridium*, and *Parabacteroides johnsonii* in OB NAFLD; ↓ *Alistipes*, *Paraprevotella*, *Bacteroides clarus*, and *Odoribacter splanchnicus* in OB and OB NAFLD; ↓ *Helicobacter*, *Helicobacter pylori* in OB
[9]	*n* = 73; HC *n* = 20; OB NAFLD *n* = 36; OB Non-NAFLD *n* = 17	↑ *Megasphaera*, *Lactobacillus* *, and *Acidaminococcus*, ↓ *Oscillospira*, *Eubacterium*, and *Akkermansia* in OB NAFLD and OB Non-NAFLD; ↑ *Streptococcus*, ↓ *Blautia*, *Alkaliphilus*, and *Flavobacterium* in OB NAFLD
[10]	*n* = 115; HC *n* = 54; OB *n* = 8; NAFLD *n* = 27; NASH *n* = 26	↑ *Bradyrhizobium*, *Anaerococcus*, *Peptoniphilus*, *Propionibacterium acnes*, *Dorea*, and *Ruminococcus*, ↓ *Oscillospira* in NAFLD, NASH and OB vs. HC
[11]	*n* = 23; HC *n* = 10; NASH *n* = 13	↑ *Lactobacillus* * in (OB-NASH vs. LN-HC), (OB-NASH vs. OB-HC) and (OB-NASH vs. OW-NASH); ↑ *Lachnospira* in (OB-NASH vs. OB-HC); ↓ *Roseburia* in (OB-NASH vs. LN-HC) and (OB-NASH vs. OB-HC); ↓ *Bifidobacterium* in (OW-NASH vs. LN-HC); ↓ *Faecalibacterium* and *Ruminococcus* in (LN-NASH vs. LN-HC) and (LN-NASH vs. OB-HC); ↓ *Ruminococcus* in (LN-NASH vs. OB-NASH) and (LN-NASH vs. OW-NASH)
[64]	*n* = 106; HC *n* = 38; OB *n* = 68	↑ *Clostridium* in HT; ↑ *Bacteroides* in IGT
[12]	*n* = 119; OB *n* = 69; Mets *n* = 50	↑ *Intestinibacter*, *Saccharibacteria genera incertae sedis*, *Clostridium sensu stricto*, *Romboutsia*, *Terrisporobacter*, and *Eggerthia*, ↓ *Rothia*, *Adlercreutzia*, *Parabacteroides*, *Paraprevotella*, *Alistipes*, *Bacteroides*, *Bilophila*, *Escherichia-Shigella*, *Lactobacillus* *, *Clostridium XIVa*, *Clostridium XIVb*, *Anaerotruncus*, and *Phascolarctobacterium* in OB vs. Mets
[65]	*n* = 60; HC *n* = 20; OB T2D *n* = 40	↑ *Eubacterium coprostanoligenes* group, *Dialister*, and *Allisonella*, ↓ *Ruminococcus 2*, *Prevotella 9*, and *Escherichia-Shigella 9* in OB T2D
[14]	*n* = 1280; LN-NonT2D *n* = 633; OB-NonT2D *n* = 494; OBT2D *n* = 153	↓ *Akkermansia*, *Faecalibacterium*, *Oscillibacter*, and *Alistipes* in OB- NonT2D and OBT2D

Table 1. *Cont.*

Ref.	Sample Size and Clinical Traits	Gut Microbiota Taxa Modification
[15]	*n* = 50; HC *n* = 15; T2D *n* = 14; DR *n* = 21	↑ *Klebsiella* and *Enterococcus*, ↓ *Faecalibacterium* and *Lachnospira* in T2D
[16]	*n* = 154; CN *n* = 73; T2DCI *n* = 81	↑ *Peptococcus*, ↓ *Bifidobacterium*, *Veillonella*, and *Pediococcus* in T2DCI
[66]	*n* = 291; HC *n* = 193; T2D *n* = 98	↑ *Peptostreptococcus*, *Eubacterium*, and *Prevotella*, ↓ *Anaerostipes*, *Ruminococcus*, *Clostridium*, *Epulopiscium*, *Cellulosilyticum ruminicola*, *Clostridium paraputrificum*, and *Clostridium butyricum* in T2D
[17]	*n* = 60; HC *n* = 40; T2D *n* = 20	↑ *Streptococcus*, *Fusobacterium*, and *Dorea*, ↓ *Parabacteroides*, *Bifidobacterium*, *Faecalibacterium*, and *Akkermansia* in T2D
[24]	*n* = 102; HC *n* = 35; pT2D *n* = 17; NewT2D *n* = 11; KnownT2D *n* = 39	↑ *Escherichia* and *Acidaminococcus*, ↓ *Sutterella* in KnownT2D; ↑ *Megasphaera and Lactobacillus* *, ↓ *Akkermansia*, *Blautia*, and *Ruminococcus* in NewT2D
[67]	*n* = 118; HC *n* = 59; T2D *n* = 59	↑ *Bifidobacterium* spp., ↓ *Bacteroides* spp. in T2D
[25]	*n* = 100; HC *n* = 35; T2D+ *n* = 49; T2D− *n* = 16	↑ *Coprococcus 1*, ↓ *Bacteroides* and *Prevotella* in T2D+ and T2D- vs. HC; ↑ *Parasutterella* in T2D+ vs. HC; ↑ *Blautia* and *Eubacterium hallii* group in T2D−vs. HC
[26]	*n* = 100; HC *n* = 50; T2D *n* = 50	↑ *Lactobacillus* *, ↓ *Clostridium leptum* and *Clostridium coccoides* in T2D
[18]	*n* = 36; HC *n* = 18; T2D *n* = 18	↓ *Faecalibacterium prausnitzii* in T2D
[19]	*n* = 36; HC *n* = 18; T2D *n* = 18	↑ *Lactobacillus* *, ↓ *Bifidobacterium* in T2D
[68]	*n* = 239; HC *n* = 54; HT *n* = 97; HL *n* = 96; T2D *n* = 162	↑ *Bifidobacterium* in HL, T2D, RISK1, and RISK2; ↑ *Collinsella* in HT, HL, T2D, RISK2, and RISK3; ↑ *Escherichia* in RISK3; ↓ *Alistipes* in HL
[27]	*n* = 98; HC *n* = 47; T1D *n* = 51	↑ *Blautia*, *Anaerostipes*, *Eubacterium hallii* group, *Dorea*, *Collinsella*, and *Klebsiella*, ↓ *Parabacteroides* and *Flavonifractor* in T1D
[69]	*n* = 29; HC *n* = 8; T1D at onset *n* = 8; T1D two years treatment *n* = 13	↑ *Bacteroides*, ↓ *Prevotella*, *Megamonas*, and *Acidaminococcus* in T1D at onset
[70]	*n* = 47; HC *n* = 7; T1D *n* = 22; T2D *n* = 18	↑ *Pseudomonas* and *Prevotella* in T1D and T2D vs. HC
[20]	*n* = 110; HC *n* = 40; T1D *n* = 21; T2D *n* = 49	↑ *Escherichia*, *Prevotella*, and *Lactobacillus* *, ↓ *Bacteroides*, *Roseburia*, and *Bifidobacterium* in T1D and T2D; ↓ *Faecalibacterium* in T1D vs. T2D and HC
[21]	*n* = 43; HC *n* = 13; T1D *n* = 15; MODY2 *n* = 15	↑ B*acteroides*, *Ruminococcus*, *Blautia*, *Veillonella*, *Streptococcus*, *Sutterella*, and *Enterobacter*, ↓ *Bifidobacterium* in T1D; ↑ *Prevotella* ↓ *Lachnospira*, *Roseburia*, *Anaerostipes*, and *Faecalibacterium* in T1D and MODY2
[71]	*n* = 60; HC *n* = 30; Metsyn patients *n* = 30	↑ *Clostridium leptum*, *Clostridium coccoides* group, and *Turicibacter* sp., ↓ *Butyricicoccus* sp., *Faecalibacterium prausnitzii*, and *Akkermansia muciniphila* in Mets
[72]	*n* = 655; MZ *n* = 306; DZ *n* = 74, Nontwin *n* = 275	↑ *Lactobacillus* *, *Sutterella*, *Dorea*, and *Methanobrevibacter*, ↓ P*arabacteroides*, *Bifidobacterium*, *Odoribacter*, *Akkermansia*, and *Paraprevotella* in Mets

Table 1. *Cont.*

Ref.	Sample Size and Clinical Traits	Gut Microbiota Taxa Modification
[13]	*n* = 20; No Mets + NGT *n* = 4; No Mets + IFG *n* = 3; No Mets + IFG + IGT *n* = 1; Mets + IFG *n* = 4; Mets + IFG + IGT *n* = 4; Mets + T2D *n* = 4	↑ *Ruminococcus*, *Dorea*, *Blautia*, and *Oscillospira* in OB, Mets, IFG, IFG + IGT, and T2D
[28]	*n* = 41; HC *n* = 20; UC *n* = 21	↓ *Ruminococcus* and *Faecalibacterium prausnitzii* in UC
[29]	*n* = 20; HC *n* = 10; UC *n* = 10	↑ *Escherichia-Shigella*, *Peptostreptococcus*, *Bacillus*, and *Veillonella*, ↓ *Akkermansia*, *Faecalibacterium*, and *Bifdobacterium* in UC
[30]	*n* = 42; HC *n* = 14; UC *n* = 28	↑ *Streptococcus*, *Escherichia-Shigella*, *Romboutsia*, *Clostridium sensu stricto*, *Enterococcus*, and *Citrobacter*, ↓ *Faecalibacterium*, *Agathobacter*, *Dorea*, *Ruminococcus*, *Prevotella*, *Alistipes*, *Parabacteroides*, and *Butyricicoccus* in UC
[73]	*n* = 53; HC *n* = 23; UC *n* = 12; PSC *n* = 11; PSC + UC *n* = 7	↑ *Bifidobacterium* in UC
[31]	*n* = 24; HC *n* = 12; CD *n* = 6; UC *n* = 6	↑ *Clostridium ramosum*, *Escherichia coli*, *Fusobacterium nucleatum*, and *Ruminococcus gnavus*, ↓ *Eubacterium rectale*, and *Faecalibacterium prausnitzii* in UC
[32]	*n* = 58; HC *n* = 29; UC *n* = 22; CD *n* = 7	↓ *Bacteroides*, *Faecalibacterium prausnitzii*, *Prevotella* spp., and *Methanobrevibacterium* spp. in IBD
[33]	*n* = 42; HC *n* = 13; CD *n* = 15; UC *n* = 14	↑ *Abiotrophia*, *Pseudoramibacter*, *Eubacterium*, and *Escherichia*, ↓ *Butyricicoccus*, *Mitsuokella*, *Haemophilus*, and *Victivallis* in CD; ↑ *Granulicatella*, *Peptostreptococcus*, *Schwartzia*, *Capnocytophaga*, *Escherichia*, *Janthinobacterium*, *Campylobacter*, *Actinomyces*, *Eggerthella*, and *Corynebacterium*, ↓ *Holdemania*, *Lachnobacterium*, *Megamonas*, *Mitsuokella*, *Alistipes*, *Butyricimonas*, *Prevotella*, *Desulfovibrio*, *Oxalobacter*, *Pyramidobacter*, and *Victivallis* in UC; ↑ *Pseudoramibacter Eubacterium*, *Desulfovibrio*, and *Slackia*, ↓ *Butyricicoccus*, *Moryella*, *Staphylococcus*, *Capnocytophaga*, *Haemophilus*, *Janthinobacterium*, *Cardiobacterium*, *Lautropia*, *Lupinus*, *Shewanella*, and *Corynebacterium* in CD/UC
[34]	*n* = 155; Non-IBD *n* = 34; CD *n* = 68; UC *n* = 53	↑ Unclassified *Roseburia* species in CD and UC; ↑ *Bifidobacterium breve* and *Clostridium symbiosum* in UC; ↑ *Blautia producta*, *Lactobacillus gasseri*, *Enterococcus faecium*, *Clostridium clostridioforme*, *Ruminococcus gnavus*, and *Escherichia coli* in CD
[74]	*n* = 1087; HC *n* = 290; IBD *n* = 512; CRC *n* = 285	↑ *Bacteroides* in IBD
[35]	*n* = 68; HC *n* = 48; IBD *n* = 20	↑*Bifidobacterium*, *Ruminococcus gnavus* group, *Streptococcus*, and *Blautia*, ↓ *Faecalibacterium*, *Subdoligranulum*, *Parabacteroides*, and *Paraprevotella* in IBD
[36]	*n* = 30; HC *n* = 8; DD *n* = 4; IBS *n* = 3; UC *n* = 5; CD *n* = 10	↑ *Dialister* spp. And *Faecalibacterium prausnitzii* in IBS; ↑ *Bacteroides fragilis*, *Dialister spp.*, and *Roseburia* spp. ↓ *Clostridium difficile* in UC vs. HC; ↑ *Parabacteroides distasonis* ↓ *Faecalibacterium prausnitzii*, and *Bacteroides fragilis* in CD
[37]	*n* = 69; HC *n* = 40; Non-PN SBS *n* = 5; SBS I *n* = 10; SBS II *n* = 14	↑ *Lactobacillus* * and *Klebsiella*, ↓ *Coprococcus*, *Faecalibacterium*, *Lachnospira*, and *Ruminococcus* in SBS patients; ↓ *Blautia*, *Bacteroides*, *Odoribacter*, *Oscillospira*, *Prevotella*, *Roseburia*, and *Sutterella* in SBS I and SBS II; ↑ *Streptococcus* and *Staphylococcus* in SBS I
[75]	*n* = 16 NAFLD	↑ *Prevotella copri* and *Prevotella stercorea* in NAFLD
[76]	*n* = 68; HC *n* = 36; NAFLD *n* = 32	↑ *Escherichia coli*, *Klebsiella pneumoniae*, and *Enterobacter cloacae*, ↓ *Akkermansia muciniphila*, *Alistipes putredinis*, *Bacteroides uniformis*, *Bacteroides fragilis*, *Oscillibacter* sp., *Ruminococcus bromii*, *Eubacterium ventriosum*, and *Gemmiger formicilis* in NAFLD

Table 1. *Cont.*

Ref.	Sample Size and Clinical Traits	Gut Microbiota Taxa Modification
[77]	*n* = 874; Non-NAFLD *n* = 669; NAFLD *n* = 205	↓ *Faecalibacterium* and *Bacteroides* in NAFLD
[78]	*n* = 766; Control *n* = 453; Developed NAFLD *n* = 40; Regressed NAFLD *n* = 35; Persistent NAFLD *n* = 238	↓ *Oscillospira*, *Odoribacter*, and *Coprococcus* in persistent NAFLD vs. Control; ↓ *Coprococcus eutactus* in regressed NAFLD and persistent NAFLD vs. Control
[79]	*n* = 67; HC *n* = 37; NAFLD *n* = 30	↑ *Porphyromonas*, *Succinivibrio*, *Clostridium*, *Blautia*, *Dorea*, *Peptococcus*, *Mitsuokella*, and *Slackia*, ↓ *Odoribacter*, *Proteus*, and *Coprococcus* in NAFLD
[80]	*n* = 47; HC *n* = 22; NAFLD *n* = 25	↑ *Escherichia-Shigella*, *Blautia*, *Clostridium XVIII*, and *Streptococcus*, ↓ *Prevotella* and *Faecalibacterium* in NAFLD
[81]	*n* = 202; no-NAFLD *n* = 31; NAFLD *n* = 171	↑ *Citrobacter*, ↓ *Coprococcus* and *Lachnospira* in significant fibrosis
[82]	*n* = 126; no-NAFLD *n* = 83; NAFLD *n* = 43	↓ *Coprococcus*, *Pseudobutyrivibrio*, *Moryella*, *Roseburia*, *Anaerosporobacter*, *Anaerotruncus*, *Ruminococcus*, *Lactobacillus* * in NAFLD
[83]	*n* = 75; HC *n* = 25; NAFLD *n* = 25; NASH *n* = 25	↑ *Bacteroides* and *Prevotella*, ↓ *Faecalibacterium* in NAFLD and NASH
[84]	*n* = 86; Mild/moderate NAFLD *n* = 72; Fibrosis *n* = 14	↑ *Eubacterium rectale* in mild/moderate NAFLD; ↑ *Bacteroides vulgatus* and *Escherichia coli*, ↓ *Ruminococcus obeum*, and *Eubacterium rectale* in fibrosis
[85]	*n* = 24; HC *n* = 8; NASH *n* = 16	↑ *Phascolarctobacterium* in NASH
[86]	*n* = 67; HC *n* = 28; NASH *n* = 24; SS *n* = 15	↓ *Ruminococcus*, *Faecalibacterium prausnitzii*, and *Coprococcus* in NAFLD and SS vs. HC
[87]	*n* = 50; HC *n* = 17; NASH *n* = 22; SS *n* = 11	↓ *Clostridium coccoides* in NASH
[88]	*n* = 60; Non significant fibrosis *n* = 35; Significant fibrosis *n* = 25	↑ *Bacteroides* and *Lactobacillus* *, ↓ *Bifidobacterium* in significant fibrosis
[89]	*n* = 40; NT *n* = 15; HT *n* = 25	↑ *Rothia* ↓ *Faecalicoccus*, *Morganella*, *Acetohalobium*, and *Phaeodactylibacter* in HT
[90]	*n* = 70; NT *n* = 47; HT *n* = 23	↑ *Acidaminococcus*, *Eubacterium*, and *Alistipes* in HT
[91]	*n* = 80; NT *n* = 32; HT *n* = 48	↑ *Ligilactobacillus salivarius*, *Bacteroides plebeius*, and *Eggerthella*, ↓ *Roseburia faecis*, *Faecalibacterium prausnitzii*, *Parabacteroides distasonis*, Unclassified *Fusobacterium*, and *Coprobacillus* in HT
[92]	*n* = 120; HC *n* = 60; HT *n* = 60	↑ *Klebsiella*, *Clostridium*, *Streptococcus*, *Parabacteroides*, *Eggerthella*, and *Salmonella*, ↓ *Faecalibacterium*, and *Roseburia* in HT
[93]	*n* = 196; HC *n* = 41; pHT *n* = 56; HT *n* = 99	↑ *Prevotella* and *Klebsiella* in pHT or HT; ↑ *Porphyromonas* and *Actinomyces* in HT; ↓ *Faecalibacterium*, *Oscillibacter*, *Roseburia*, *Subdoligranulum*, *Blautia*, *Bifidobacterium*, *Coprococcus*, *Butyrivibrio*, *Eggerthella*, *Streptococcus*, and *Akkermansia* in pHT and HT
[94]	*n* = 900; HC *n* = 300; HT *n* = 300; CAD *n* = 300	↑ *Escherichia* in HT
[95]	*n* = 235; HC *n* = 42; NH *n* = 63; AH *n* = 104; HLD *n* = 26	↑ *Blautia*, *Bacteroides*, and *Faecalibacterium* in NH; ↑ *Bacteroides* and *Faecalibacterium* in HLD and HC

Table 1. *Cont.*

Ref.	Sample Size and Clinical Traits	Gut Microbiota Taxa Modification
[96]	*n* = 502; HC *n* = 100; ACS *n* = 402	↑ *Escherichia coli* and *Streptococcus*, ↓ *Lactobacillus* * in ACS
[97]	*n* = 64; HC *n* = 32; CAS *n* = 32	↑ *Acidaminococcus*, *Christensenella*, and *Lactobacillus* *, ↓ *Anaerostipes*, *Fusobacterium*, *Gemella*, *Parvimonas*, *Romboutsia*, and *Clostridium XVIII/XlVa/XlVb* in CAS
[98]	*n* = 345; No SCA *n* = 201; SCA *n* = 144	↑ *Escherichia* and *Oscillospira* in SCA
[99]	Sweden cohort *n* = 25; Control 1 *n* = 13; Atherosclerosis 1 *n* = 12; China cohort *n* = 385; Control 2 *n* = 171; Atherosclerosis 2 *n* = 214	↑ *Bifidobacterium adolescentis*, *Collinsella aerofaciens*, *Blautia hydrogenotrophica*, and *Anaerotruncus colihominis* in atherosclerosis 1; ↑ *Bacteroides fragilis*, *Streptococcus salivarius*, *Clostridium nexile*, *Ruminococcus gnavus*, *Ruminococcus torques*, *coli*, *Klebsiella pneumoniae*, and *Akkermansia muciniphila* in atherosclerosis 2
[100]	*n* = 106; Control *n* = 53; CAD *n* = 53	↑ *Porphyromonas*, *Prevotella*, *Agathobacter*, *Ruminococcus gnavus*, *Catenibacterium*, and *Succiniclasticum*, ↓ *Anaerosporobacter*, *Coprococcus*, *Eisenbergiella*, *Fusocatenibacter*, *Eubacterium hallii*, *Ruminococcus gauvreauii*, *Fournierella*, and *Veillonella* in CAD
[101]	*n* = 201; HC *n* = 40; CAD *n* = 161	↑ *Actinomyces*, *Haemophilus*, *Granulicatella*, *Weissella*, *Veillonella*, *Streptococcus*, *Klebsiella*, *Rothia*, *Enterococcus* (CAG17); ↓ *Faecalibacterium*, *Roseburia*, *Oscilibacter* (CAG4); *Ruminococcus 2*, *Dorea*, *Blautia*, *Clostridium XVIII* (CAG14); *Anaerostipes*, *Blautia*, *Lactobacillus* *, *Fusocatenibacter*, *Clostridium XIVa*, *Gemella*, *Bifidobacterium*, *Saccharibacteria genera incertae sedis* (CAG15); *Roseburia*, *Clostridium XIVb*, *Parasutterella*, *Butyricicoccus* (CAG16) in CAD
[102]	*n* = 405; HC *n* = 187; ACVD *n* = 218	↑ *Escherichia coli*, *Klebsiella* spp., *Enterobacter aerogenes*, *Streptococcus* spp., *Ligilactobacillus salivarius*, *Solobacterium moorei*, *Atopobium parvulum*, *Ruminococcus gnavus*, and *Eggerthella lenta*, ↓ *Roseburia intestinalis*, *Faecalibacterium prausnitzii*, *Bacteroides* spp., *Prevotella copri*, and *Alistipes shahii* in ACVD

AbOB: abdominal obesity; ACS: acute coronary syndrome; ACVD: atherosclerotic cardiovascular disease; AH: hypertensive patients undergoing anti-hypertensive treatment; CAD: coronary artery disease; CAG: co-abundance group; CAS: carotid atherosclerosis; CD: Crohn's disease; CN: cognitive normal group; CRC: colorectal cancer; DD: diverticular disease; DR: diabetic retinopathy; Dys: dyslipidemia; DZ: dizygotic twin pairs; HC: healthy control; HL: hyperlipidemia; HLD: normal blood pressure but with hyperlipidemia; HT: hypertension; IBD: inflammatory bowel disease; IBS: irritable bowel syndrome; IFG: impaired fasting glycemia; IGT: impaired glucose tolerance; KnownT2D: diabetics on antidiabetic treatment; LN: lean; Mets: metabolic syndrome; MODY2: maturity-onset diabetes of the young 2; MZ: monozygotic twin pairs; NAFLD: non-alcoholic fatty liver disease; NASH: non-alcoholic steatohepatitis; NewT2D: newly diagnosed diabetic; NGT: normal glucose tolerance; NH: hypertensive patients with treatment-naive hypertension; Non-PN SBS: parenteral nutrition-independent short bowel syndrome; NT: normotension; OB: obese; OW: overweight; pHT: prehypertension; PSC: primary sclerosing cholangitis; pT2D: prediabetic; RISK1: patients with only one disease; RISK2: patients with two diseases; RISK3: patients with three diseases; SBS I: parenteral nutrition-dependent short bowel syndrome I; SBS II: parenteral nutrition-dependent short bowel syndrome II; SCA: subclinical carotid atherosclerosis; SS: simple steatosis; T1D: type 1 diabetes; T2D: type 2 diabetes; T2D+: type 2 diabetes with chronic complications; T2D-: type 2 diabetes without chronic complications; T2DCI: type 2 diabetes cognitive impairment group; UC: ulcerative colitis. * *Lactobacillus* includes species from Lactobacillaceae family [22]. ↑ Taxa increasement and ↓ Taxa decreasement.

2.2. Differential Microbial Metabolites and Stratification According to Their Representation in Metabolic Diseases

The analysis of the 16 selected studies involving correlations between gut microbiota taxa altered in patients suffering from metabolic diseases, metabolites, and host health status allowed us to shed light on potential critical pathways to modulate homeostatic processes (complete data are available in Supplementary Material S2 [103–118] Figure 4 summarizes available information about gut microbiota–metabolite correlations and host health status.

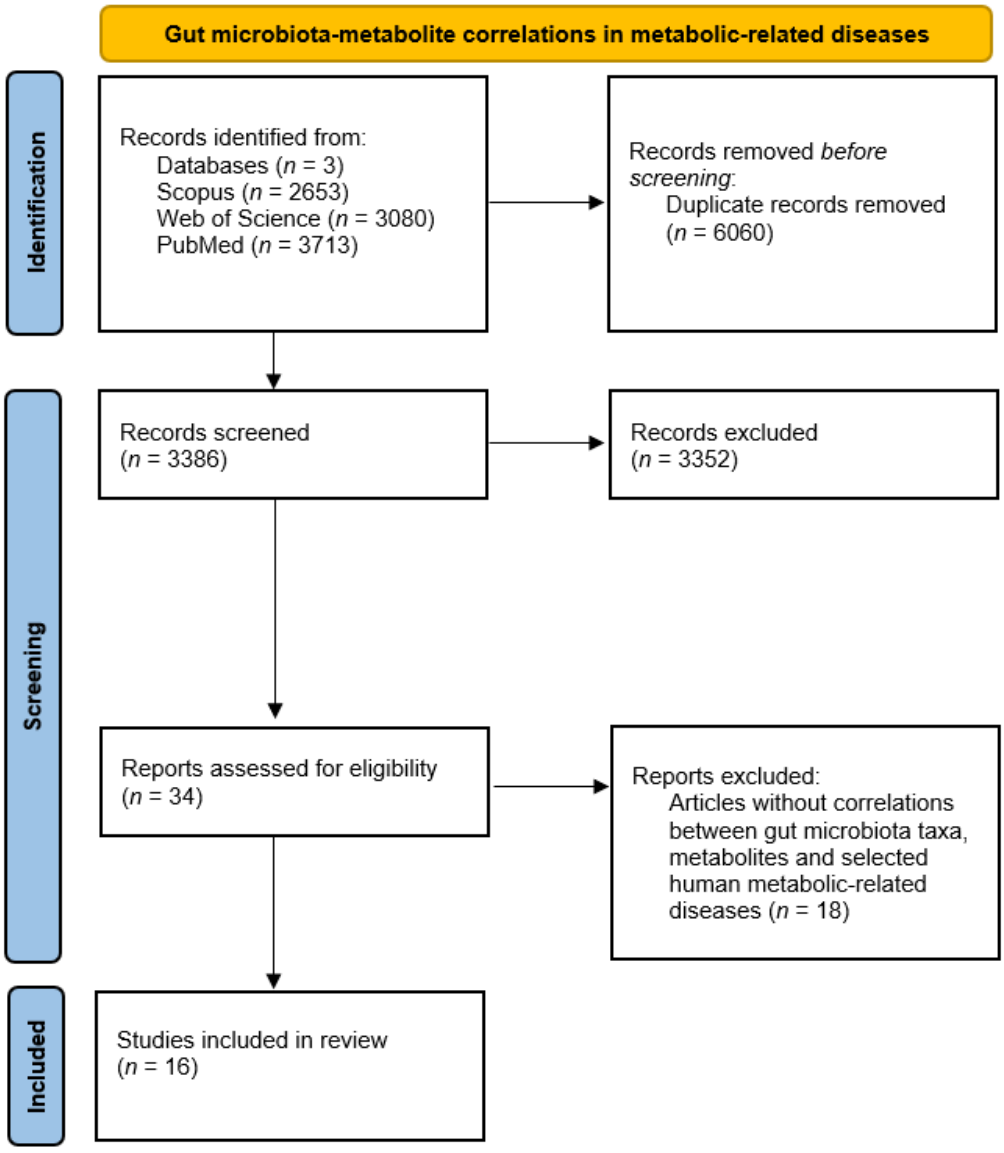

Figure 4. PRISMA diagram for gut microbiota–metabolite correlations and host status.

Several gut microbiota taxa showed a high metabolite count linked to disease or health status. In that regard, increased microbial metabolite counts in health status were obtained in gut microbiota genera such as *Holdemania*, *Porphyromonas*, and *Dialister*; further, they were also higher for *Bacteroides*, *Clostridium*, and *Alistipes*, but with more similar counts in both groups. Figure 5 shows representative genera differential values associated to health-related metabolite count analysis.

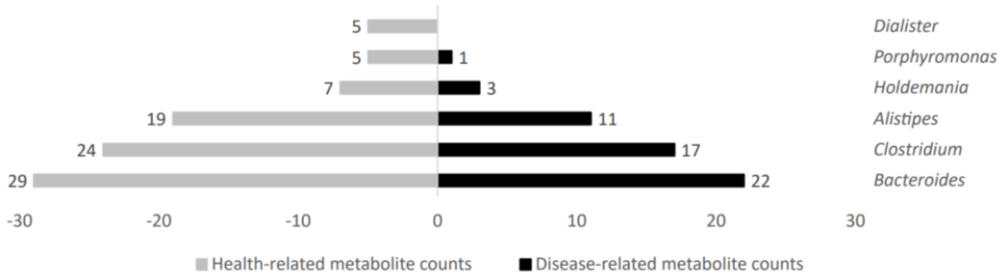

Figure 5. Health−related metabolite counts stratified according to gut microbiota taxa producers.

Increased metabolite counts related to disease status were linked to gut microbiota taxa such as *Ruminococcus*, *Eubacterium*, *Blautia*, *Roseburia*, *Oscillibacter*, *Subdoligranulum*, *Gemmiger*, *Butyricicoccus*, *Akkermansia*, *Veillonella*, *Dorea*, *Coprococcus*, *Escherichia*, *Parabacteroides*, *Enterobacter*, *Lachnospira*, *Gemella*, and *Fusobacterium*. Figure 6 shows representative genera differential values associated to disease-related metabolite count analysis.

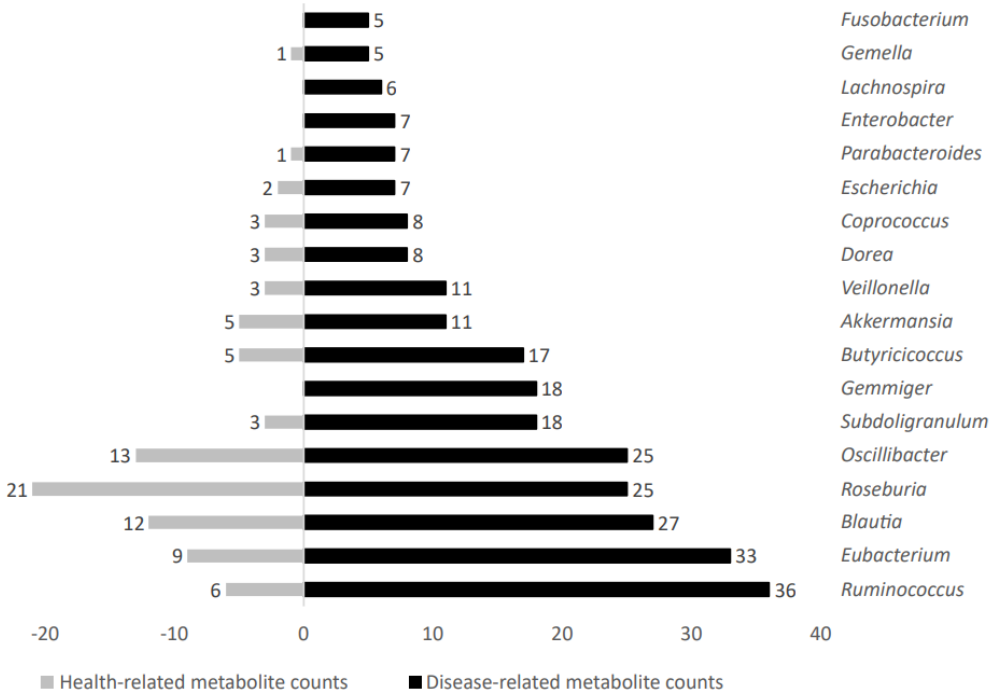

Figure 6. Disease−related metabolite counts stratified according to gut microbiota taxa producers.

According to the total metabolites linked to disease and health status, 171 metabolites were associated with metabolic-related diseases; among these, 143 were exclusively associated with this group and 28 were shared with health status. Moreover, 63 metabolites were related to health status, and 35 were exclusively associated with this group. A qualitative metabolite analysis was performed considering total disease/health-related metabolites. Table 2 shows disease/health-related metabolites classified according to three main chemical groups: fatty acids and conjugates, amino acids and derivatives, and bile acids and derivatives.

A further association analysis of the number of studies where a specific association between a metabolite and a bacterial genus was found showed very interesting clustering patterns. For instance, butyrate-producer genera when present in a healthy status associated with bile acid metabolites and, to a lesser extent, with essential amino acids; however, when they are overrepresented in metabolic diseases, they are associated with lipid metabolism, clustering in two distinct groups. We also observed that essential amino acids clustered

together, and they might have an important role for the metabolism of *Bacteroides* in health status, according to Figure 7.

Table 2. Disease/health-related metabolites and chemical classification.

Health-Related Metabolites	Disease-Related Metabolites
Fatty Acid Pathways—Metabolites and conjugates	
10-Heptadecenoate (17:1n7)	(+)-Cucurbic acid
2-Hydroxyhexadecanoate	12,13-Dihydroxy-11-methoxy-9-octadecenoic acid
Acetate	17-Oxo-octadecanoic acid
Azelaic acid	2-Hydroxyadipate
Caproic acid	2-Methyl-tridecanedioic acid
Caprylic acid	3-Keto stearic acid
Isovalerate	8,11,14-Eicosatrienoic acid
Undecanedionate	8Z-Decen-4,6-diynoic acid
	9,10-Dichloro-octadecanoic acid
	Adrenic acid
	Arachidonic acid
	Diamino-pimelic acid
	Dihomo-linolenate (20:3n3 or n6)
	Docosahexaenoic acid
	Docosanedioic acid
	Eicosatrienoic acid
	Linolenic acid
Amino Acid Pathways—Metabolites and derivatives	
Glycylvaline	Asymmetric dimethylarginine (ADMA)
Isoleucine	Carnosine
N6,N6,N6-Trimethyllysine	Cinnamoylglycine
N-Acetylalanine	Citrulline
S-Carboxymethyl-L-cysteine	ɣ-Glutamylglutamine
Valine	Glycine
	Homocitrulline
	Homocysteine
	L-Lysine
	N6-Carboxymethyllysine
	Nα-Acetyl-L-arginine
	Propionylglutamine
Biliary Acid Pathways—Metabolites and derivatives	
Chenodeoxyglycocholate	12-Dehydrocholic acid
Glycoursodeoxycholic acid	3-Dehydrocholic acid
	3β-Cholic acid
	6,7-Diketolithocholic acid
	6-Keto-Lithocholic acid
	7,12-Diketolithocholic acid
	7-Dehydrocholic acid
	7-Ketolithocholic acid
	Allocholic acid
	Chenodeoxycholic acid
	Chenodeoxycholic acid-3Gln
	Cholate sulfate
	Dehydrocholic acid
	Glycochenodeoxycholic acid
	Glycodeoxycholic acid
	Glycolithocholic acid
	Hyodeoxycholic acid
	Lithocholic acid
	Murocholic acid
	Nordeoxycholic acid

Table 2. *Cont.*

Health-Related Metabolites	Disease-Related Metabolites
Biliary Acid Pathways—Metabolites and derivatives	
	Taurocholic acid Taurohyocholic acid Taurolithocholic acid Tauroursodeoxycholic acid αMuricholic acid βDeoxycholic acid βMuricholic acid

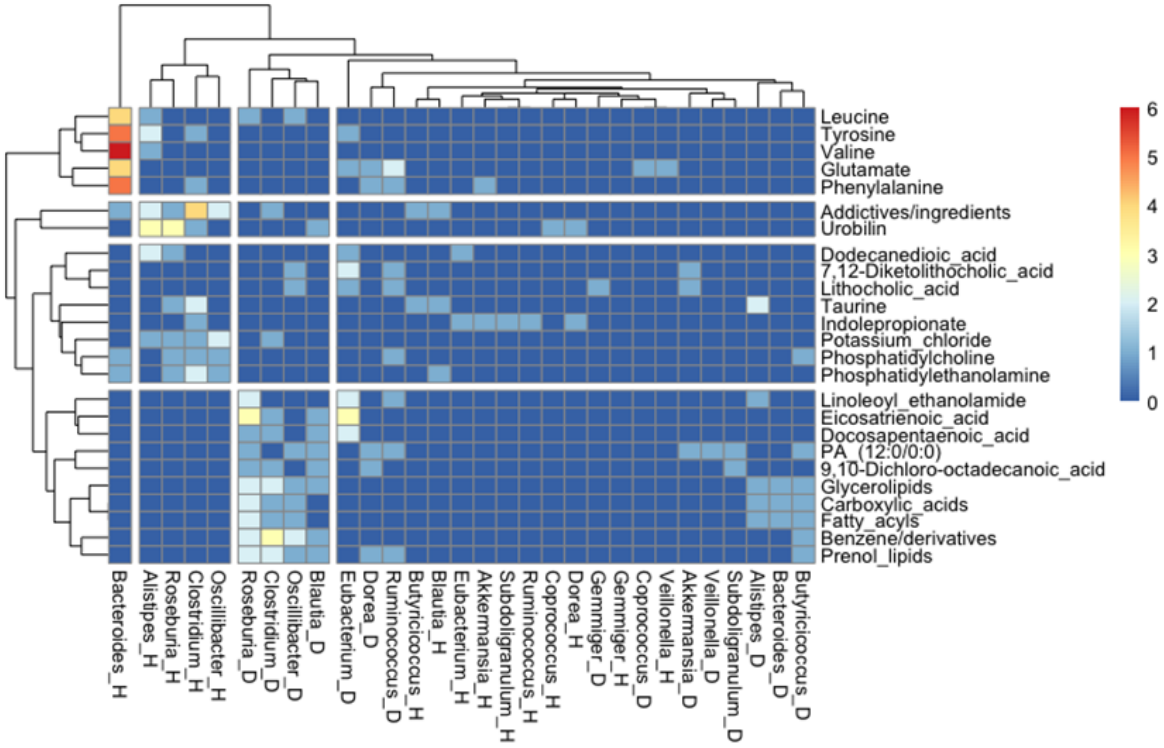

Figure 7. Heatmap showing the analysis where specific associations between a metabolite and a bacterial genus was found in a health and/or a disease stage (as indicated by "_H" or "_D", respectively). For simplicity, only the representative genera and the most found metabolites were included.

3. Materials and Methods

We performed a comprehensive literature search covering the period from 1995 to November 2022 using Scopus, Web of Science, and PubMed databases, using the search strategies showed in systematic review and dividing this review into two main study issues: gut microbial taxa variations in metabolic-related diseases and gut microbiota–metabolite correlations in metabolic-related diseases.

Studies involving changes in gut microbial taxa in atherosclerosis, colitis, diabetes, hyperlipidemia, hypertension, metabolic syndrome, NAFLD, NASH, obesity, and steatosis and studies involving microbiota–metabolite correlations in metabolic-related diseases were assessed, screened, and selected according to PRISMA 2020 flow diagrams (Figures 1 and 4) [111].

In the microbial taxa variation analysis, gut microbial taxa identified in selected studies were divided into two groups: decreased in metabolic-related diseases and increased in metabolic-related diseases, based on research findings. Metabolite counts were calculated for each microbial genus. To determine representative gut microbiota taxa, an arbitrary

criterion was applied. Microbial genera were considered representative if the absolute frequency difference between decreased–increased counts was greater than three.

In the gut microbiota–metabolite correlation analysis, gut microbiota, microbial metabolites, and host status correlations were assessed. First, gut microbial genera were classified into increased in health status or increased in diseases, according to metabolite absolute frequencies displayed for each genus. Second, considering metabolites related to representative genera in health or disease status, a qualitative metabolite analysis was performed. Metabolites correlated with health or disease status were classified into three main groups: fatty acids and conjugates (FA), amino acids and derivatives (AA), and bile acids and derivatives (BA), according to PubChem and related chemical database classification. Furthermore, a bioinformatics analysis was performed to establish potential biomarkers, which revealed the association between specific disease/health balances. Heatmap shows the analysis where a specific association between a metabolite and bacterial genera was found in a health and/or a disease stage (as indicated by "_H" or "_D", respectively). For simplicity, only the representative genera and the most found metabolites (metabolites that appeared least five times either associated with health or disease in the studies analyzed here) were included. First, we selected only the genera with more than 10 metabolites associated and then we kept only the metabolites that appeared at least five times, either associated with health or disease, in the studies analyzed here. Figure 7 shows the performance of R (version 4.1.1.) using the package "pheatmap" [112].

4. Discussion

There is a growing interest in the analysis of the gut microbiome and its metabolome [113,114]. However, integrating data from both fields to understand how gut microbiota, microbial metabolites, and host status are correlated not always provide concise information. Thus, it can hinder researchers in establishing clear links between the presence of a particular gut bacterial taxa and/or metabolites and disease or health status. This task is especially challenging in the context of searching gut microbial biomarkers that allow predicting future phenotypes or classifying individuals into disease and non-disease status. This is mainly due to the fact that contradictory results about microbial taxa abundance and metabolites related to disease or non-disease status can be found in the literature. In this case, this approach showed that *Faecalibacterium, Bifidobacterium, Ruminococcus, Parabacteroides, Roseburia, Akkermansia, Alistipes, Coprococcus, Oscillospira, Oscillibacter, Butyricicoccus, Odoribacter,* and *Paraprevotella* could represent a downregulated microbial cluster in metabolic-related disease patients and, on the contrary, *Escherichia,* species from Lactobacillaceae family, *Blautia*, *Streptococcus*, *Klebsiella*, *Collinsella*, *Dorea*, and *Enterococcus* cluster upregulation could be involved in metabolic-related disease status. Due to relevant information underlined by many authors and results obtained in this review, *Ruminococcus* and *Bifidobacterium*, as well as taxa belonging to Lactobacillaceae family, *Blautia*, and *Dorea* should be identified at the species level to establish similarities with the results already available in the microbiological databases.

According to metabolite absolute frequencies in disease and health status and representative gut microbiota taxa, we tried to search for possible trends between those elements and host physiopathology. When we compared representative metabolites and microbial taxa results, only *Alistipes*, from the down-regulated proposed cluster, showed high counts in both gut microbial taxa variation analysis and metabolite count analysis related to health. In the same way, *Escherichia, Blautia, Streptococcus, Collinsella, Dorea*, and *Enterococcus,* from the proposed upregulated cluster, showed high counts in both gut microbial taxa analysis and metabolite count analysis in disease/disorder group.

Following this approach, *Faecalibacterium* and *Akkermansia* genera [115,116], frequently described as key microorganisms related to health status, were decreased in metabolic-related diseases, indicating a possible relationship with health status. However, a link with disease status could be identified according to metabolite absolute frequencies described for both genera *Faecalibacterium* and *Akkermansia*. A similar result can be observed in other

microorganisms frequently associated with metabolic diseases [117], where microbial taxa analysis showed links with obesity-related diseases. However, metabolite absolute counts showed links with health status.

Interestingly, preliminary data results derived from the biomarker search have demonstrated the positive association of essential amino acids with health in the genera *Bacteroides*, and conversely, benzene derivatives have been related to disease and the genera *Clostridium*. We also observed that lipid metabolites grouped several taxa overrepresented in diseases, but it will be necessary to determine the results to the species level.

These results showed which bacterial taxa of the gut microbiota and their derived metabolites could be related to host status manifestations. However, study limitations and lack of available data in some fields make it impossible to establish final and solid conclusions in this way.

Human health is not only affected by gut microbiota composition and its derived metabolites but also many exogenous and endogenous factors, which can also impact in genotypic and phenotypic manifestations. Recently, the holistic concept of the One Health approach and the exposome include multidisciplinary analysis of a complex reality that affect different but linked items [118]. Nowadays, solid evidence about specific microbial and metabolite signatures in cases of metabolic-related disease is still limited and more concrete information on the correlations between gut microbiota, gut metabolites, and host health status is needed. This synergic approach will lead to a better management of well-known microbiota–metabolic related diseases.

To increase the availability of scientific data on the interaction between gut microbiota taxa in different health contexts, metabolite synthesis, and metabolite modification and impact on the host health, integrated metagenome and metabolome analysis should be continually reviewed, since it seems to be a possible cornerstone involved in the determination of potential microbial and metabolite signatures related to physiological alterations.

5. Conclusions

Despite the existence of microbial taxa–metabolite-health correlations, there is no evidence of a clear gut microbiota and derived metabolite patterns into healthy or metabolic-related disease status that is able to predict or classify patients into one or the other.

Most of the taxa and metabolites did not show representative oscillations between disease and health groups, so bacterial genera with potential interest should continue to be monitored as new information on their abundance in metabolic-related disease appearance.

Implementation of the One Health holistic approach combined with exposome principles can provide new perspectives and evidence about how endogenous and exogenous substances interact with gut microbiota and microbial-derived substances and how the pull of interactions finally affects human homeostasis.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/ijms24054519/s1.

Author Contributions: Conceptualization, A.T.-S. and M.A.; Methodology, A.T.-S.; Writing—Original Draft Preparation, A.T.-S.; Writing—Review and Editing, P.O., A.R.-R. and M.A.; Supervision, A.R.-R. and M.A.; Project Administration, M.A.; Funding Acquisition, M.A. All authors have read and agreed to the published version of the manuscript.

Funding: This work was carried out within the framework of the project and in the framework of several projects: FEDER Project Infrastructure: IE_2019-198; Junta de Andalucía Proyectos de Excelencia: Consejería de Universidad, Investigación e Innovación P21-00341 and the project Instituto de Salud Carlos III-PI20/01278. A.T.-S. holds a contract from FIBAO. A.R.-R. holds a Maria Zambrano Talent Grant (Next Generation EU-University of Granada).

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Acknowledgments: Part of the results are from the doctoral thesis of Alfonso Torres-Sánchez in the Nutrition and Food Technology Doctorate Programme of the University of Granada.

Conflicts of Interest: The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

References

1. Duan, M.; Wang, Y.; Zhang, Q.; Zou, R.; Guo, M.; Zheng, H. Characteristics of Gut Microbiota in People with Obesity. *PLoS ONE* **2021**, *16*, e0255446. [CrossRef] [PubMed]
2. Da Silva, C.C.; Monteil, M.A.; Davis, E.M. Overweight and Obesity in Children Are Associated with an Abundance of Firmicutes and Reduction of Bifidobacterium in Their Gastrointestinal Microbiota. *Child Obes* **2020**, *16*, 204–210. [CrossRef] [PubMed]
3. Chen, X.; Sun, H.; Jiang, F.; Shen, Y.; Li, X.; Hu, X.; Shen, X.; Wei, P. Alteration of the Gut Microbiota Associated with Childhood Obesity by 16S RRNA Gene Sequencing. *PeerJ* **2020**, *8*, e8317. [CrossRef] [PubMed]
4. Gao, R.; Zhu, C.; Li, H.; Yin, M.; Pan, C.; Huang, L.; Kong, C.; Wang, X.; Zhang, Y.; Qu, S.; et al. Dysbiosis Signatures of Gut Microbiota Along the Sequence from Healthy, Young Patients to Those with Overweight and Obesity. *Obesity* **2018**, *26*, 351–361. [CrossRef]
5. Hou, Y.-P.; He, Q.-Q.; Ouyang, H.-M.; Peng, H.-S.; Wang, Q.; Li, J.; Lv, X.-F.; Zheng, Y.-N.; Li, S.-C.; Liu, H.-L.; et al. Human Gut Microbiota Associated with Obesity in Chinese Children and Adolescents. *BioMed Res. Int.* **2017**, *2017*, 7585989. [CrossRef] [PubMed]
6. Riva, A.; Borgo, F.; Lassandro, C.; Verduci, E.; Morace, G.; Borghi, E.; Berry, D. Pediatric Obesity Is Associated with an Altered Gut Microbiota and Discordant Shifts in Firmicutes Populations. *Environ. Microbiol.* **2017**, *19*, 95–105. [CrossRef]
7. Kashtanova, D.A.; Tkacheva, O.N.; Doudinskaya, E.N.; Strazhesko, I.D.; Kotovskaya, Y.V.; Popenko, A.S.; Tyakht, A.V.; Alexeev, D.G. Gut Microbiota in Patients with Different Metabolic Statuses: Moscow Study. *Microorganisms* **2018**, *6*, E98. [CrossRef] [PubMed]
8. Zhao, Y.; Zhou, J.; Liu, J.; Wang, Z.; Chen, M.; Zhou, S. Metagenome of Gut Microbiota of Children with Nonalcoholic Fatty Liver Disease. *Front. Pediatr.* **2019**, *7*, 518. [CrossRef]
9. Nistal, E.; Sáenz de Miera, L.E.; Ballesteros Pomar, M.; Sánchez-Campos, S.; García-Mediavilla, M.V.; Álvarez-Cuenllas, B.; Linares, P.; Olcoz, J.L.; Arias-Loste, M.T.; García-Lobo, J.M.; et al. An Altered Fecal Microbiota Profile in Patients with Non-Alcoholic Fatty Liver Disease (NAFLD) Associated with Obesity. *Rev. Esp. Enferm. Dig.* **2019**, *111*, 275–282. [CrossRef]
10. Del Chierico, F.; Nobili, V.; Vernocchi, P.; Russo, A.; De Stefanis, C.; Gnani, D.; Furlanello, C.; Zandonà, A.; Paci, P.; Capuani, G.; et al. Gut Microbiota Profiling of Pediatric Nonalcoholic Fatty Liver Disease and Obese Patients Unveiled by an Integrated Meta-Omics-Based Approach. *Hepatology* **2017**, *65*, 451–464. [CrossRef] [PubMed]
11. Duarte, S.M.B.; Stefano, J.T.; Miele, L.; Ponziani, F.R.; Souza-Basqueira, M.; Okada, L.S.R.R.; de Barros Costa, F.G.; Toda, K.; Mazo, D.F.C.; Sabino, E.C.; et al. Gut Microbiome Composition in Lean Patients with NASH Is Associated with Liver Damage Independent of Caloric Intake: A Prospective Pilot Study. *Nutr. Metab. Cardiovasc. Dis.* **2018**, *28*, 369–384. [CrossRef] [PubMed]
12. Cortés-Martín, A.; Iglesias-Aguirre, C.E.; Meoro, A.; Selma, M.V.; Espín, J.C. There Is No Distinctive Gut Microbiota Signature in the Metabolic Syndrome: Contribution of Cardiovascular Disease Risk Factors and Associated Medication. *Microorganisms* **2020**, *8*, 416. [CrossRef]
13. Lippert, K.; Kedenko, L.; Antonielli, L.; Kedenko, I.; Gemeier, C.; Leitner, M.; Kautzky-Willer, A.; Paulweber, B.; Hackl, E. Gut Microbiota Dysbiosis Associated with Glucose Metabolism Disorders and the Metabolic Syndrome in Older Adults. *Benef. Microbes* **2017**, *8*, 545–556. [CrossRef] [PubMed]
14. Thingholm, L.B.; Rühlemann, M.C.; Koch, M.; Fuqua, B.; Laucke, G.; Boehm, R.; Bang, C.; Franzosa, E.A.; Hübenthal, M.; Rahnavard, A.; et al. Obese Individuals with and without Type 2 Diabetes Show Different Gut Microbial Functional Capacity and Composition. *Cell Host Microbe* **2019**, *26*, 252–264.e10. [CrossRef]
15. Zhou, Z.; Zheng, Z.; Xiong, X.; Chen, X.; Peng, J.; Yao, H.; Pu, J.; Chen, Q.; Zheng, M. Gut Microbiota Composition and Fecal Metabolic Profiling in Patients with Diabetic Retinopathy. *Front. Cell Dev. Biol.* **2021**, *9*, 2684. [CrossRef]
16. Zhang, Y.; Lu, S.; Yang, Y.; Wang, Z.; Wang, B.; Zhang, B.; Yu, J.; Lu, W.; Pan, M.; Zhao, J.; et al. The Diversity of Gut Microbiota in Type 2 Diabetes with or without Cognitive Impairment. *Aging Clin. Exp. Res.* **2021**, *33*, 589–601. [CrossRef]
17. Li, Q.; Chang, Y.; Zhang, K.; Chen, H.; Tao, S.; Zhang, Z. Implication of the Gut Microbiome Composition of Type 2 Diabetic Patients from Northern China. *Sci. Rep.* **2020**, *10*, 5450. [CrossRef]
18. Navab-Moghadam, F.; Sedighi, M.; Khamseh, M.E.; Alaei-Shahmiri, F.; Talebi, M.; Razavi, S.; Amirmozafari, N. The Association of Type II Diabetes with Gut Microbiota Composition. *Microb. Pathog.* **2017**, *110*, 630–636. [CrossRef]
19. Sedighi, M.; Razavi, S.; Navab-Moghadam, F.; Khamseh, M.E.; Alaei-Shahmiri, F.; Mehrtash, A.; Amirmozafari, N. Comparison of Gut Microbiota in Adult Patients with Type 2 Diabetes and Healthy Individuals. *Microb. Pathog.* **2017**, *111*, 362–369. [CrossRef] [PubMed]
20. Ejtahed, H.; Hoseini-Tavassol, Z.; Khatami, S.; Zangeneh, M.; Behrouzi, A.; Badi, S.A.; Moshiri, A.; Hasani-Ranjbar, S.; Soroush, A.; Vaziri, F.; et al. Main Gut Bacterial Composition Differs between Patients with Type 1 and Type 2 Diabetes and Non-Diabetic Adults. *J. Diabetes Metab. Disord.* **2020**, *19*, 265–271. [CrossRef]

21. Leiva-Gea, I.; Sánchez-Alcoholado, L.; Martín-Tejedor, B.; Castellano-Castillo, D.; Moreno-Indias, I.; Urda-Cardona, A.; Tinahones, F.J.; Fernández-García, J.C.; Queipo-Ortuño, M.I. Gut Microbiota Differs in Composition and Functionality between Children with Type 1 Diabetes and MODY2 and Healthy Control Subjects: A Case-Control Study. *Diabetes Care* **2018**, *41*, 2385–2395. [CrossRef] [PubMed]
22. Qiao, N.; Wittouck, S.; Mattarelli, P.; Zheng, J.; Lebeer, S.; Felis, G.E.; Gänzle, M.G. After the Storm—Perspectives on the Taxonomy of Lactobacillaceae. *JDS Commun.* **2022**, *3*, 222–227. [CrossRef] [PubMed]
23. Sroka-Oleksiak, A.; Młodzińska, A.; Bulanda, M.; Salamon, D.; Major, P.; Stanek, M.; Gosiewski, T. Metagenomic Analysis of Duodenal Microbiota Reveals a Potential Biomarker of Dysbiosis in the Course of Obesity and Type 2 Diabetes: A Pilot Study. *J. Clin. Med.* **2020**, *9*, 369. [CrossRef] [PubMed]
24. Gaike, A.H.; Paul, D.; Bhute, S.; Dhotre, D.P.; Pande, P.; Upadhyaya, S.; Reddy, Y.; Sampath, R.; Ghosh, D.; Chandraprabha, D.; et al. The Gut Microbial Diversity of Newly Diagnosed Diabetics but Not of Prediabetics Is Significantly Different from That of Healthy Nondiabetics. *mSystems* **2020**, *5*, e00578-19. [CrossRef] [PubMed]
25. Zhao, L.; Lou, H.; Peng, Y.; Chen, S.; Zhang, Y.; Li, X. Comprehensive Relationships between Gut Microbiome and Faecal Metabolome in Individuals with Type 2 Diabetes and Its Complications. *Endocrine* **2019**, *66*, 526–537. [CrossRef]
26. Chen, P.-C.; Chien, Y.-W.; Yang, S.-C. The Alteration of Gut Microbiota in Newly Diagnosed Type 2 Diabetic Patients. *Nutrition* **2019**, *63–64*, 51–56. [CrossRef]
27. Liu, X.; Cheng, Y.-W.; Shao, L.; Sun, S.-H.; Wu, J.; Song, Q.-H.; Zou, H.-S.; Ling, Z.-X. Gut Microbiota Dysbiosis in Chinese Children with Type 1 Diabetes Mellitus: An Observational Study. *World J. Gastroenterol.* **2021**, *27*, 2394–2414. [CrossRef]
28. Ahmed, E.A.; Ahmed, S.M.; Zakaria, N.H.; Baddour, N.M.; Header, D.A. Estudio del microbioma intestinal en pacientes egipcios con colitis ulcerosa crónica idiopática. *Rev. Gastroenterol. México* **2022**, *843*, 1–10. [CrossRef]
29. Zakerska-Banaszak, O.; Tomczak, H.; Gabryel, M.; Baturo, A.; Wolko, L.; Michalak, M.; Malinska, N.; Mankowska-Wierzbicka, D.; Eder, P.; Dobrowolska, A.; et al. Dysbiosis of Gut Microbiota in Polish Patients with Ulcerative Colitis: A Pilot Study. *Sci. Rep.* **2021**, *11*, 2166. [CrossRef]
30. Dai, L.; Tang, Y.; Zhou, W.; Dang, Y.; Sun, Q.; Tang, Z.; Zhu, M.; Ji, G. Gut Microbiota and Related Metabolites Were Disturbed in Ulcerative Colitis and Partly Restored after Mesalamine Treatment. *Front. Pharmacol.* **2021**, *11*, 620724. [CrossRef]
31. Knoll, R.L.; Forslund, K.; Kultima, J.R.; Meyer, C.U.; Kullmer, U.; Sunagawa, S.; Bork, P.; Gehring, S. Gut Microbiota Differs between Children with Inflammatory Bowel Disease and Healthy Siblings in Taxonomic and Functional Composition: A Metagenomic Analysis. *Am. J. Physiol.-Gastrointest. Liver Physiol.* **2017**, *312*, G327–G339. [CrossRef] [PubMed]
32. Heidarian, F.; Alebouyeh, M.; Shahrokh, S.; Balaii, H.; Zali, M.R. Altered Fecal Bacterial Composition Correlates with Disease Activity in Inflammatory Bowel Disease and the Extent of IL8 Induction. *Curr. Res. Transl. Med.* **2019**, *67*, 41–50. [CrossRef] [PubMed]
33. Ma, H.-Q.; Yu, T.-T.; Zhao, X.-J.; Zhang, Y.; Zhang, H.-J. Fecal Microbial Dysbiosis in Chinese Patients with Inflammatory Bowel Disease. *World J. Gastroenterol.* **2018**, *24*, 1464–1477. [CrossRef]
34. Franzosa, E.A.; Sirota-Madi, A.; Avila-Pacheco, J.; Fornelos, N.; Haiser, H.J.; Reinker, S.; Vatanen, T.; Hall, A.B.; Mallick, H.; McIver, L.J.; et al. Gut Microbiome Structure and Metabolic Activity in Inflammatory Bowel Disease. *Nat. Microbiol.* **2019**, *4*, 293–305. [CrossRef]
35. Chang, T.-E.; Luo, J.-C.; Yang, U.-C.; Huang, Y.-H.; Hou, M.-C.; Lee, F.-Y. Fecal Microbiota Profile in Patients with Inflammatory Bowel Disease in Taiwan. *J. Chin. Med. Assoc.* **2021**, *84*, 580–587. [CrossRef] [PubMed]
36. Lopetuso, L.R.; Petito, V.; Graziani, C.; Schiavoni, E.; Paroni Sterbini, F.; Poscia, A.; Gaetani, E.; Franceschi, F.; Cammarota, G.; Sanguinetti, M.; et al. Gut Microbiota in Health, Diverticular Disease, Irritable Bowel Syndrome, and Inflammatory Bowel Diseases: Time for Microbial Marker of Gastrointestinal Disorders. *Dig. Dis.* **2018**, *36*, 56–65. [CrossRef]
37. Budinska, E.; Gojda, J.; Heczkova, M.; Bratova, M.; Dankova, H.; Wohl, P.; Bastova, H.; Lanska, V.; Kostovcik, M.; Dastych, M.; et al. Microbiome and Metabolome Profiles Associated with Different Types of Short Bowel Syndrome: Implications for Treatment. *J. Parenter. Enter. Nutr.* **2020**, *44*, 105–118. [CrossRef]
38. Ikeda, T.; Nishida, A.; Yamano, M.; Kimura, I. Short-Chain Fatty Acid Receptors and Gut Microbiota as Therapeutic Targets in Metabolic, Immune, and Neurological Diseases. *Pharmacol. Ther.* **2022**, *239*, 108273. [CrossRef]
39. Su, X.; Gao, Y.; Yang, R. Gut Microbiota-Derived Tryptophan Metabolites Maintain Gut and Systemic Homeostasis. *Cells* **2022**, *11*, 2296. [CrossRef]
40. Qian, B.; Zhang, K.; Li, Y.; Sun, K. Update on Gut Microbiota in Cardiovascular Diseases. *Front. Cell. Infect. Microbiol.* **2022**, *12*, 1694. [CrossRef]
41. Cai, J.; Rimal, B.; Jiang, C.; Chiang, J.Y.L.; Patterson, A.D. Bile Acid Metabolism and Signaling, the Microbiota, and Metabolic Disease. *Pharmacol. Ther.* **2022**, *237*, 108238. [CrossRef]
42. Ohtani, N.; Kawada, N. Role of the Gut–Liver Axis in Liver Inflammation, Fibrosis, and Cancer: A Special Focus on the Gut Microbiota Relationship. *Hepatol. Commun.* **2019**, *3*, 456–470. [CrossRef]
43. Zhang, Y.-L.; Li, Z.-J.; Gou, H.-Z.; Song, X.-J.; Zhang, L. The Gut Microbiota–Bile Acid Axis: A Potential Therapeutic Target for Liver Fibrosis. *Front. Cell. Infect. Microbiol.* **2022**, *12*, 1416. [CrossRef] [PubMed]
44. Koppel, N.; Maini Rekdal, V.; Balskus, E.P. Chemical Transformation of Xenobiotics by the Human Gut Microbiota. *Science* **2017**, *356*, eaag2770. [CrossRef]

45. Abdelsalam, N.A.; Ramadan, A.T.; ElRakaiby, M.T.; Aziz, R.K. Toxicomicrobiomics: The Human Microbiome vs. Pharmaceutical, Dietary, and Environmental Xenobiotics. *Front. Pharmacol.* **2020**, *11*, 390. [CrossRef]
46. Tan, H.; Zhai, Q.; Chen, W. Investigations of Bacteroides Spp. towards next-Generation Probiotics. *Food Res. Int.* **2019**, *116*, 637–644. [CrossRef] [PubMed]
47. Food and Agriculture Organization of the United Nations; World Health Organization (Eds.) *Probiotics in Food: Health and Nutritional Properties and Guidelines for Evaluation*; FAO food and nutrition paper; Food and Agriculture Organization of the United Nations; World Health Organization: Rome, Italy, 2006; ISBN 978-92-5-105513-7.
48. Zhao, S.; Liu, W.; Wang, J.; Shi, J.; Sun, Y.; Wang, W.; Ning, G.; Liu, R.; Hong, J. *Akkermansia muciniphila* Improves Metabolic Profiles by Reducing Inflammation in Chow Diet-Fed Mice. *J. Mol. Endocrinol.* **2017**, *58*, 1–14. [CrossRef]
49. López-Almela, I.; Romaní-Pérez, M.; Bullich-Vilarrubias, C.; Benítez-Páez, A.; Gómez Del Pulgar, E.M.; Francés, R.; Liebisch, G.; Sanz, Y. *Bacteroides uniformis* Combined with Fiber Amplifies Metabolic and Immune Benefits in Obese Mice. *Gut Microbes* **2021**, *13*, 1–20. [CrossRef]
50. Yang, J.-Y.; Lee, Y.-S.; Kim, Y.; Lee, S.-H.; Ryu, S.; Fukuda, S.; Hase, K.; Yang, C.-S.; Lim, H.S.; Kim, M.-S.; et al. Gut Commensal Bacteroides Acidifaciens Prevents Obesity and Improves Insulin Sensitivity in Mice. *Mucosal Immunol.* **2017**, *10*, 104–116. [CrossRef]
51. Plovier, H.; Everard, A.; Druart, C.; Depommier, C.; Van Hul, M.; Geurts, L.; Chilloux, J.; Ottman, N.; Duparc, T.; Lichtenstein, L.; et al. A Purified Membrane Protein from *Akkermansia muciniphila* or the Pasteurized Bacterium Improves Metabolism in Obese and Diabetic Mice. *Nat. Med.* **2017**, *23*, 107–113. [CrossRef] [PubMed]
52. Wu, F.; Guo, X.; Zhang, M.; Ou, Z.; Wu, D.; Deng, L.; Lu, Z.; Zhang, J.; Deng, G.; Chen, S.; et al. An *Akkermansia muciniphila* Subtype Alleviates High-Fat Diet-Induced Metabolic Disorders and Inhibits the Neurodegenerative Process in Mice. *Anaerobe* **2020**, *61*, 102138. [CrossRef] [PubMed]
53. Fabersani, E.; Portune, K.; Campillo, I.; López-Almela, I.; la Paz, S.M.; Romaní-Pérez, M.; Benítez-Páez, A.; Sanz, Y. Bacteroides Uniformis CECT 7771 Alleviates Inflammation within the Gut-Adipose Tissue Axis Involving TLR5 Signaling in Obese Mice. *Sci. Rep.* **2021**, *11*, 11788. [CrossRef]
54. Munukka, E.; Rintala, A.; Toivonen, R.; Nylund, M.; Yang, B.; Takanen, A.; Hänninen, A.; Vuopio, J.; Huovinen, P.; Jalkanen, S.; et al. *Faecalibacterium prausnitzii* Treatment Improves Hepatic Health and Reduces Adipose Tissue Inflammation in High-Fat Fed Mice. *ISME J.* **2017**, *11*, 1667–1679. [CrossRef]
55. Kim, S.; Lee, Y.; Kim, Y.; Seo, Y.; Lee, H.; Ha, J.; Lee, J.; Choi, Y.; Oh, H.; Yoon, Y. *Akkermansia muciniphila* Prevents Fatty Liver Disease, Decreases Serum Triglycerides, and Maintains Gut Homeostasis. *Appl. Environ. Microbiol.* **2020**, *86*, e03004-19. [CrossRef] [PubMed]
56. Grander, C.; Adolph, T.E.; Wieser, V.; Lowe, P.; Wrzosek, L.; Gyongyosi, B.; Ward, D.V.; Grabherr, F.; Gerner, R.R.; Pfister, A.; et al. Recovery of Ethanol-Induced *Akkermansia muciniphila* Depletion Ameliorates Alcoholic Liver Disease. *Gut* **2018**, *67*, 891–901. [CrossRef]
57. Zhang, L.; Qin, Q.; Liu, M.; Zhang, X.; He, F.; Wang, G. *Akkermansia muciniphila* Can Reduce the Damage of Gluco/Lipotoxicity, Oxidative Stress and Inflammation, and Normalize Intestine Microbiota in Streptozotocin-induced Diabetic Rats. *Pathog. Dis.* **2018**, *76*, fty028. [CrossRef] [PubMed]
58. Ou, Z.; Deng, L.; Lu, Z.; Wu, F.; Liu, W.; Huang, D.; Peng, Y. Protective Effects of *Akkermansia muciniphila* on Cognitive Deficits and Amyloid Pathology in a Mouse Model of Alzheimer's Disease. *Nutr. Diabetes* **2020**, *10*, 12. [CrossRef]
59. Gómez del Pulgar, E.M.; Benítez-Páez, A.; Sanz, Y. Safety Assessment of *Bacteroides uniformis* CECT 7771, a Symbiont of the Gut Microbiota in Infants. *Nutrients* **2020**, *12*, 551. [CrossRef]
60. Jia, L.; Shan, K.; Pan, L.-L.; Feng, N.; Lv, Z.; Sun, Y.; Li, J.; Wu, C.; Zhang, H.; Chen, W.; et al. *Clostridium butyricum* CGMCC0313.1 Protects against Autoimmune Diabetes by Modulating Intestinal Immune Homeostasis and Inducing Pancreatic Regulatory T Cells. *Front. Immunol.* **2017**, *8*, 1345. [CrossRef]
61. Péan, N.; Le Lay, A.; Brial, F.; Wasserscheid, J.; Rouch, C.; Vincent, M.; Myridakis, A.; Hedjazi, L.; Dumas, M.-E.; Grundberg, E.; et al. Dominant Gut *Prevotella copri* in Gastrectomised Non-Obese Diabetic Goto–Kakizaki Rats Improves Glucose Homeostasis through Enhanced FXR Signalling. *Diabetologia* **2020**, *63*, 1223–1235. [CrossRef]
62. Zhai, R.; Xue, X.; Zhang, L.; Yang, X.; Zhao, L.; Zhang, C. Strain-Specific Anti-Inflammatory Properties of Two *Akkermansia muciniphila* Strains on Chronic Colitis in Mice. *Front. Cell. Infect. Microbiol.* **2019**, *9*, 239. [CrossRef] [PubMed]
63. Torres-Sánchez, A.; Ruiz-Rodríguez, A.; Ortiz, P.; Moreno, M.A.; Ampatzoglou, A.; Gruszecka-Kosowska, A.; Monteoliva-Sánchez, M.; Aguilera, M. Exploring Next Generation Probiotics for Metabolic and Microbiota Dysbiosis Linked to Xenobiotic Exposure: Holistic Approach. *Int. J. Mol. Sci.* **2022**, *23*, 12917. [CrossRef] [PubMed]
64. Del Chierico, F.; Manco, M.; Gardini, S.; Guarrasi, V.; Russo, A.; Bianchi, M.; Tortosa, V.; Quagliariello, A.; Shashaj, B.; Fintini, D.; et al. Fecal Microbiota Signatures of Insulin Resistance, Inflammation, and Metabolic Syndrome in Youth with Obesity: A Pilot Study. *Acta Diabetol.* **2021**, *58*, 1009–1022. [CrossRef]
65. Ahmad, A.; Yang, W.; Chen, G.; Shafiq, M.; Javed, S.; Zaidi, S.S.A.; Shahid, R.; Liu, C.; Bokhari, H. Analysis of Gut Microbiota of Obese Individuals with Type 2 Diabetes and Healthy Individuals. *PLoS ONE* **2019**, *14*, e0226372. [CrossRef]
66. Doumatey, A.P.; Adeyemo, A.; Zhou, J.; Lei, L.; Adebamowo, S.N.; Adebamowo, C.; Rotimi, C.N. Gut Microbiome Profiles Are Associated with Type 2 Diabetes in Urban Africans. *Front. Cell. Infect. Microbiol.* **2020**, *10*, 63. [CrossRef]

67. Adachi, K.; Sugiyama, T.; Yamaguchi, Y.; Tamura, Y.; Izawa, S.; Hijikata, Y.; Ebi, M.; Funaki, Y.; Ogasawara, N.; Goto, C.; et al. Gut Microbiota Disorders Cause Type 2 Diabetes Mellitus and Homeostatic Disturbances in Gut-Related Metabolism in Japanese Subjects. *J. Clin. Biochem. Nutr.* **2019**, *64*, 231–238. [CrossRef]
68. Takagi, T.; Naito, Y.; Kashiwagi, S.; Uchiyama, K.; Mizushima, K.; Kamada, K.; Ishikawa, T.; Inoue, R.; Okuda, K.; Tsujimoto, Y.; et al. Changes in the Gut Microbiota Are Associated with Hypertension, Hyperlipidemia, and Type 2 Diabetes Mellitus in Japanese Subjects. *Nutrients* **2020**, *12*, 2996. [CrossRef] [PubMed]
69. Mejía-León, M.E.; Petrosino, J.F.; Ajami, N.J.; Domínguez-Bello, M.G.; de la Barca, A.M.C. Fecal Microbiota Imbalance in Mexican Children with Type 1 Diabetes. *Sci. Rep.* **2014**, *4*, 3814. [CrossRef]
70. Radwan, S.; Gilfillan, D.; Eklund, B.; Radwan, H.M.; Menofy, N.G.E.; Lee, J.; Kapuscinski, M.; Abdo, Z. A Comparative Study of the Gut Microbiome in Egyptian Patients with Type I and Type II Diabetes. *PLoS ONE* **2020**, *15*, e0238764. [CrossRef]
71. Gradisteanu Pircalabioru, G.; Ilie, I.; Oprea, L.; Picu, A.; Petcu, L.M.; Burlibasa, L.; Chifiriuc, M.-C.; Musat, M. Microbiome, Mycobiome and Related Metabolites Alterations in Patients with Metabolic Syndrome—A Pilot Study. *Metabolites* **2022**, *12*, 218. [CrossRef]
72. Lim, M.Y.; You, H.J.; Yoon, H.S.; Kwon, B.; Lee, J.Y.; Lee, S.; Song, Y.-M.; Lee, K.; Sung, J.; Ko, G. The Effect of Heritability and Host Genetics on the Gut Microbiota and Metabolic Syndrome. *Gut* **2017**, *66*, 1031–1038. [CrossRef] [PubMed]
73. Cortez, R.V.; Moreira, L.N.; Padilha, M.; Bibas, M.D.; Toma, R.K.; Porta, G.; Taddei, C.R. Gut Microbiome of Children and Adolescents with Primary Sclerosing Cholangitis in Association with Ulcerative Colitis. *Front. Immunol.* **2021**, *11*, 598152. [CrossRef] [PubMed]
74. Ma, Y.; Zhang, Y.; Jiang, H.; Xiang, S.; Zhao, Y.; Xiao, M.; Du, F.; Ji, H.; Kaboli, P.J.; Wu, X.; et al. Metagenome Analysis of Intestinal Bacteria in Healthy People, Patients with Inflammatory Bowel Disease and Colorectal Cancer. *Front. Cell. Infect. Microbiol.* **2021**, *11*, 599734. [CrossRef] [PubMed]
75. Jee, J.J.; Lim, J.; Park, S.; Koh, H.; Lee, H.W. Gut Microbial Community Differentially Characterizes Patients with Nonalcoholic Fatty Liver Disease. *J. Gastroenterol. Hepatol.* **2022**, *37*, 1822–1832. [CrossRef]
76. Yu, J.; Zhang, H.; Chen, L.; Ruan, Y.; Chen, Y.; Liu, Q. Disease-Associated Gut Microbiota Reduces the Profile of Secondary Bile Acids in Pediatric Nonalcoholic Fatty Liver Disease. *Front. Cell. Infect. Microbiol.* **2021**, *11*, 698852. [CrossRef] [PubMed]
77. Iino, C.; Endo, T.; Mikami, K.; Hasegawa, T.; Kimura, M.; Sawada, N.; Nakaji, S.; Fukuda, S. Significant Decrease in *Faecalibacterium* among Gut Microbiota in Nonalcoholic Fatty Liver Disease: A Large BMI- and Sex-Matched Population Study. *Hepatol. Int.* **2019**, *13*, 748–756. [CrossRef] [PubMed]
78. Kim, H.-N.; Joo, E.-J.; Cheong, H.S.; Kim, Y.; Kim, H.-L.; Shin, H.; Chang, Y.; Ryu, S. Gut Microbiota and Risk of Persistent Nonalcoholic Fatty Liver Diseases. *J. Clin. Med.* **2019**, *8*, 1089. [CrossRef]
79. Li, F.; Sun, G.; Wang, Z.; Wu, W.; Guo, H.; Peng, L.; Wu, L.; Guo, X.; Yang, Y. Characteristics of Fecal Microbiota in Non-Alcoholic Fatty Liver Disease Patients. *Sci. China Life Sci.* **2018**, *61*, 770–778. [CrossRef]
80. Shen, F.; Zheng, R.-D.; Sun, X.-Q.; Ding, W.-J.; Wang, X.-Y.; Fan, J.-G. Gut Microbiota Dysbiosis in Patients with Non-Alcoholic Fatty Liver Disease. *Hepatobiliary Pancreat. Dis. Int.* **2017**, *16*, 375–381. [CrossRef] [PubMed]
81. Lee, G.; You, H.J.; Bajaj, J.S.; Joo, S.K.; Yu, J.; Park, S.; Kang, H.; Park, J.H.; Kim, J.H.; Lee, D.H.; et al. Distinct Signatures of Gut Microbiome and Metabolites Associated with Significant Fibrosis in Non-Obese NAFLD. *Nat. Commun.* **2020**, *11*, 4982. [CrossRef]
82. Wang, B.; Jiang, X.; Cao, M.; Ge, J.; Bao, Q.; Tang, L.; Chen, Y.; Li, L. Altered Fecal Microbiota Correlates with Liver Biochemistry in Nonobese Patients with Non-Alcoholic Fatty Liver Disease. *Sci. Rep.* **2016**, *6*, 32002. [CrossRef]
83. Tsai, M.-C.; Liu, Y.-Y.; Lin, C.-C.; Wang, C.-C.; Wu, Y.-J.; Yong, C.-C.; Chen, K.-D.; Chuah, S.-K.; Yao, C.-C.; Huang, P.-Y.; et al. Gut Microbiota Dysbiosis in Patients with Biopsy-Proven Nonalcoholic Fatty Liver Disease: A Cross-Sectional Study in Taiwan. *Nutrients* **2020**, *12*, 820. [CrossRef] [PubMed]
84. Loomba, R.; Seguritan, V.; Li, W.; Long, T.; Klitgord, N.; Bhatt, A.; Dulai, P.S.; Caussy, C.; Bettencourt, R.; Highlander, S.K.; et al. Gut Microbiome-Based Metagenomic Signature for Non-Invasive Detection of Advanced Fibrosis in Human Nonalcoholic Fatty Liver Disease. *Cell Metab.* **2017**, *25*, 1054–1062.e5. [CrossRef] [PubMed]
85. Sobhonslidsuk, A.; Chanprasertyothin, S.; Pongrujikorn, T.; Kaewduang, P.; Promson, K.; Petraksa, S.; Ongphiphadhanakul, B. The Association of Gut Microbiota with Nonalcoholic Steatohepatitis in Thais. *BioMed Res. Int.* **2018**, *2018*, e9340316. [CrossRef] [PubMed]
86. Da Silva, H.E.; Teterina, A.; Comelli, E.M.; Taibi, A.; Arendt, B.M.; Fischer, S.E.; Lou, W.; Allard, J.P. Nonalcoholic Fatty Liver Disease Is Associated with Dysbiosis Independent of Body Mass Index and Insulin Resistance. *Sci. Rep.* **2018**, *8*, 1466. [CrossRef]
87. Mouzaki, M.; Comelli, E.M.; Arendt, B.M.; Bonengel, J.; Fung, S.K.; Fischer, S.E.; McGilvray, I.D.; Allard, J.P. Intestinal Microbiota in Patients with Nonalcoholic Fatty Liver Disease. *Hepatology* **2013**, *58*, 120–127. [CrossRef]
88. Bastian, W.P.; Hasan, I.; Lesmana, C.R.A.; Rinaldi, I.; Gani, R.A. Gut Microbiota Profiles in Nonalcoholic Fatty Liver Disease and Its Possible Impact on Disease Progression Evaluated with Transient Elastography: Lesson Learnt from 60 Cases. *Case Rep. Gastroenterol.* **2019**, *13*, 125–133. [CrossRef] [PubMed]
89. Wang, P.; Dong, Y.; Zuo, K.; Han, C.; Jiao, J.; Yang, X.; Li, J. Characteristics and Variation of Fecal Bacterial Communities and Functions in Isolated Systolic and Diastolic Hypertensive Patients. *BMC Microbiol.* **2021**, *21*, 128. [CrossRef]
90. Nakai, M.; Ribeiro, R.V.; Stevens, B.R.; Gill, P.; Muralitharan, R.R.; Yiallourou, S.; Muir, J.; Carrington, M.; Head, G.A.; Kaye, D.M.; et al. Essential Hypertension Is Associated with Changes in Gut Microbial Metabolic Pathways: A Multisite Analysis of Ambulatory Blood Pressure. *Hypertension* **2021**, *78*, 804–815. [CrossRef] [PubMed]

91. Silveira-Nunes, G.; Durso, D.F.; de Oliveira, L.R.A., Jr.; Cunha, E.H.M.; Maioli, T.U.; Vieira, A.T.; Speziali, E.; Corrêa-Oliveira, R.; Martins-Filho, O.A.; Teixeira-Carvalho, A.; et al. Hypertension Is Associated With Intestinal Microbiota Dysbiosis and Inflammation in a Brazilian Population. *Front. Pharmacol.* **2020**, *11*, 258. [CrossRef]
92. Yan, Q.; Gu, Y.; Li, X.; Yang, W.; Jia, L.; Chen, C.; Han, X.; Huang, Y.; Zhao, L.; Li, P.; et al. Alterations of the Gut Microbiome in Hypertension. *Front. Cell. Infect. Microbiol.* **2017**, *7*, 381. [CrossRef] [PubMed]
93. Li, J.; Zhao, F.; Wang, Y.; Chen, J.; Tao, J.; Tian, G.; Wu, S.; Liu, W.; Cui, Q.; Geng, B.; et al. Gut Microbiota Dysbiosis Contributes to the Development of Hypertension. *Microbiome* **2017**, *5*, 14. [CrossRef]
94. Wan, C.; Zhu, C.; Jin, G.; Zhu, M.; Hua, J.; He, Y. Analysis of Gut Microbiota in Patients with Coronary Artery Disease and Hypertension. *Evid.-Based Complement. Altern. Med.* **2021**, *2021*, 7195082. [CrossRef]
95. Li, H.; Liu, B.; Song, J.; An, Z.; Zeng, X.; Li, J.; Jiang, J.; Xie, L.; Wu, W. Characteristics of Gut Microbiota in Patients with Hypertension and/or Hyperlipidemia: A Cross-Sectional Study on Rural Residents in Xinxiang County, Henan Province. *Microorganisms* **2019**, *7*, 399. [CrossRef]
96. Gao, J.; Wang, J.; Zhao, L.-L.; Yao, T.-T.; Chen, Y.; Ma, J.; Zhang, X.; Wang, J.-X.; Wang, Y.; Cui, Z.; et al. Gut *Lactobacillus* Level Is a Predictive Marker for Coronary Atherosclerotic Lesions Progress and Prognosis in Patients with Acute Coronary Syndrome. *Front. Cell. Infect. Microbiol.* **2021**, *11*, 687827. [CrossRef] [PubMed]
97. Ji, L.; Chen, S.; Gu, G.; Zhou, J.; Wang, W.; Ren, J.; Wu, J.; Yang, D.; Zheng, Y. Exploration of Crucial Mediators for Carotid Atherosclerosis Pathogenesis through Integration of Microbiome, Metabolome, and Transcriptome. *Front. Physiol.* **2021**, *12*, 645212. [CrossRef] [PubMed]
98. Baragetti, A.; Severgnini, M.; Olmastroni, E.; Dioguardi, C.C.; Mattavelli, E.; Angius, A.; Rotta, L.; Cibella, J.; Caredda, G.; Consolandi, C.; et al. Gut Microbiota Functional Dysbiosis Relates to Individual Diet in Subclinical Carotid Atherosclerosis. *Nutrients* **2021**, *13*, 304. [CrossRef]
99. Liu, S.; Zhao, W.; Liu, X.; Cheng, L. Metagenomic Analysis of the Gut Microbiome in Atherosclerosis Patients Identify Cross-Cohort Microbial Signatures and Potential Therapeutic Target. *FASEB J.* **2020**, *34*, 14166–14181. [CrossRef]
100. Toya, T.; Corban, M.T.; Marrietta, E.; Horwath, I.E.; Lerman, L.O.; Murray, J.A.; Lerman, A. Coronary Artery Disease Is Associated with an Altered Gut Microbiome Composition. *PLoS ONE* **2020**, *15*, e0227147. [CrossRef]
101. Liu, H.; Chen, X.; Hu, X.; Niu, H.; Tian, R.; Wang, H.; Pang, H.; Jiang, L.; Qiu, B.; Chen, X.; et al. Alterations in the Gut Microbiome and Metabolism with Coronary Artery Disease Severity. *Microbiome* **2019**, *7*, 68. [CrossRef]
102. Jie, Z.; Xia, H.; Zhong, S.-L.; Feng, Q.; Li, S.; Liang, S.; Zhong, H.; Liu, Z.; Gao, Y.; Zhao, H.; et al. The Gut Microbiome in Atherosclerotic Cardiovascular Disease. *Nat. Commun.* **2017**, *8*, 845. [CrossRef]
103. Loftfield, E.; Herzig, K.-H.; Caporaso, J.G.; Derkach, A.; Wan, Y.; Byrd, D.A.; Vogtmann, E.; Männikkö, M.; Karhunen, V.; Knight, R.; et al. Association of Body Mass Index with Fecal Microbial Diversity and Metabolites in the Northern Finland Birth Cohort. *Cancer Epidemiol. Biomark. Prev.* **2020**, *29*, 2289–2299. [CrossRef] [PubMed]
104. Zhou, L.; Ni, Z.; Yu, J.; Cheng, W.; Cai, Z.; Yu, C. Correlation Between Fecal Metabolomics and Gut Microbiota in Obesity and Polycystic Ovary Syndrome. *Front. Endocrinol.* **2020**, *11*, 628. [CrossRef] [PubMed]
105. Liu, R.; Hong, J.; Xu, X.; Feng, Q.; Zhang, D.; Gu, Y.; Shi, J.; Zhao, S.; Liu, W.; Wang, X.; et al. Gut Microbiome and Serum Metabolome Alterations in Obesity and after Weight-Loss Intervention. *Nat. Med.* **2017**, *23*, 859–868. [CrossRef]
106. Nogacka, A.M.; de los Reyes-Gavilán, C.G.; Martínez-Faedo, C.; Ruas-Madiedo, P.; Suarez, A.; Mancabelli, L.; Ventura, M.; Cifuentes, A.; León, C.; Gueimonde, M.; et al. Impact of Extreme Obesity and Diet-Induced Weight Loss on the Fecal Metabolome and Gut Microbiota. *Mol. Nutr. Food Res.* **2021**, *65*, 2000030. [CrossRef] [PubMed]
107. Nuli, R.; Azhati, J.; Cai, J.; Kadeer, A.; Zhang, B.; Mohemaiti, P. Metagenomics and Faecal Metabolomics Integrative Analysis towards the Impaired Glucose Regulation and Type 2 Diabetes in Uyghur-Related Omics. *J. Diabetes Res.* **2019**, *2019*, e2893041. [CrossRef]
108. Qi, Q.; Li, J.; Yu, B.; Moon, J.-Y.; Chai, J.C.; Merino, J.; Hu, J.; Ruiz-Canela, M.; Rebholz, C.; Wang, Z.; et al. Host and Gut Microbial Tryptophan Metabolism and Type 2 Diabetes: An Integrative Analysis of Host Genetics, Diet, Gut Microbiome and Circulating Metabolites in Cohort Studies. *Gut* **2021**, *71*, 1095–1105. [CrossRef]
109. Zhu, S.; Liu, S.; Li, H.; Zhang, Z.; Zhang, Q.; Chen, L.; Zhao, Y.; Chen, Y.; Gu, J.; Min, L.; et al. Identification of Gut Microbiota and Metabolites Signature in Patients With Irritable Bowel Syndrome. *Front. Cell. Infect. Microbiol.* **2019**, *9*, 346. [CrossRef]
110. Alferink, L.J.M.; Radjabzadeh, D.; Erler, N.S.; Vojinovic, D.; Medina-Gomez, C.; Uitterlinden, A.G.; de Knegt, R.J.; Amin, N.; Ikram, M.A.; Janssen, H.L.A.; et al. Microbiomics, Metabolomics, Predicted Metagenomics, and Hepatic Steatosis in a Population-Based Study of 1,355 Adults. *Hepatology* **2021**, *73*, 968–982. [CrossRef]
111. Page, M.J.; McKenzie, J.E.; Bossuyt, P.M.; Boutron, I.; Hoffmann, T.C.; Mulrow, C.D.; Shamseer, L.; Tetzlaff, J.M.; Akl, E.A.; Brennan, S.E.; et al. The PRISMA 2020 Statement: An Updated Guideline for Reporting Systematic Reviews. *BMJ* **2021**, *372*, n71. [CrossRef]
112. Kolde, R. Pheatmap: Pretty Heatmaps 2019. Pheatmap: Pretty Heatmaps. R Package Version 1.0.12. Available online: https://CRAN.R-project.org/package=pheatmap (accessed on 28 January 2023).
113. Chen, M.X.; Wang, S.-Y.; Kuo, C.-H.; Tsai, I.-L. Metabolome Analysis for Investigating Host-Gut Microbiota Interactions. *J. Formos. Med. Assoc.* **2019**, *118* (Suppl. S1), S10–S22. [CrossRef]
114. Visconti, A.; Le Roy, C.I.; Rosa, F.; Rossi, N.; Martin, T.C.; Mohney, R.P.; Li, W.; de Rinaldis, E.; Bell, J.T.; Venter, J.C.; et al. Interplay between the Human Gut Microbiome and Host Metabolism. *Nat. Commun.* **2019**, *10*, 4505. [CrossRef] [PubMed]

115. Xu, Y.; Wang, N.; Tan, H.-Y.; Li, S.; Zhang, C.; Feng, Y. Function of Akkermansia muciniphila in Obesity: Interactions with Lipid Metabolism, Immune Response and Gut Systems. *Front. Microbiol.* **2020**, *11*, 219. [CrossRef] [PubMed]
116. Maioli, T.U.; Borras-Nogues, E.; Torres, L.; Barbosa, S.C.; Martins, V.D.; Langella, P.; Azevedo, V.A.; Chatel, J.-M. Possible Benefits of Faecalibacterium prausnitzii for Obesity-Associated Gut Disorders. *Front. Pharmacol.* **2021**, *12*, 740636. [CrossRef]
117. López-Moreno, A.; Suárez, A.; Avanzi, C.; Monteoliva-Sánchez, M.; Aguilera, M. Probiotic Strains and Intervention Total Doses for Modulating Obesity-Related Microbiota Dysbiosis: A Systematic Review and Meta-Analysis. *Nutrients* **2020**, *12*, 1921. [CrossRef] [PubMed]
118. Gao, P. The Exposome in the Era of One Health. *Environ. Sci. Technol.* **2021**, *55*, 2790–2799. [CrossRef]