



The human gut microbiota and glucose metabolism: a scoping review of key bacteria and the potential role of SCFAs

Downloaded from: <https://research.chalmers.se>, 2023-01-21 01:00 UTC

Citation for the original published paper (version of record):

Palmnäs, M., Costabile, G., Vetrani, C. et al (2022). The human gut microbiota and glucose metabolism: a scoping review of key bacteria and the potential role of SCFAs. *American Journal of Clinical Nutrition*, In Press.
<http://dx.doi.org/10.1093/ajcn/nqac217>

N.B. When citing this work, cite the original published paper.

The human gut microbiota and glucose metabolism: a scoping review of key bacteria and the potential role of SCFAs

Marie SA Palmnäs-Bédard,¹ Giuseppina Costabile,^{2,3} Claudia Vetrani,² Sebastian Åberg,¹ Yommine Hjalmarsson,⁴ Johan Dicksved,⁵ Gabriele Riccardi,^{2,3} and Rikard Landberg^{1,6}

¹Department of Biology and Biological Engineering, Division of Food and Nutrition Science, Chalmers University of Technology, Gothenburg, Sweden; ²Department of Clinical Medicine and Surgery, University of Naples Federico II, Naples, Italy; ³Task Force on Microbiome Studies, University of Naples Federico II, Naples, Italy; ⁴Department of Communication and Learning in Science, Chalmers University of Technology, Gothenburg, Sweden; ⁵Department of Animal Nutrition and Management, Swedish University of Agricultural Sciences, Uppsala, Sweden; and ⁶Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden

ABSTRACT

The gut microbiota plays a fundamental role in human nutrition and metabolism and may have direct implications for type 2 diabetes and associated preconditions. An improved understanding of relations between human gut microbiota and glucose metabolism could lead to novel opportunities for type 2 diabetes prevention, but human observational studies reporting on such findings have not been extensively reviewed. Here, we review the literature on associations between gut microbiota and markers and stages of glucose dysregulation and insulin resistance in healthy adults and in adults with metabolic disease and risk factors. We present the current evidence for identified key bacteria and their potential roles in glucose metabolism independent of overweight, obesity, and metabolic drugs. We provide support for SCFAs mediating such effects and discuss the role of diet, as well as metabolites derived from diet and gut microbiota interactions. From 5983 initially identified PubMed records, 45 original studies were eligible and reviewed. α Diversity and 45 bacterial taxa were associated with selected outcomes. Six taxa were most frequently associated with glucose metabolism: *Akkermansia muciniphila*, *Bifidobacterium longum*, *Clostridium leptum* group, *Faecalibacterium prausnitzii*, and *Faecalibacterium* (inversely associated) and *Dorea* (directly associated). For *Dorea* and *A. muciniphila*, associations were independent of metabolic drugs and body measures. For *A. muciniphila* and *F. prausnitzii*, limited evidence supported SCFA mediation of potential effects on glucose metabolism. We conclude that observational studies applying metagenomics sequencing to identify species-level relations are warranted, as are studies accounting for confounding factors and investigating SCFA and postprandial glucose metabolism. Such advances in the field will, together with mechanistic and prospective studies and investigations into diet–gut microbiota interactions, have the potential to bring critical insight into roles of gut microbiota and microbial metabolites in human glucose metabolism and to contribute toward the development of novel prevention strategies for type 2 diabetes, including precision nutrition. *Am J Clin Nutr* 2022;0:1–13.

Keywords: glucose metabolism, gut microbiota, humans, insulin resistance, prediabetes, short-chain fatty acids, microbial metabolites, diet–gut microbiota interactions, type 2 diabetes prevention, precision nutrition

Introduction

Mounting evidence has linked the gut microbiota to health status in humans. It has become evident that gut microbes play a fundamental role in human nutrition and metabolism (1, 2) and that alterations in microbiota composition, diversity, and function may have direct implications for metabolic derangements including type 2 diabetes and associated preconditions (1, 3). This insight has led to extensive research to identify microbial taxa and functions which could dictate or be targets for

Author disclosures: The authors report no conflicts of interest

This work is part of the Food4GutMarKIT project, supported by FORMAS grant 2019-04639 (to RL). MSAP-B is supported by FORMAS grant 2017-02003 under the umbrella of the European Joint Programming Initiative “A Healthy Diet for a Healthy Life” (JPI HDHL) and of the ERA-NET Cofund ERA-HDHL (GA No. 727565 of the EU Horizon 2020 Research and Innovation Programme). RL is supported by FORMAS research grant Dnr 2020-01113 and by Swedish Research Council grant 2019-01264. The funders did not have a role in the design, implementation, analysis, or interpretation in the present scoping review.

Supplemental Figures 1 and 2 and Supplemental Tables 1–5 are available from the “Supplementary data” link in the online posting of the article and from the same link in the online table of contents at <https://academic.oup.com/ajcn/>.

GR and RL contributed equally to this work as senior investigators.

Address correspondence to MSAP-B (e-mail: marie.palmnas@chalmers.se).

Received April 29, 2022. Accepted for publication August 16, 2022.

First published online August 26, 2022; doi: <https://doi.org/10.1093/ajcn/nqac217>.

preventative actions and treatment, including dietary strategies (4–6). At present, we recognize that specific dietary components, such as certain dietary fibers, can increase the abundance of specific gut bacteria (7, 8) or result in differential health responses determined by specific bacteria (9). Yet, it is unknown which gut bacteria, and if bacteria determined a priori, can be utilized for precision prevention in the general population or in different risk groups.

Type 2 diabetes is a global epidemic and prevalence is projected to increase (10, 11). Human observational studies show significant differences in the composition and function of the gut microbiota between healthy individuals and people with prevalent type 2 diabetes (3, 12, 13). However, these observations could partly or entirely be driven by antidiabetic medication, drugs for common metabolic comorbidities (14, 15), overweight or obesity (16, 17), and other confounding factors. Causal evidence for the role of gut microbiota in the etiology of type 2 diabetes is mostly limited to animal studies and it remains unclear in what specific processes of the pathogenesis gut microbiota may be involved (3).

Perturbed glucose metabolism plays a central role in type 2 diabetes development. Interactions between the gut microbiota and diet, especially dietary fibers, are closely linked with glucose regulation (18–22), potentially through mechanisms involving microbial metabolites including, but not limited to, SCFAs and succinate (13, 23–25). Novel insights into relations between gut microbiota, microbial metabolites, and dysregulations in glucose metabolism can contribute to the understanding of the role of gut microbiota in type 2 diabetes development and lead to novel opportunities for prevention. Yet, despite the increasing number of human observational studies in this field, this literature has not been extensively reviewed.

The aim of this scoping review was to identify and summarize the evidence for gut bacteria most frequently and consistently associating with markers and stages of glucose dysregulation and insulin resistance in adults with and without metabolic disease and common metabolic risk factors. We assessed if there was evidence supporting a role for these bacteria in glucose metabolism independent of overweight, obesity, and metabolic drugs and the potential mediation by SCFAs and succinate. Finally, we identified limitations in the current literature and provide future directives that could contribute toward the development of novel microbiota-based prevention strategies for type 2 diabetes, including precision nutrition.

Methods

A scoping review was conducted through PubMed literature searches to capture studies reporting on associations between fecal bacteria at different taxonomic levels, as well as α diversity, and diabetes risk outcomes related to blood glucose and insulin. Glucose-related outcomes included fasting and postprandial glucose, glycated hemoglobin (HbA1c), and presence of prediabetes as opposed to normoglycemia. Insulin-related outcomes included fasting and postprandial insulin concentrations and insulin resistance, e.g., HOMA-IR, insulin sensitivity measured with euglycemic clamp, and presence of insulin resistance.

The included literature was identified and reviewed based on defined search strategies, criteria, and research questions

defined using the PICO (population or problem, interest, and context) framework (26, 27) and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) checklist (**Supplemental Figure 1, Supplemental Table 1**). No protocol was registered or published a priori. PubMed-specific title and abstract words (TiAb) and Medical Subject Headings (MeSH) search terms were used for title and abstract words and study index categories, respectively (**Supplemental Tables 2–4**). Three literature searches acted complementarily: 1 initial search (22 November, 2019) and 2 searches specified to capture the most recently published literature (14 June, 2021) and to expand the review on associations with postprandial glucose and insulin (21 December, 2021), respectively (**Supplemental Tables 2–4**). Duplicate articles were removed using the Amsterdam Efficient Deduplication (AED) method (28). The gut microbiota-related search terms were general to allow for identification of any relevant associations for fecal bacteria regardless of prior knowledge. A broad range of study designs were eligible, including intervention studies from which baseline associations were extracted. For quality control purposes, studies with populations or groups (for group-based comparisons) with ≤ 5 participants were excluded (**Supplemental Table 1**). Studies were also excluded if populations had undergone recent treatments that could influence the gut microbiota (e.g., antibiotic or antidiarrheal treatment) or presented with extreme bowel habits or gastrointestinal symptoms. Other exclusion criteria were non-English publications and studies with populations with diseases other than type 2 diabetes or cardiovascular disease or traits that were considered nonrepresentative of the general population, e.g., professional athletes and pregnant females.

Records were first assessed based on titles and abstracts using Rayyan QCRI (29); each record was evaluated by 2 individuals in a blinded manner and conflicting assessments were resolved upon discussion or assessment of the full text. Eligible full texts were read by ≥ 1 individuals. Each included study was charted through an independent process and a piloted form and extracted results were limited to statistically significant results and, if applicable, results that remained statistically significant after adjusting for multiple comparisons (**Supplemental Table 5**). Adjustments, including adjustments for diet, sex, and age, were noted for each included article, as were whether studies reported on SCFAs, SCFA-associated enzymes, other metabolites, or incretins. Results were only included if there were ≥ 2 studies supporting an inverse/direct association with either glucose- or insulin-related outcomes. Any studies reporting on contradictory findings were also included. For example, if 2 studies found direct associations between a bacterium and glucose outcomes, and 1 study found an inverse association, all 3 studies were reviewed and reported. Taxa were reported using the name recognized by NCBI Taxonomy (30) at time of submission, bacteria reported under different synonyms were merged, and any strain-level results were reported as species. Notably, results for “*Clostridium leptum*” were reported as “*C. leptum* group” when group-specific qPCR primers had been used, because the *C. leptum* group (also known as Clostridial cluster IV) includes other species and is predominated by *Faecalibacterium prausnitzii*, not *C. leptum* (31).

Charted data on study characteristics were summarized and visualized as a bar plot. Taxonomic trees were generated using

PhyloT version 2 (32) and visualized and annotated using iTOL version 6 (33). Venn diagrams were created using tools available at <http://bioinformatics.psb.ugent.be>.

Results

Characteristics of reviewed studies

A total of 45 studies out of 5982 initially identified records were eligible and included in this review (Figure 1, Supplemental Table 5). This included 20 cross-sectional studies, 15 case-control studies, and 10 intervention-based designs, many with study populations ranging from 100 to 2000 participants (Figure 2) and the majority published in the past 5 y ($n = 33$). Most studies ($n = 40$) included females and males and had 1 study location, but 2 studies included populations from different countries (34, 35) and 1 study included a discovery cohort and a validation cohort based in the same country (Sweden) (36). Asian ($n = 21$) and European ($n = 15$) populations were overrepresented. Most studies ($n = 28$) had applied 16S ribosomal RNA (rRNA) gene amplification and sequencing to measure the gut microbiota, fewer had used metagenomic shotgun sequencing ($n = 11$) or qPCR ($n = 6$). Only 3 studies had investigated postprandial glucose and insulin response in relation to gut microbiota (18, 37, 38), 1 of which also reported on associations with fasting glucose and insulin concentrations (37) (Supplemental Figure 2B).

Bacteria associated with glucose metabolism outcomes and their taxonomic relations

In total, 45 taxa (phyla, orders, families, genera, and species) and α diversity were identified to be related to the studied outcomes (Tables 1 and 2, Supplemental Figure 2A). Out of these, 40 taxa were associated with glucose and 17 were associated with insulin. Most taxa were presented as species. Based on the totality of the studies included, we found that *F. prausnitzii* was inversely associated with both fasting (39–41) and postprandial insulin (37, 38) and HOMA-IR (42). Enterobacteriaceae had a direct association with fasting (35, 43) and postprandial glucose (18) and *Haemophilus parainfluenzae* was inversely associated with fasting glucose and HbA1c (40), prediabetes (44), and postprandial glucose (37) (Tables 1 and 2, Supplemental Table 5). [*Ruminococcus*] *gnavus* had a higher abundance in groups with prediabetes (45) and glucose intolerance (36) and was elevated with postprandial glucose (37).

The taxonomic relations between bacteria were investigated in relation to our findings (Figures 3 and 4). Overall, there were consistent inverse associations with glucose and insulin for taxa belonging to the Oscillospiraceae family (formerly known as Ruminococcaceae) including *Faecalibacterium*, *F. prausnitzii*, and the *C. leptum* group. Inverse associations were also found with insulin for *Bifidobacterium* and *Bifidobacterium longum* (Figure 4). For glucose, direct associations were observed with Enterobacteriaceae and its taxa *Escherichia-Shigella* and *Escherichia coli*, *Megasphaera* and *Megasphaera elsdenii*, and with *Streptococcus* and *Streptococcus salivarius* (Figure 3). The Bacteroidetes phylum and genera (*Prevotella*, *Bacteroides*, and *Alistipes*) as well as *Akkermansia* and *Akkermansia muciniphila*

were inversely associated with glucose. Results were typically more consistent for genera and species than for phyla and orders.

Evidence for the role of key gut bacteria in glucose regulation

The most consistent and inverse associations with glucose- and/or insulin-related outcomes were found for *A. muciniphila*, *B. longum*, *Faecalibacterium*, the *C. leptum* group, and *F. prausnitzii* (Tables 1 and 2, Figures 3 and 4). *Dorea* was consistently elevated with prediabetes and positively associated with glucose concentrations. The findings for these bacteria are discussed in greater detail in what follows. Special attention was given to taxonomic relations and associations with SCFAs and microbial genes encoding for enzymes involved in SCFA biosynthesis. We also report on evidence that supports or contradicts the potential role of these taxa in glucose metabolism independent of body weight, body composition, and metabolic drugs.

A. muciniphila and *Akkermansia*

The abundance of *A. muciniphila* was inversely associated with fasting glucose and HbA1c (45–49) and with insulin concentrations and insulin resistance (46–48, 50) and was lower in treatment-naïve individuals with prediabetes than in normoglycemic controls (45, 51) (Tables 1 and 2, Figures 3 and 4). Inverse associations were also found for the genus level (52, 53), where the association between *Akkermansia* and fasting glucose withstood statistical correction for metabolic disease diagnosis, use of metabolic drugs, as well as sex, age, and lifestyle factors (52) (Table 1, Figure 3). Similarly, several studies found the relation between *A. muciniphila* and blood glucose and insulin to be independent of BMI (45, 47), diabetes diagnosis and treatment (45), as well as sex and age (46, 47, 50) (Supplemental Table 5). In 2 studies, bimodal distributions of *A. muciniphila* were identified, where individuals with the lower *A. muciniphila* abundance had higher glycemic and insulinemic measures (46, 47), including an elevated glucose response after an oral-glucose-tolerance test (46). Another study found that patients with refractory diabetes, defined as a persistent elevation in HbA1c despite glucose-lowering medications, had lower *A. muciniphila* abundance than individuals with type 2 diabetes and lower HbA1c levels (49).

A. muciniphila is a mucin-degrading bacterium known to produce acetate and propionate (54), 2 SCFAs which have been suggested to affect β -cell function and insulin secretion (55–57) (Figure 5). In the study by Dao et al. (46), *A. muciniphila* was correlated with circulating acetate, consistent with the proposed mechanisms. Neither propionate nor butyrate were measured, nor were SCFAs in feces.

F. prausnitzii, *C. leptum* group, *Faecalibacterium*, and Oscillospiraceae

We found consistent evidence for reduced abundances of *F. prausnitzii* (37–42), *C. leptum* group (42, 48, 58, 59), and Oscillospiraceae (45, 60) with elevated insulin concentrations and insulin resistance (Table 2, Figure 4). This included 2 studies

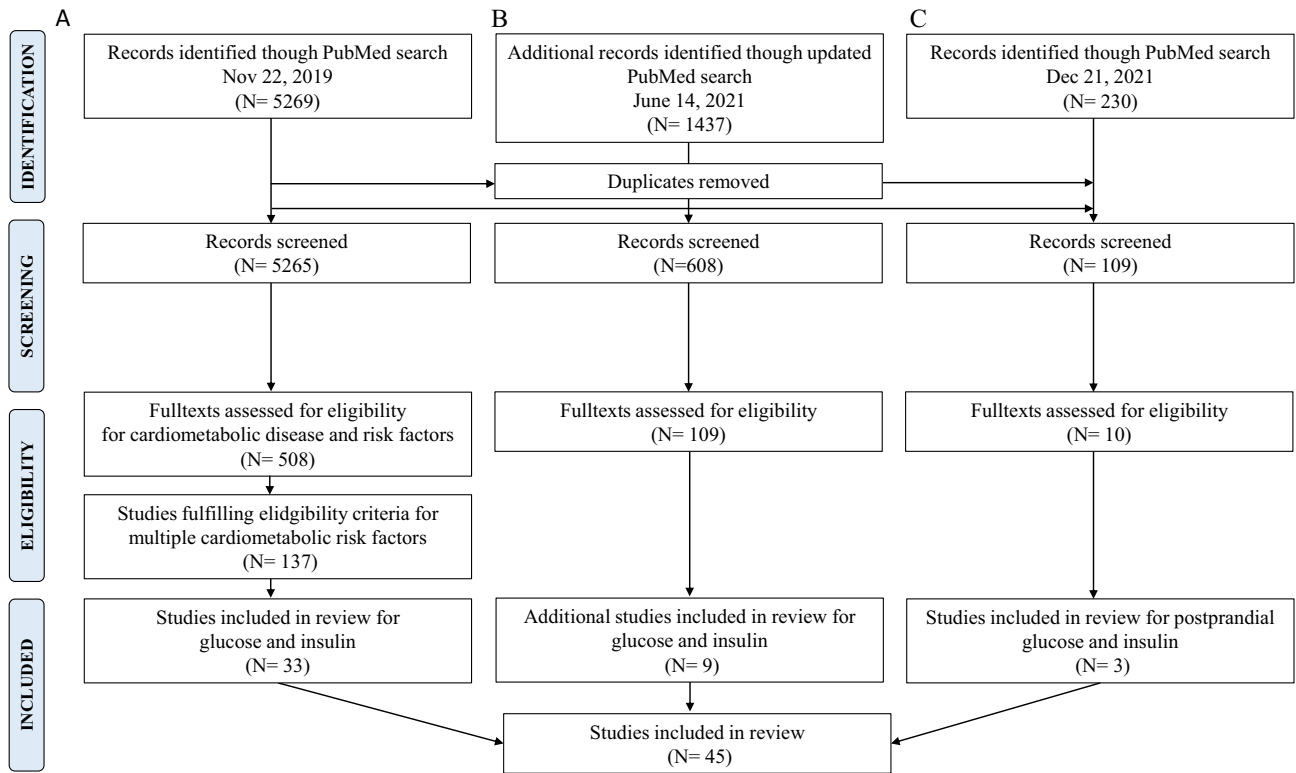


FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram summarizing the process of screening and identification of the literature in the scoping review. (A) Original literature search. (B) Updated literature search specified to capture recent studies reporting on associations with glucose and insulin and differences across glycemetic and insulinemic groups. (C) Literature search specified for postprandial glucose and insulin.

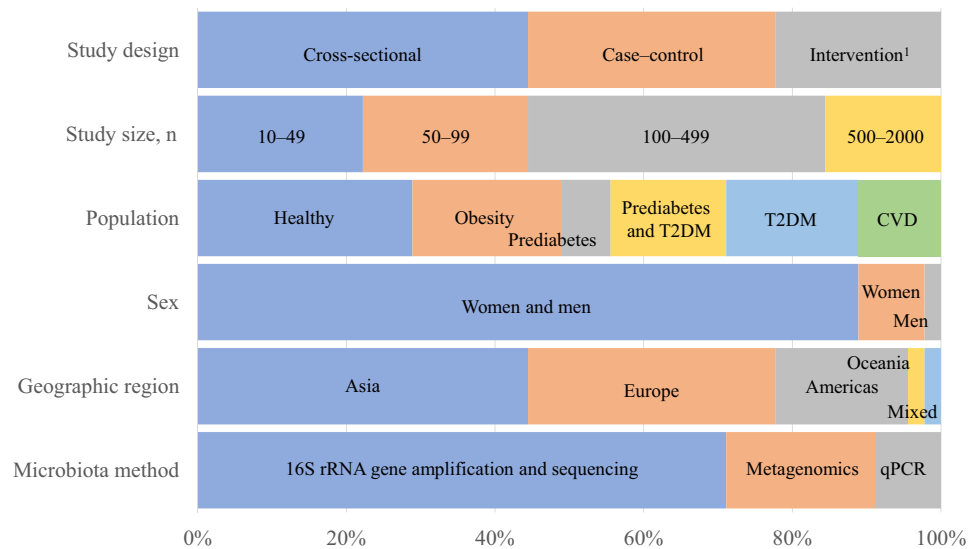


FIGURE 2 Bar plot of main characteristics of reviewed studies ($n = 45$). Data are presented as percentages of studies belonging to the different categories of study design, study size, type of population with regards to metabolic disease and obesity, sex, geographical country of population, and main type of methods measuring the gut microbiota. ¹Only baseline results from intervention studies were included. CVD, cardiovascular disease; rRNA, ribosomal RNA; T2DM, type 2 diabetes mellitus.

TABLE 1 Summary of reported associations between bacteria on different taxonomic levels and glucose-related outcomes¹

Gut microbiota	Glucose ²			SCFAs or enzymes measured	Postprandial glucose
	Unadjusted association	Adjusted for body measures ³	Adjusted for metabolic drugs ⁴		
Phyla					
Bacteroidetes	↓ (48, 88)				
Firmicutes	↓ (48, 60)		↓ (39)	(60)	
	↑ (89)		↑ (39)		
Synergistetes	↑ (90)	↑ (51)	↑ (51)		
Order					
Eubacteriales ⁵		↓ (45)	↓ (41, 45)		
			↑ (39)		
Families					
Christensenellaceae	↓ (73)	↓ (45)	↓ (45)	(73)	
Enterobacteriaceae	↑ (43)	↑ (35)		(35, 43)	↑ (18)
Lachnospiraceae			↓ (39, 45)		
		↑ (34)	↑ (34)	(43)	
Oscillospiraceae ⁶	↓ (43, 67)	↑ (34)	↓ (45)	(43)	
	↑ (35)	↑ (34)	↑ (34)	(35)	
Veillonellaceae	↑ (43)	↑ (34)	↑ (34)	(35)	
		↑ (34)		(43)	
Genera					
<i>Akkermansia</i>	↓ (53)		↓ (52)		
<i>Alistipes</i>	↓ (61, 91)				
<i>Anaerostipes</i>	↑ (73, 92)			(73)	
<i>Bacteroides</i>	↓ (92)	↓ (45)	↓ (45)		
		↑ (34)	↓ (45)		
<i>Blautia</i>	↓ (93)	↑ (34)	↑ (34, 39, 45)		
			↓ (39, 45)		
<i>Clostridium</i>			↑ (39)		
		↑ (34, 39, 78)	↑ (34, 39, 45, 78)		
<i>Dorea</i>	↑ (65, 87)				
<i>Escherichia-Shigella</i>	↓ (61–65)	↓ (34, 39)	↓ (34)		
<i>Faecalibacterium</i>		↑ (34)	↑ (34)		
		↑ (34, 59)	↑ (34, 59)		
<i>Lactobacillus</i>	↑ (53)	↑ (34)	↑ (34)		
<i>Megasphaera</i>	↑ (53, 92)				
<i>Parasutterella</i>	↓ (90, 92)	↑ (34)	↑ (34)		
<i>Prevotella</i>	↓ (62)	↓ (34)	↓ (34)		
		↑ (34)	↑ (34)		
<i>Ruminococcus</i>	↓ (61, 91)	↓ (45)	↓ (45)		
<i>Slackia</i>	↑ (90)	↑ (34)	↑ (34)		
<i>Streptococcus</i>		↑ (34, 45)	↑ (34, 45)		
Species					
<i>Akkermansia muciniphila</i>	↓ (46, 48, 49)	↓ (45, 47)	↓ (45, 47)	(46)	

(Continued)

TABLE 1 (Continued)

Gut microbiota	Glucose ²			SCFAs or enzymes measured	Postprandial glucose
	Unadjusted association	Adjusted for body measures ³	Adjusted for metabolic drugs ⁴		
<i>Bifidobacterium longum</i>	↓ (74, 75)	↓ (36, 39)	↓ (36, 39)	(36)	
<i>Blautia coxcooides</i> group	↓ (83)		↓ (59)	(83)	
<i>Blautia obeum</i>		↓ (36)	↓ (36)	(36)	
		↑ (34)	↑ (34)		
<i>Blautia wexlerae</i>		↑ (34, 36)	↑ (34, 36)	(36)	
<i>Clostridium leptum</i> group ⁷	↓ (42, 48, 61)	↓ (59)	↓ (59)		
<i>Clostridium leptum</i> ⁷	↑ (94)				
<i>Dialister invisus</i>	↓ (40)	↓ (44)	↓ (44)		
<i>Escherichia coli</i>	↑ (42)	↑ (44)	↑ (44)		
<i>Enterocloster bolteae</i>	↑ (75)	↑ (36, 39)	↑ (36, 39)	(36)	
<i>Faecalibacterium prausnitzii</i>	↓ (40, 42)	↓ (36, 44)	↓ (36, 39, 44)	(36)	
	↑ (66)	↑ (34, 45)	↑ (34, 45)		
<i>Haemophilus parainfluenzae</i>	↓ (40)	↓ (44)			↓ (37)
<i>Intestinibacter bartlettii</i>	↓ (75)	↓ (39)	↓ (39)		
<i>Megasphaera elsdenii</i>		↑ (34, 44)	↑ (34, 44)		
[<i>Ruminococcus</i>] <i>gnavus</i>		↑ (36)	↑ (36, 45)	(36)	↑ (37)
<i>Streptococcus salivarius</i>	↑ (75)	↑ (44)			
Diversity					
α Diversity	↓ (35)	↓ (51)	↓ (45, 51)	(35)	
	↑ (73)			(73)	

¹ Associations with postprandial glucose concentrations and remaining glucose outcomes are shown separately and further divided according to whether estimations were unadjusted or accounting for body measures and/or metabolic drugs and whether SCFAs or genes encoding for enzymes in SCFA biosynthesis were analyzed. ↓ and ↑ refer to inverse and direct associations, respectively. HbA1c, glycated hemoglobin.

² Glucose includes the studied outcomes fasting and nonfasting glucose measures, HbA1c, and comparisons between groups of individuals with or without prediabetes.

³ Body measures refers to BMI, body weight, body fat or body fat percentage, waist circumference, or waist-to-hip ratio.

⁴ Metabolic drugs include drugs such as antidiabetic drugs and drugs lowering blood pressure or blood lipids.

⁵ Previously Clostridiales.

⁶ Previously Ruminococcaceae.

⁷ Articles reporting *C. leptum* were investigated for methodology and divided into *C. leptum* when using group-level primers and qPCR and *C. leptum* when based on universal primers, 16S ribosomal RNA gene sequencing, and databases. *C. leptum* group is predominated by the species *F. prausnitzii* and these results were merged with those reported as Clostridium cluster IV (synonym).

TABLE 2 Summary of reported associations between bacteria on different taxonomic levels and insulin-related outcomes¹

Gut microbiota	Insulin ²				Postprandial insulin
	Unadjusted association	Adjusted for body measures ³	Adjusted for metabolic drugs ⁴	SCFAs or enzymes measured	
Phyla					
Bacteroidetes	↓ (48, 89)				
		↑ (60)		(60)	
Firmicutes	↓ (48)	↓ (41, 60)	↓ (39, 41)	(60)	
			↑ (39)		
Proteobacteria		↓ (41)	↓ (41)		
	↑ (89)	↑ (60)		(60)	
Order					
Eubacteriales ⁵			↓ (39, 41)		
			↑ (39)		
Families					
Clostridiaceae		↓ (45, 78, 95)	↓ (45, 78)		
Lachnospiraceae			↓ (39, 41, 45)		
			↑ (41)		
Oscillospiraceae ⁶	↓ (60)		↓ (45)	(60)	
Genera					
<i>Bifidobacterium</i>	↓ (48)	↓ (58)	↓ (58)		
<i>Blautia</i>			↑ (39, 45)		
<i>Clostridium</i>		↓ (78)	↓ (39, 45, 78)		
			↑ (39)		
<i>Prevotella</i>	↑ (48, 87)				
Species					
<i>Akkermansia muciniphila</i>	↓ (46, 48, 50)	↓ (47)	↓ (47)	(46)	
<i>Bacteroides intestinalis</i>	↓ (40)		↓ (41)		
<i>Bifidobacterium longum</i>	↓ (58)	↓ (39)	↓ (39)		
<i>Blautia coccoides</i> group		↓ (58)	↓ (58, 59)		
<i>Clostridium leptum</i> group	↓ (42, 48)	↓ (59)	↓ (58, 59)		
<i>Faecalibacterium prausnitzii</i>	↓ (40, 42)	↓ (41)	↓ (39, 41)		↓ (37, 38)

¹Associations with postprandial insulin concentrations and remaining insulin outcomes are shown separately and further divided according to whether estimations were unadjusted or accounting for body measures and/or metabolic drugs and whether SCFAs or genes encoding for enzymes in SCFA biosynthesis were analyzed. ↓ and ↑ refer to inverse and direct associations, respectively.

²Insulin includes the studied outcomes fasting insulin, HOMA-IR, and measures of insulin resistance/sensitivity and comparisons between groups of individuals with or without insulin resistance.

³Body measures refers to BMI, body weight, body fat or body fat percentage, waist circumference, or waist-to-hip ratio.

⁴Metabolic drugs include drugs such as antidiabetic drugs and drugs lowering blood pressure or blood lipids.

⁵Previously Clostridiales.

⁶Previously Ruminococcaceae.

that reported on postprandial insulin responses and inverse associations with *F. prausnitzii* (37, 38). Several studies had excluded participants taking antidiabetic medications (39, 45, 59) and other metabolic drugs (59) and 1 study found null associations with metformin, a common antidiabetic drug (41) (Supplemental Table 5). There was limited and overall inconclusive evidence for potential bias of overweight and obesity.

Consistent inverse associations were also observed for glucose with the *C. leptum* group (42, 48, 59, 61) and *Faecalibacterium* (39, 61–65), with the exception of 1 study with inconclusive results for *Faecalibacterium* and prediabetes (34) (Table 1, Figure 3). Five studies, which had applied metagenomics sequencing (36, 39, 40, 44) or qPCR (42), showed consistent

inverse associations between *F. prausnitzii* and fasting glucose, HbA1c, and prediabetes. In contrast, 3 studies using 16S rRNA gene amplification and sequencing (with lower specificity for *F. prausnitzii*) found direct associations with fasting glucose and prediabetes (34, 45, 66). Inconsistent results were also found for Oscillospiraceae but could not be attributed to differences in methodology (34, 35, 43, 45, 67) (Supplemental Table 5). There was no conclusive evidence regarding the role of adiposity and metabolic drugs in the associations with glucose for the *C. leptum* group, *F. prausnitzii*, *Faecalibacterium*, or Oscillospiraceae.

None of the studies for *F. prausnitzii*, the *C. leptum* group, Oscillospiraceae, or *Faecalibacterium* had measured butyrate, a

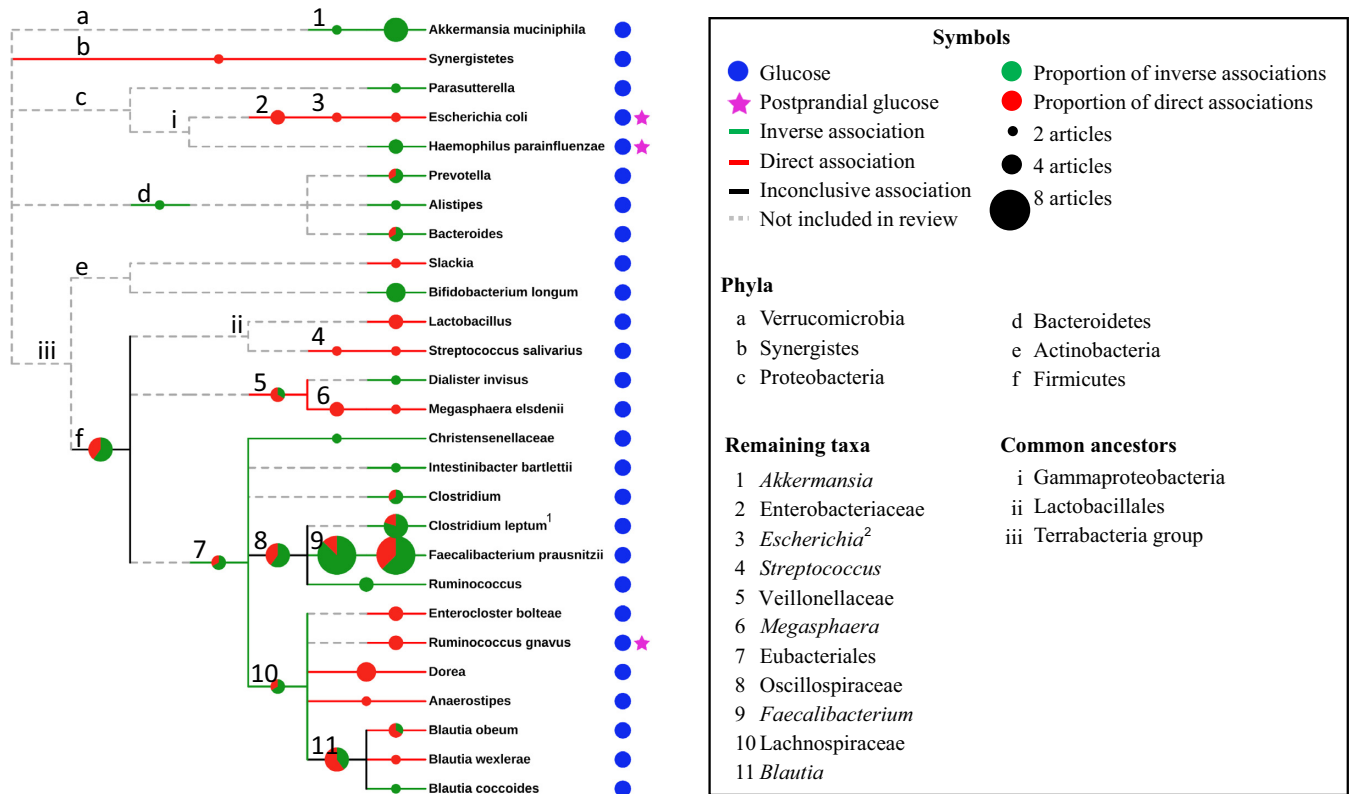


FIGURE 3 Taxonomic trees for fecal bacteria associating with glucose-related outcomes and differences across glycemic groups. The 40 bacterial taxa associating with glucose belonged to 5 phyla and organized into 27 leaves. Meaning of symbols and colors are explained in the accompanying box. Pie charts show the proportion of studies that reported on inverse and direct associations, respectively. The size of the pie chart is proportional to the number of studies and studies that reported on both an inverse and a direct association for any given taxon were counted twice (supporting both the inverse and the direct association). ¹*Clostridium leptum* refers to results both for the *C. leptum* group, where all studies showed inverse associations, and for *C. leptum* with unknown specificity, showing a direct association with insulin. ²*Escherichia* refers to results for *Escherichia-Shigella*.

major fermentation product for these taxa (e.g., after dietary fiber degradation (68)) and an SCFA which has been shown to affect fasting and postprandial glucose metabolism through various mechanisms (23, 57, 69–72) (Figure 5). However, Wu et al. (36) found that the lower abundance of *F. prausnitzii* in individuals with prediabetes was accompanied by a reduction of bacterial genes linked to butyrate biosynthesis. Some Oscillospiraceae taxa produce acetate, and 2 studies found a direct association between Oscillospiraceae and circulating acetate (60, 73). Plasma acetate was furthermore inversely correlated to HbA1c and was lower in individuals with obesity and insulin resistance than in insulin-sensitive controls with obesity (60).

B. longum and *Bifidobacterium*

The abundance of *B. longum* was frequently found to be lower with elevated glucose (36, 39, 74, 75) and insulin measures (39, 58) (Tables 1 and 2, Figures 3 and 4). Several studies reported on relations that were independent of BMI, body fat, age, and sex (36, 39), and dietary intake (39, 58), but not for BMI and dietary intake combined (58) (Supplemental Table 5). Similar results were found on the genus level. *Bifidobacterium* was inversely associated with insulin and insulin

resistance in participants with obesity in 2 studies (48, 58), where 1 of the studies had adjusted for dietary intake and for BMI and excluded participants taking any medications (58) (Table 2, Figure 4). Two studies reporting on *B. longum* (39) and *Bifidobacterium* (48) had excluded participants based on probiotic consumption (e.g., *B. longum*) before enrollment.

Notably, there were inverse associations between baseline *B. longum* and 2-h glucose measures at a 4-y follow-up time point as well as the change in glucose concentrations over time, in a nested case-control study where *B. longum* had correlated with fasting glucose at baseline (75).

Bifidobacteria mainly produce acetate (and formate) during fermentation (76, 77) (Figure 5). No study reporting on *Bifidobacterium* or *B. longum* had measured acetate or other SCFAs.

Dorea

Dorea was consistently and positively associated with glucose measures, possibly independently of metabolic drugs as shown in all 4 studies (34, 39, 45, 78) (Table 1, Figure 3). Fasting glucose was positively correlated with *Dorea* in 3 studies (39,

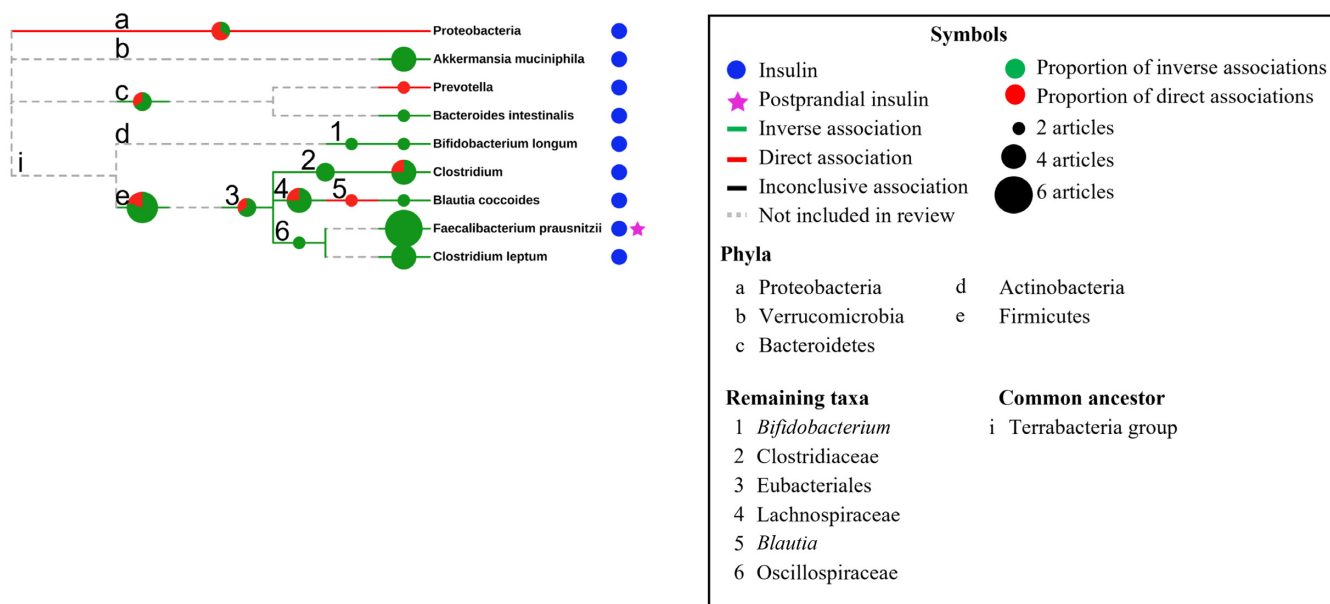


FIGURE 4 Taxonomic trees for fecal bacteria associating with insulin-related outcomes and differences across insulinemic groups. The 17 bacterial taxa associating with insulin belonged to 5 phyla and organized into 9 leaves. Meaning of symbols and colors are explained in the accompanying box. Pie charts show the proportion of studies that reported on inverse and direct associations, respectively. The size of the pie chart is proportional to the number of studies and studies that reported on both an inverse and a direct association for any given taxon were counted twice (supporting both the inverse and the direct association).

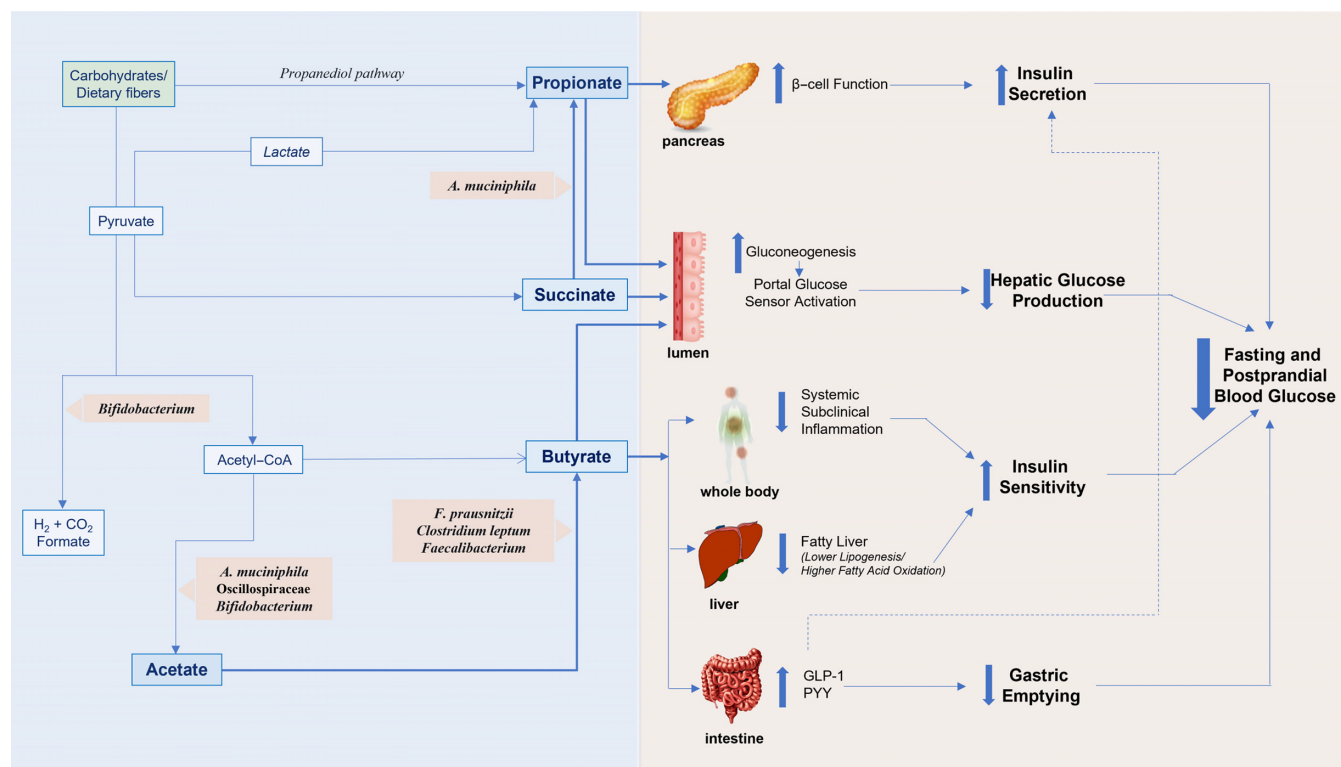


FIGURE 5 Proposed mechanisms of how SCFA-producing bacteria and SCFAs affect fasting and postprandial glucose metabolism in humans in the context of dietary fiber and based on present knowledge. SCFA-producing bacteria included in this review are shown. *A. muciniphila*, *Akkermansia muciniphila*; *F. prausnitzii*, *Faecalibacterium prausnitzii*; GLP-1, glucagon-like peptide-1; PYY, peptide YY.

45, 78), a correlation which remained statistically significant after adjustment for age, body fat, and diet in females with obesity (39), and was not associated with BMI in a population with overweight and obesity (78) (Supplemental Table 5). Two studies showed elevated concentrations in subjects with prediabetes in comparisons with normoglycemic controls, matched or adjusted for age and sex (34, 45) and for waist-to-hip ratio and inflammatory markers (34). In 1 of these studies, *Dorea* was only elevated in Danish but not Indian individuals with prediabetes (34). However, 2 *Dorea* species (*D. formicigenerans* and *D. longicatena*) were elevated in the Indian group of individuals with prediabetes which had comparable weight and waist-to-hip ratio with the normoglycemic controls. Three of the 4 studies included Danish populations (34, 39, 45).

None of the studies measured acetate, one of the main end products of fermentation for *Dorea*.

Discussion

In this scoping review we identified α diversity and 45 taxa, from phyla to species, that were associated with the selected glucose metabolism outcomes. Among these, *A. muciniphila*, *B. longum*, *Faecalibacterium*, the *C. leptum* group, and *F. prausnitzii* were most consistently inversely associated with glucose and/or insulin, whereas *Dorea* was directly associated with glucose. These taxa represent key candidates for future investigations and development of type 2 diabetes prevention strategies. Moreover, there was some evidence to suggest that associations may be independent of body measures, metabolic drugs, and other covariates (e.g., age, sex, and diet), particularly for *A. muciniphila* and *Dorea*, as well as potential mediation by SCFAs for *A. muciniphila* and *F. prausnitzii*.

Our findings should be placed in context with the strengths and limitations of the reviewed literature. Of the 45 eligible studies, the majority were published in the past 5 y, many with moderate to large study populations (100–2000) and mixed-sex study populations. Study design, glucose metabolism outcomes, and the presence of metabolic disease and risk factors varied. There was a lack of metagenomics sequencing, postprandial measures of glucose and insulin, and SCFA analysis; study populations were predominantly Asian or European; and there is a need for procedures accounting for confounding factors. Importantly, evidence from prospective studies and well-controlled intervention trials in this field is warranted to infer causality. Owing to the broad nature of this scoping review and for feasibility purposes, null, rare, or statistically nonsignificant associations were not included, neither were associations for co-occurring bacteria or groups of bacteria sharing functional traits (e.g., butyrate-producing bacteria). For the same reason, although we assessed whether studies had accounted for diet when reporting gut microbiota–glucose metabolism associations, we did not assess response to dietary trials. We regard work on gut microbiota–diet interactions and evidence toward using diet to alter the abundance and activity of specific (key) bacteria as crucial and complementary to the current literature and the present review.

Some microbial taxa belonging to the same lineage had similar relations with glucose metabolism outcomes. This can reflect shared attributes among bacteria within a taxon but also

result from differences in sequencing depth across studies. In other words, associations for taxa at higher taxonomic ranks (including *Akkermansia* and *Faecalibacterium*) may to a large extent reflect associations for 1 or few prominent taxa at lower ranks (e.g., *A. muciniphila* and *F. prausnitzii*). Studying relations at the species level, and also strain and clade level, using metagenomic sequencing is warranted to elucidate relations for gut microbiota with glucose metabolism in humans and to distinguish between similarities and unique characteristics for bacteria within a given taxon. This includes investigating whether *F. prausnitzii* or other bacteria drive the associations for the *C. leptum* group. Metagenomic sequencing can also provide information on bacterial function and metabolic capabilities and thus provide insight on functional gene redundancy independent of taxonomic origin as well as on potential underlying mechanisms. It is also important to acknowledge that methodological steps such as DNA isolation and extraction can affect gut microbiota analysis and contribute to differences in results between studies and that method harmonization is needed (79–82).

SCFA production remains one of the best-characterized metabolic attributes of human gut bacteria and SCFAs are commonly proposed to underlie observed relations between gut microbiota and health outcomes in humans. Despite this, only 5 studies in the current literature reported on SCFAs (43, 46, 60, 73, 83), 2 reported on genes that encode for enzymes involved in SCFA biosynthesis (35, 36), and no study reported on succinate. Yet, taken together, results support the proposed mechanism: direct associations for *A. muciniphila* and Oscillospiraceae with circulating acetate (46, 60, 73), a coinciding reduction of *F. prausnitzii* and bacterial genes related to butyrate production with prediabetes (36), an inverse association between plasma acetate and insulin resistance (60), and inverse associations for total organic acid content, acetate, and propionate with HbA1c. The exception is the direct association between *Dorea* and glucose concentrations and the acetate-producing capabilities of *Dorea*. It is well established that SCFA concentrations measured in feces and blood poorly reflect SCFA production in the gut but are meaningful indicators of the locally and systemically available SCFAs that could exhibit different biological effects (84). Ongoing research is investigating SCFA concentrations, and differences in SCFA production across individuals, after the consumption of different dietary fibers (6, 8, 85) and whether supplementation of butyrate or butyrate-producing bacteria can prevent or delay development of type 2 diabetes (13). There are also investigations into cross-feedings and co-occurrence of bacteria, the flux of SCFAs, and shifts in the gut microbiota metabolism with type 2 diabetes (1, 57). This development will contribute complementary and critical insight to the role of SCFAs in glucose regulation as well as to the complex relations between human gut bacteria and potentially toward novel preventative strategies for diabetes. Importantly, SCFA production may only represent a fraction of the mechanisms through which gut microbiota may affect glucose metabolism and effects may also be mediated by microbial metabolites such as trimethylamine N-oxide (TMAO), indole-3-propionic acid (IPA), imidazole propionate (ImP), and bile acids, and be contingent on diet (86).

Lastly, *Bifidobacterium*, *A. muciniphila*, *Faecalibacterium*, and *F. prausnitzii* have consistently been found at lower

abundances in individuals with prevalent type 2 diabetes than in individuals with normal glucose regulation (12), thus supporting a potential role of these bacteria in contrasting the progression toward type 2 diabetes. The inverse associations between baseline *B. longum* and type 2 diabetes incidence and the change in blood glucose over time (75) are also promising in terms of prevention but require further investigation. Mechanistic studies are required to disentangle the roles of individual bacteria in type 2 diabetes etiology and whether gut bacteria are involved in specific steps of diabetes development. In the present literature we found little support for a gradual shift toward the type 2 diabetic state for taxa reported in this review (36, 41, 44, 51, 53, 75, 87), with the exception of *Akkermansia* (53) and a shift in the overall microbial composition toward impaired glucose tolerance and untreated type 2 diabetes (36). Future studies may also evaluate the potential to use baseline *A. muciniphila* abundance for screening and stratification purposes for type 2 diabetes prevention, based on the bimodal abundance reported (46, 47).

Conclusions

In this scoping review we identified and extensively reviewed 45 original studies and identified *A. muciniphila*, *B. longum*, *Faecalibacterium*, the *C. leptum* group, *F. prausnitzii*, and *Dorea* as key bacteria for future investigation. For some of these bacteria, there was evidence to suggest SCFA mediation as well as associations independent of overweight, obesity, and metabolic drugs, and all, except *Dorea*, have previously been consistently and inversely associated with prevalent type 2 diabetes. Yet, several limitations in the present literature must be addressed in future studies, including an increased application of metagenomic sequencing with harmonized sample preparation procedures, increasing diverse representation in study populations, taking measures to account for confounding factors, and increasing investigations into postprandial glucose metabolism and mediation by SCFAs and other microbial metabolites. In addition, prospective studies, well-controlled intervention trials, and studies investigating the role of diet–gut microbiota interactions are needed to infer causality. Taken together, this will have the potential to bring critical insight into roles of gut microbiota and microbial metabolites in human glucose metabolism and to contribute toward the development of novel prevention strategies for type 2 diabetes, including precision nutrition.

The authors' responsibilities were as follows—MSAP-B, RL, GR, SÅ, and YH: designed the research; MSAP-B, SÅ, YH, GC, and CV: conducted the research; MSAP-B, GC, CV, and JD: analyzed the data; MSAP-B and RL: wrote the paper; RL: had primary responsibility for the final content; and all authors: read and approved the final manuscript.

Data availability

Data described in the article, code book, and analytic code will be made available upon request pending application and all data used in this article are derived from the charted data present in Supplemental Table 5.

References

- Daisley BA, Koenig D, Engelbrecht K, Doney L, Hards K, Al KF, et al. Emerging connections between gut microbiome bioenergetics and chronic metabolic diseases. *Cell Rep* 2021;37(10):110087.
- Fan Y, Pedersen O. Gut microbiota in human metabolic health and disease. *Nat Rev Microbiol* 2021;19(1):55–71.
- Koh A, Bäckhed F. From association to causality: the role of the gut microbiota and its functional products on host metabolism. *Mol Cell* 2020;78(4):584–96.
- Brunkwall L, Orho-Melander M. The gut microbiome as a target for prevention and treatment of hyperglycaemia in type 2 diabetes: from current human evidence to future possibilities. *Diabetologia* 2017;60(6):943–51.
- Zhang X, Cai X, Zheng X. Gut microbiome-oriented therapy for metabolic diseases: challenges and opportunities towards clinical translation. *Trends Pharmacol Sci* 2021;42(12):984–7.
- Rivellese A. Short-chain fatty acids in plasma after intake of fermentable cereal fibres—an extended postprandial study [Internet]. 2022. *Clinicaltrials.gov* identifier: NCT05443828. [Accessed 2022 Jul 6]. Available from: <http://www.clinicaltrials.gov/ct2/show/NCT05443828>.
- Deehan EC, Yang C, Perez-Muñoz ME, Nguyen NK, Cheng CC, Triador L, et al. Precision microbiome modulation with discrete dietary fiber structures directs short-chain fatty acid production. *Cell Host Microbe* 2020;27(3):389–404.e6.
- So D, Whelan K, Rossi M, Morrison M, Holtmann G, Kelly JT, et al. Dietary fiber intervention on gut microbiota composition in healthy adults: a systematic review and meta-analysis. *Am J Clin Nutr* 2018;107(6):965–83.
- Christensen L, Sørensen CV, Wøhlk FU, Kjølbæk L, Astrup A, Sanz Y, et al. Microbial enterotypes beyond genus level: *Bacteroides* species as a predictive biomarker for weight change upon controlled intervention with arabinoxylan oligosaccharides in overweight subjects. *Gut Microbes* 2020;12(1):1847627.
- Saeedi P, Petersohn I, Salpea P, Malanda B, Karuranga S, Unwin N, et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: results from the International Diabetes Federation Diabetes Atlas 9th edition. *Diabetes Res Clin Pract* 2019;157:107843.
- Ge K. The transition of Chinese dietary guidelines and food guide pagoda. *Asia Pac J Clin Nutr* 2011;20(3):439–46.
- Gurung M, Li Z, You H, Rodrigues R, Jump DB, Morgun A, et al. Role of gut microbiota in type 2 diabetes pathophysiology. *EBioMedicine* 2020;51:102590.
- Arora T, Tremaroli V. Therapeutic potential of butyrate for treatment of type 2 diabetes. *Front Endocrinol (Lausanne)* 2021;12:761834.
- Vieira-Silva S, Falony G, Belda E, Nielsen T, Aron-Wisnewsky J, Chakaroun R, et al. Statin therapy is associated with lower prevalence of gut microbiota dysbiosis. *Nature* 2020;581(7808):310–15.
- Wu H, Esteve E, Tremaroli V, Khan MT, Caesar R, Manneras-Holm L, et al. Metformin alters the gut microbiome of individuals with treatment-naïve type 2 diabetes, contributing to the therapeutic effects of the drug. *Nat Med* 2017;23(7):850–8.
- Safari S, Abdoli M, Amini M, Aminorroaya A, Feizi A. A 16-year prospective cohort study to evaluate effects of long-term fluctuations in obesity indices of prediabetics on the incidence of future diabetes. *Sci Rep* 2021;11(1):11635.
- Goossens GH. The metabolic phenotype in obesity: fat mass, body fat distribution, and adipose tissue function. *Obes Facts* 2017;10(3):207–15.
- Zeevi D, Korem T, Zmora N, Israeli D, Rothschild D, Weinberger A, et al. Personalized nutrition by prediction of glycemic responses. *Cell* 2015;163(5):1079–94.
- Berry SE, Valdes AM, Drew DA, Asnicar F, Mazidi M, Wolf J, et al. Human postprandial responses to food and potential for precision nutrition. *Nat Med* 2020;26(6):964–73.
- Hjorth MF, Christensen L, Kjølbæk L, Larsen LH, Roager HM, Kiielerich P, et al. Pretreatment *Prevotella*-to-*Bacteroides* ratio and markers of glucose metabolism as prognostic markers for dietary weight loss maintenance. *Eur J Clin Nutr* 2020;74(2):338–47.
- Korem T, Zeevi D, Zmora N, Weissbrod O, Bar N, Lotan-Pompan M, et al. Bread affects clinical parameters and induces gut microbiome-associated personal glycemic responses. *Cell Metab* 2017;25(6):1243–53.e5.

22. Kovatcheva-Datchary P, Nilsson A, Akrami R, Lee YS, De Vadder F, Arora T, et al. Dietary fiber-induced improvement in glucose metabolism is associated with increased abundance of *Prevotella*. *Cell Metab* 2015;22(6):971–82.
23. De Vadder F, Kovatcheva-Datchary P, Goncalves D, Vinera J, Zitoun C, Duchamp A, et al. Microbiota-generated metabolites promote metabolic benefits via gut-brain neural circuits. *Cell* 2014;156(1–2):84–96.
24. De Vadder F, Kovatcheva-Datchary P, Zitoun C, Duchamp A, Backhed F, Mithieux G. Microbiota-produced succinate improves glucose homeostasis via intestinal gluconeogenesis. *Cell Metab* 2016;24(1):151–7.
25. Yamashita H. Biological function of acetic acid—improvement in obesity and glucose tolerance by acetic acid in type 2 diabetic rats. *Crit Rev Food Sci Nutr* 2016;56(sup1):S171–5.
26. Richardson WS, Wilson MC, Nishikawa J, Hayward RS. The well-built clinical question: a key to evidence-based decisions. *ACP J Club* 1995;123(3):A12–13.
27. Miller SA, Forrest JL. Enhancing your practice through evidence-based decision making: PICO, learning how to ask good questions. *J Evid Based Dent Pract* 2001;1(2):136–41.
28. Otten R, Vries RD, Schoonmade L. Amsterdam Efficient Deduplication (AED) method. 2019. Available from: <https://doi.org/10.5281/ZENODO.3582927>.
29. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan—a web and mobile app for systematic reviews. *Syst Rev* 2016;5(1):210.
30. Schoch CL, Ciufo S, Domrachev M, Hotton CL, Kannan S, Khovanskaya R, et al. NCBI Taxonomy: a comprehensive update on curation, resources and tools. *Database* 2020;baaa062.
31. Lay C, Dore J, Rigottier-Gois L. Separation of bacteria of the *Clostridium leptum* subgroup from the human colonic microbiota by fluorescence-activated cell sorting or group-specific PCR using 16S rRNA gene oligonucleotides. *FEMS Microbiol Ecol* 2007;60(3):513–20.
32. PhyloT v2: a phylogenetic tree generator, based on NCBI or GTD taxonomy [Internet]. 2022. [cited 14 February, 2022]. Ivica Letunic, Heidelberg, Germany. Available from: <https://phylot.biobyte.de/>.
33. Letunic I, Bork P. Interactive Tree Of Life (iTOL) v5: an online tool for phylogenetic tree display and annotation. *Nucleic Acids Res* 2021;49(W1):W293–6.
34. Pinna NK, Anjana RM, Saxena S, Dutta A, Gnanaprakash V, Rameshkumar G, et al. Trans-ethnic gut microbial signatures of prediabetic subjects from India and Denmark. *Genome Med* 2021;13(1):36.
35. Fei N, Bernabé BP, Lie L, Baghdan D, Bedu-Addo K, Plange-Rhule J, et al. The human microbiota is associated with cardiometabolic risk across the epidemiologic transition. *PLoS One* 2019;14(7):e0215262.
36. Wu H, Tremaroli V, Schmidt C, Lundqvist A, Olsson LM, Krämer M, et al. The gut microbiota in prediabetes and diabetes: a population-based cross-sectional study. *Cell Metab* 2020;32(3):379–90.e3.
37. Asnicar F, Berry SE, Valdes AM, Nguyen LH, Piccinno G, Drew DA, et al. Microbiome connections with host metabolism and habitual diet from 1,098 deeply phenotyped individuals. *Nat Med* 2021;27(2):321–32.
38. Xu J, Lian F, Zhao L, Zhao Y, Chen X, Zhang X, et al. Structural modulation of gut microbiota during alleviation of type 2 diabetes with a Chinese herbal formula. *ISME J* 2015;9(3):552–62.
39. Brahe LK, Le Chatelier E, Prifti E, Pons N, Kennedy S, Hansen T, et al. Specific gut microbiota features and metabolic markers in postmenopausal women with obesity. *Nutr Diabetes* 2015;5(6):e159.
40. Liu R, Hong J, Xu X, Feng Q, Zhang D, Gu Y, et al. Gut microbiome and serum metabolome alterations in obesity and after weight-loss intervention. *Nat Med* 2017;23(7):859–68.
41. Karlsson FH, Tremaroli V, Nookaew I, Bergström G, Behre CJ, Fagerberg B, et al. Gut metagenome in European women with normal, impaired and diabetic glucose control. *Nature* 2013;498(7452):99–103.
42. Furet J-P, Kong L-C, Tap J, Poitou C, Basdevant A, Bouillot J-L, et al. Differential adaptation of human gut microbiota to bariatric surgery-induced weight loss: links with metabolic and low-grade inflammation markers. *Diabetes* 2010;59(12):3049–57.
43. Gonai M, Shigehisa A, Kigawa I, Kurasaki K, Chonan O, Matsuki T, et al. Galacto-oligosaccharides ameliorate dysbiotic *Bifidobacteriaceae* decline in Japanese patients with type 2 diabetes. *Benef Microbes* 2017;8(5):705–16.
44. Zhong H, Ren H, Lu Y, Fang C, Hou G, Yang Z, et al. Distinct gut metagenomics and metaproteomics signatures in prediabetics and treatment-naïve type 2 diabetics. *EBioMedicine* 2019;47:373–83.
45. Allin KH, Tremaroli V, Caesar R, Jensen BAH, Damaard MTF, Bahl MI, et al. Aberrant intestinal microbiota in individuals with prediabetes. *Diabetologia* 2018;61(4):810–20.
46. Dao MC, Everard A, Aron-Wisnewsky J, Sokolovska N, Prifti E, Verger EO, et al. *Akkermansia muciniphila* and improved metabolic health during a dietary intervention in obesity: relationship with gut microbiome richness and ecology. *Gut* 2016;65(3):426–36.
47. Mitsou EK, Detopoulou M, Kakali A, Fragopoulou E, Nomikos T, Antonopoulou S, et al. Mining possible associations of faecal *A. muciniphila* colonisation patterns with host adiposity and cardiometabolic markers in an adult population. *Benef Microbes* 2019;10(7):741–9.
48. Tabasi M, Eybpoosh S, Sadeghpour Heravi F, Siadat SD, Mousavian G, Elyasinia F, et al. Gut microbiota and serum biomarker analyses in obese patients diagnosed with diabetes and hypothyroid disorder. *Metab Syndr Relat Disord* 2021;19(3):144–51.
49. Shih C-T, Yeh Y-T, Lin C-C, Yang L-Y, Chiang C-P. *Akkermansia muciniphila* is negatively correlated with hemoglobin A1c in refractory diabetics. *Microorganisms* 2020;8(9):1360.
50. Yassour M, Lim MY, Yun HS, Tickle TL, Sung J, Song Y-M, et al. Sub-clinical detection of gut microbial biomarkers of obesity and type 2 diabetes. *Genome Med* 2016;8(1):17.
51. Nuli R, Cai J, Kadeer A, Zhang Y, Mohemaiti P. Integrative analysis toward different glucose tolerance-related gut microbiota and diet. *Front Endocrinol* 2019;10:295.
52. Zhong X, Harrington JM, Millar SR, Perry IJ, O’Toole PW, Phillips CM. Gut microbiota associations with metabolic health and obesity status in older adults. *Nutrients* 2020;12(8):2364.
53. Gaïke AH, Paul D, Bhute S, Dhote DP, Pande P, Upadhyaya S, 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(2):e00578–19.
54. Derrien M, Vaughan EE, Plugge CM, de Vos WM. *Akkermansia muciniphila* gen. nov., sp. nov., a human intestinal mucin-degrading bacterium. *Int J Syst Evol Microbiol* 2004;54(5):1469–76.
55. Chambers ES, Byrne CS, Morrison DJ, Murphy KG, Preston T, Tedford C, et al. Dietary supplementation with inulin-propionate ester or inulin improves insulin sensitivity in adults with overweight and obesity with distinct effects on the gut microbiota, plasma metabolome and systemic inflammatory responses: a randomised cross-over trial. *Gut* 2019;68(8):1430–8.
56. Tilg H, Cani PD, Mayer EA. Gut microbiome and liver diseases. *Gut* 2016;65(12):2035–44.
57. Blaak EE, Canfora EE, Theis S, Frost G, Groen AK, Mithieux G, et al. Short chain fatty acids in human gut and metabolic health. *Benef Microbes* 2020;11(5):411–55.
58. Teixeira TFS, Grzeškowiak ŁM, Salminen S, Laitinen K, Bressan J, do Carmo Gouveia Peluzio M. Faecal levels of *Bifidobacterium* and *Clostridium coccoïdes* but not plasma lipopolysaccharide are inversely related to insulin and HOMA index in women. *Clin Nutr* 2013;32(6):1017–22.
59. 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: 51–6.
60. Moreno-Navarrete JM, Serino M, Blasco-Baque V, Azalbert V, Barton RH, Cardellini M, et al. Gut microbiota interacts with markers of adipose tissue browning, insulin action and plasma acetate in morbid obesity. *Mol Nutr Food Res* 2018;62(3):201700721.
61. Zeng Q, Li D, He Y, Li Y, Yang Z, Zhao X, et al. Discrepant gut microbiota markers for the classification of obesity-related metabolic abnormalities. *Sci Rep* 2019;9(1):13424.
62. Tao S, Li L, Li L, Liu Y, Ren Q, Shi M, et al. Understanding the gut–kidney axis among biopsy-proven diabetic nephropathy, type 2 diabetes mellitus and healthy controls: an analysis of the gut microbiota composition. *Acta Diabetol* 2019;56(5):581–92.
63. Aron-Wisnewsky J, Prifti E, Belda E, Ichou F, Kayser BD, Dao MC, et al. Major microbiota dysbiosis in severe obesity: fate after bariatric surgery. *Gut* 2019;68(1):70–82.
64. Salamon D, Sroka-Oleksiak A, Kapusta P, Szopa M, Mrozińska S, Ludwig-Słomczyńska AH, et al. Characteristics of gut microbiota in adult patients with type 1 and type 2 diabetes based on next-generation

- sequencing of the 16S rRNA gene fragment. *Pol Arch Intern Med* 2018;128(6):336–43.
65. Gao R, Zhu C, Li H, Yin M, Pan C, Huang L, et al. Dysbiosis signatures of gut microbiota along the sequence from healthy, young patients to those with overweight and obesity. *Obesity (Silver Spring)* 2018;26(2):351–61.
 66. Feng J, Tang H, Li M, Pang X, Wang L, Zhang M, et al. The abundance of fecal *Faecalibacterium prausnitzii* in relation to obesity and gender in Chinese adults. *Arch Microbiol* 2014;196(1):73–7.
 67. Leite AZ, Rodrigues NC, Gonzaga MI, Paiolo JCC, de Souza CA, Stefanutto NAV, et al. Detection of increased plasma interleukin-6 levels and prevalence of *Prevotella copri* and *Bacteroides vulgatus* in the feces of type 2 diabetes patients. *Front Immunol* 2017;8:1107.
 68. Louis P, Flint HJ. Diversity, metabolism and microbial ecology of butyrate-producing bacteria from the human large intestine. *FEMS Microbiol Lett* 2009;294(1):1–8.
 69. Chen J, Vitetta L. Gut microbiota metabolites in NAFLD pathogenesis and therapeutic implications. *Int J Mol Sci* 2020;21(15):5214.
 70. Bouter K, Bakker GJ, Levin E, Hartstra AV, Kootte RS, Udayappan SD, et al. Differential metabolic effects of oral butyrate treatment in lean versus metabolic syndrome subjects. *Clin Transl Gastroenterol* 2018;9(5):e155.
 71. Canfora EE, Jocken JW, Blaak EE. Short-chain fatty acids in control of body weight and insulin sensitivity. *Nat Rev Endocrinol* 2015;11(10):577–91.
 72. Zhao L, Zhang F, Ding X, Wu G, Lam Y, Wang X, et al. Gut bacteria selectively promoted by dietary fibers alleviate type 2 diabetes. *Science* 2018;359(6380):1151–6.
 73. Org E, Blum Y, Kasela S, Mehrabian M, Kuusisto J, Kangas AJ, et al. Relationships between gut microbiota, plasma metabolites, and metabolic syndrome traits in the METSIM cohort. *Genome Biol* 2017;18(1):70.
 74. Haro C, Garcia-Carpintero S, Alcalá-Díaz JF, Gomez-Delgado F, Delgado-Lista J, Perez-Martínez P, et al. The gut microbial community in metabolic syndrome patients is modified by diet. *J Nutr Biochem* 2016;27:27–31.
 75. Wang L, Yu X, Xu X, Ming J, Wang Z, Gao B, et al. The fecal microbiota is already altered in normoglycemic individuals who go on to have type 2 diabetes. *Front Cell Infect Microbiol* 2021;11:598672.
 76. Tsukuda N, Yahagi K, Hara T, Watanabe Y, Matsumoto H, Mori H, et al. Key bacterial taxa and metabolic pathways affecting gut short-chain fatty acid profiles in early life. *ISME J* 2021;15(9):2574–90.
 77. Moens F, Verce M, De Vuyst L. Lactate- and acetate-based cross-feeding interactions between selected strains of lactobacilli, bifidobacteria and colon bacteria in the presence of inulin-type fructans. *Int J Food Microbiol* 2017;241:225–36.
 78. Naderpoor N, Mousa A, Gomez-Arango LF, Barrett HL, Dekker Nitert M, de Courten B. Faecal microbiota are related to insulin sensitivity and secretion in overweight or obese adults. *J Clin Med* 2019;8(4):452.
 79. Fiedorova K, Radvansky M, Némecova E, Grombirikova H, Bosak J, Cernochova M, et al. The impact of DNA extraction methods on stool bacterial and fungal microbiota community recovery. *Front Microbiol* 2019;10:821.
 80. Greathouse KL, Sinha R, Vogtmann E. DNA extraction for human microbiome studies: the issue of standardization. *Genome Biol* 2019;20(1):212.
 81. Lim MY, Song E-J, Kim SH, Lee J, Nam Y-D. Comparison of DNA extraction methods for human gut microbial community profiling. *Syst Appl Microbiol* 2018;41(2):151–7.
 82. Yang F, Sun J, Luo H, Ren H, Zhou H, Lin Y, et al. Assessment of fecal DNA extraction protocols for metagenomic studies. *Gigascience* 2020;9(7):giaa071.
 83. Yamashiro K, Tanaka R, Urabe T, Ueno Y, Yamashiro Y, Nomoto K, et al. Gut dysbiosis is associated with metabolism and systemic inflammation in patients with ischemic stroke. *PLoS One* 2017;12(2):e0171521.
 84. Müller M, González Hernández MA, Goossens GH, Reijnders D, Holst JJ, Jocken JWE, et al. Circulating but not faecal short-chain fatty acids are related to insulin sensitivity, lipolysis and GLP-1 concentrations in humans. *Sci Rep* 2019;9(1):12515.
 85. Amalia R, Noer ER, Muniroh M, Afifah DN, Kumoro AC, Pramono A. The effect of fibre intervention on serum and faecal short-chain fatty acids in human with overweight or obesity: a systematic review of human intervention studies. *J Biomed Transl Res* 2022;8(1):38–44.
 86. Zhu T, Goodarzi MO. Metabolites linking the gut microbiome with risk for type 2 diabetes. *Curr Nutr Rep* 2020;9(2):83–93.
 87. Diener C, Reyes-Escogido ML, Jimenez-Ceja LM, Matus M, Gomez-Navarro CM, Chu ND, et al. Progressive shifts in the gut microbiome reflect prediabetes and diabetes development in a treatment-naive Mexican cohort. *Front Endocrinol* 2020;11:602326.
 88. Emoto T, Yamashita T, Sasaki N, Hirota Y, Hayashi T, So A, et al. Analysis of gut microbiota in coronary artery disease patients: a possible link between gut microbiota and coronary artery disease. *J Atheroscler Thromb* 2016;23(8):908–21.
 89. Sanchez-Alcoholado L, Castellano-Castillo D, Jordán-Martínez L, Moreno-Indias I, Cardila-Cruz P, Elena D, et al. Role of gut microbiota on cardio-metabolic parameters and immunity in coronary artery disease patients with and without type-2 diabetes mellitus. *Front Microbiol* 2017;8:1936.
 90. Yang J, Summanen PH, Henning SM, Hsu M, Lam H, Huang J, et al. Xylooligosaccharide supplementation alters gut bacteria in both healthy and prediabetic adults: a pilot study. *Front Physiol* 2015;6:216.
 91. Li N, Wang X, Sun C, Wu X, Lu M, Si Y, et al. Change of intestinal microbiota in cerebral ischemic stroke patients. *BMC Microbiol* 2019;19(1):191.
 92. Li H, Liu B, Song J, An Z, Zeng X, Li J, et al. 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(10):399.
 93. Inoue R, Ohue-Kitano R, Tsukahara T, Tanaka M, Masuda S, Inoue T, et al. Prediction of functional profiles of gut microbiota from 16S rRNA metagenomic data provides a more robust evaluation of gut dysbiosis occurring in Japanese type 2 diabetic patients. *J Clin Biochem Nutr* 2017;61(3):217–21.
 94. Zupancic ML, Cantarel BL, Liu Z, Drabek EF, Ryan KA, Cirimotich S, et al. Analysis of the gut microbiota in the Old Order Amish and its relation to the metabolic syndrome. *PLoS One* 2012;7(8):e43052.
 95. Zhou W, Sailani MR, Contrepois K, Zhou Y, Ahadi S, Leopold SR, et al. Longitudinal multi-omics of host–microbe dynamics in prediabetes. *Nature* 2019;569(7758):663–71.