MICROBIOTA

Gut bacteria selectively promoted by dietary fibers alleviate type 2 diabetes

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The gut microbiota benefits humans via short-chain fatty acid (SCFA) production from carbohydrate fermentation, and deficiency in SCFA production is associated with type 2 diabetes mellitus (T2DM). We conducted a randomized clinical study of specifically designed isoenergetic diets, together with fecal shotgun metagenomics, to show that a select group of SCFA-producing strains was promoted by dietary fibers and that most other potential producers were either diminished or unchanged in patients with T2DM. When the fiber-promoted SCFA producers were present in greater diversity and abundance, participants had better improvement in hemoglobin A1c levels, partly via increased glucagon-like peptide-1 production. Promotion of these positive responders diminished producers of metabolically detrimental compounds such as indole and hydrogen sulfide. Targeted restoration of these SCFA producers may present a novel ecological approach for managing T2DM.

The gut microbiota is a complex microbial ecosystem, and maintaining a mutualistic relationship with it is critical for human health (*1*). A notable example of such a relationship is the production of short-chain fatty acids (SCFAs) through bacterial fermentation of carbohydrates: The human host diet provides nondigestible carbohydrates to support bacterial growth, and in return, the bacteria generate SCFAs that provide an energy substrate to colonocytes, mitigate inflammation, and regulate satiety, etc. (*2*, *3*). Deficiency in SCFA production has been associated with diseases, including type 2 diabetes mellitus (T2DM) (*4*–*7*). In clinical trials, increased intake of nondigestible but fermentable carbohydrates (dietary fibers) alleviated the disease phenotypes of T2DM but was associated with vastly different treatment responses (*8*–*10*). Hundreds of gut bacterial species across many taxa share the genes for fermenting carbohydrates into SCFAs (*11*). Strains of the same SCFA-producing species also show different responses to increased availability of dietary fibers (*12*, *13*). To improve the clinical efficacy of dietary fiber interventions, it is critical to understand how members of the gut ecosystem respond as individual strains as well as how they interact with one another as functional groups when exposed to increased carbohydrates as a new environmental resource. In this study, we used exposure to a large amount of diverse fibers from dietary sources to perturb the gut ecosystem. We then applied a strain-level, microbiome-wide association approach to characterize the dynamics of the gut microbiota and its impact on glucose homeostasis in patients with T2DM. This strategy has led to the identification of a specific group of SCFA producers that alleviate T2DM by increasing SCFA production. This increased SCFA production restores a mutualistic relationship with the human host and diminishes producers of metabolically detrimental compounds.

We randomized patients with clinically diagnosed T2DM to receive either the usual care [patient education and dietary recommendations based on the 2013 Chinese Diabetes Society guidelines for T2DM (*14*)] as the control group (U group; n = 16 patients) or a high-fiber diet composed of whole grains, traditional Chinese medicinal foods, and prebiotics (the WTP diet; see materials and methods and table S1 in the supplementary materials) as the treatment group (W group; n = 27 patients) in an open-label, parallel-group study designated the GUT2D study (fig. S1). Both groups received acarbose (an amylase inhibitor) as the standardized medication. Acarbose transforms part of the starch in the diet into a "fiber" by reducing its digestion and making it more available as fermentable carbohydrate in the colon (*15*). By design, the W group had a significantly higher intake of dietary fibers with diverse structures than the U group, but the daily energy and macronutrient intakes were similar across groups (table S2). The level of hemoglobin A1c (HbA1c), our primary outcome measure, decreased significantly from baseline in a time-dependent manner in both groups; from day 28 onward, however, there was a greater reduction in the W group (Fig. 1A). The proportion of participants who achieved adequate glycemic control (HbA1c < 7%) at the end of the intervention was also significantly higher in the W group (89% versus 50% in the U group) (Fig. 1B). There was a temporal difference in fasting blood glucose levels—only the W group achieved a significant reduction by day 28, although at the end of the intervention there was no difference between groups (Fig. 1C)—and a similar trend was observed for postprandial glucose (Fig. 1D). The W group also showed greater reduction in body weight and better blood lipid profiles than the U group (table S3). Our clinical data indicate that increased availability of nondigestible but fermentable carbohydrates is sufficient to induce clinically relevant metabolic improvements in patients with T2DM, as demonstrated by the response to increasing undigested starch with acarbose in the U group. We observed more significant and faster improvement in clinical outcomes in the W group when more diverse carbohydrates were provided as added fibers in the diet.

To determine causality between the gut microbiota and fiber-induced improvement of host glycemic control, we transplanted the pre- and postintervention gut microbiota from the same participants into germ-free C57BL/6J mice. The mice that received pre- or postintervention microbiota showed more similarity in gut microbiota to their donors than to each other (fig. S2). Mice transplanted with the postintervention microbiota from either the W or U group showed better metabolic health parameters than those with the preintervention microbiota from the corresponding group. Mice that received postintervention microbiota from the W group had the lowest fasting and postprandial blood glucose levels among all gnotobiotic mice (Fig. 1E and fig. S3), a result that mirrored the better metabolic outcomes in participants of the W group than in those of the U group. The transferable effects of our treatments via microbial transplantation provide evidence for a causative contribution of the gut microbiota, modulated by dietary fibers, to improved glucose homeostasis in patients with T2DM.

Next we determined how the increased dietary fibers altered the global structure of the gut microbiota. Shotgun metagenomic sequencing was performed on 172 fecal samples collected at four time points (days 0, 28, 56, and 84) (table S4), which led to a catalog of 4,893,833 nonredundant microbial genes. Both groups had a notable reduction in gene richness (the number of genes identified per sample) from day 0 to day 28, along with significant clinical improvements, with no further changes afterward (Fig. 1F). Our

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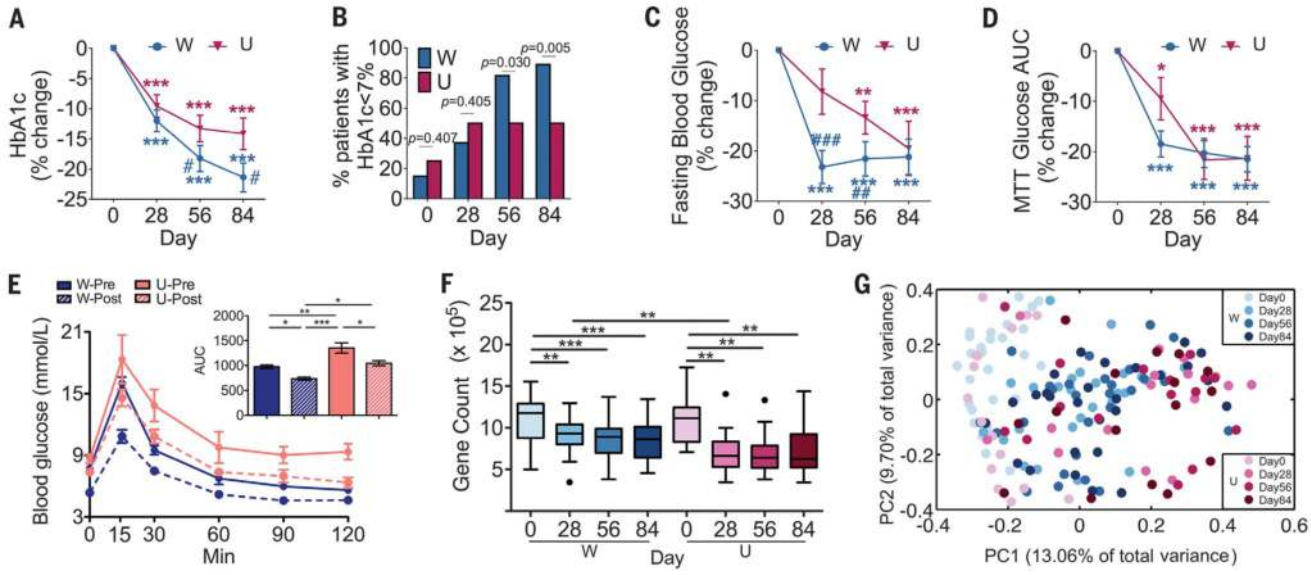

Fig. 1. A high-fiber diet alters the gut microbiota and improves glucose homeostasis in participants with T2DM. Changes in (**A**) HbA1c, (**B**) the percentage of participants with adequate glycemic control, (**C**) fasting blood glucose, and (**D**) the glucose area under the curve (AUC) in a meal tolerance test (MTT) for participants during the intervention are shown. Data are presented as percent changes from day 0 (± SE). A two-way repeated-measures analysis of variance (ANOVA) with Tukey's post hoc test was used for intra- and intergroup comparisons. *P < 0.05, **P < 0.01, and ***P < 0.001 for comparison with the day 0 value for the same group; #P < 0.05, ##P < 0.01, and ###P < 0.001 for comparison with the U group value at the same time point. n = 27 patients in the W group and 16 patients in the U group for all analyses except the MTT in (D), where n = 15 patients in the U group. (**E**) Oral glucose tolerance test (2 weeks after transplantation) of mice receiving transplanted pre- and postintervention human gut microbiota. The transplant material was derived from representative donors, one from the W group and one from the U group, both before (Pre; day 0) and after (Post; day 84) the intervention. n = 5 mice receiving transplanted material in each of the W-Pre, W-Post, and U-Pre groups, and n = 4 mice receiving transplanted material in the U-Post group. *P < 0.05, **P < 0.01, and ***P < 0.001 by one-way ANOVA with Tukey's post hoc test for intra- and intergroup comparisons. (**F**) Gut microbiota diversity (gene richness). The change in gene counts was adjusted to 31 million mapped reads per sample. Boxes show the medians and the interquartile ranges (IQRs), the whiskers denote the lowest and highest values that were within 1.5 times the IQR from the first and third quartiles, and outliers are shown as individual points. Wilcoxon matched-pair signed-rank tests (two tailed) were used to analyze each pairwise comparison within each group. A Mann-Whitney test was used to analyze differences between the W and U groups at the same time point. **P < 0.01 and ***P < 0.001 [adjusted by the Benjamini-Hochberg procedure (*35*)]. (**G**) Overall gut microbial structure. Principal coordinates analysis was performed on the basis of the Bray-Curtis distance for 422 bacterial genomes [co-abundance gene groups (CAGs)]. PC1, principal coordinate 1; PC2, principal coordinate 2.

data challenged the current notion that greater overall diversity implies better health (*16*). However, gene richness tended to be higher in the W group than in the U group after day 28, and this trend was associated with better clinical outcomes in the W group (Fig. 1F). Individual genes were binned into co-abundance gene groups (CAGs) with a canopy-based algorithm (*17*). A total of 422 CAGs containing >700 genes were inferred to represent the genomes of ecologically distinct bacterial populations (fig. S4). On the basis of Bray-Curtis distances from the 422 CAGs, the overall structure of the gut microbiota showed significant alteration from day 0 to day 28 in both groups, with no further changes afterward (Fig. 1G and fig. S5). At the end of the intervention (day 84), significant differences between the W and U groups reflected a distinct modulatory effect of the high-fiber intervention on the gut microbiota. A Procrustes analysis with all bioclinical variables combined and the 422 bacterial CAGs showed that compositional changes in the gut microbiota were associated with improvements in clinical outcomes (fig. S6).

We then conducted a gene-centric analysis of the metagenomic data sets to explore the functional changes in the gut microbiota that might contribute to improved host clinical outcomes (fig. S7). Both the WTP diet and acarbose increased the availability of fermentable carbohydrates, which led us to focus on genes for carbohydrate utilization (*18*). A total of 192,236 carbohydrate-active enzyme (CAZy)–encoding genes were identified and grouped into 315 CAZy gene families. The richness of CAZy genes followed a pattern similar to that of the total gene richness; that is, both decreased compared with the baseline but remained higher in the W group than in the U group after day 28 (fig. S8). We observed significant segregation between the pre- and all postintervention samples on the basis of the CAZy family profile (Fig. 2A and fig. S8). Among the CAZy genes for metabolizing different carbohydrate substrates, those contributing to starch and inulin degradation were significantly enriched, whereas those related to the use of pectin and mucin were depleted in both the W and U groups (fig. S8). There were intervention-specific effects on the capacity for carbohydrate metabolism (fig. S8); for instance, enrichment of genes encoding cohesin and dockerin as part of a multienzyme complex for plant cell wall degradation was observed only in the W group. Our data suggest that it is not global gene richness per se but the abundance distribution of specific functional genes such as those for CAZys that is more relevant for identifying health-related changes in the gut microbiota.

Pursuing our central hypothesis that SCFAs from increased intake of dietary fibers are one of the key mediators of the observed effects of the microbiota on host glucose homeostasis, we specifically examined the genes involved in the production of these metabolites. We used the abundance of genes that encode key enzymes to indicate the enrichment of production pathways—e.g., *fhs* for acetate and *but* for butyrate formation (*19*). In both W and U groups, the production pathways for acetic acid were significantly enriched (Fig. 2B). Four distinct pathways contribute to butyric acid production (*20*), and the most abundant of these (with *but* as the terminal gene) in the human gut increased significantly only in the W group after the intervention (Fig. 2C and fig. S9). Genes encoding other SCFA production pathways were unchanged or significantly reduced (fig. S9). The shifts in the abundance of genes encoding the SCFA production pathways

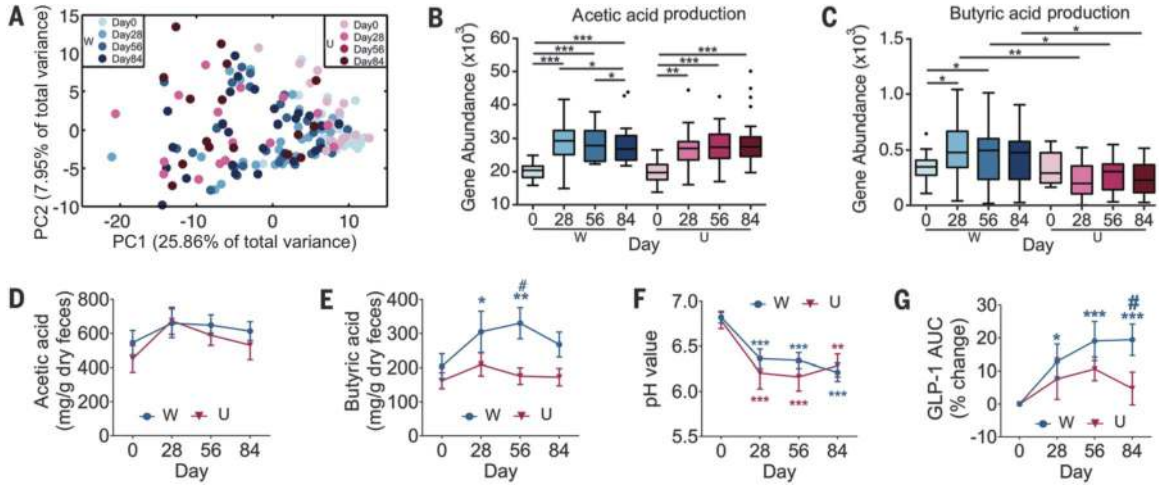

Fig. 2. A high-fiber diet alters gut bacterial fermentation of carbohydrates in participants with T2DM. (**A**) Changes in the abundance of carbohydrate-active enzyme (CAZy) family genes. Principal components analysis was conducted on the abundance (log transformed) of all 192,236 CAZy genes. PC1, principal component 1; PC2, principal component 2. (**B** and **C**) Changes in the abundance of genes that encode the key enzymes in (B) acetic acid production (formate-tetrahydrofolate ligase) and (C) butyric acid production [butyryl–coenzyme A (butyryl-CoA):acetate CoA transferase, represented by *but*]. Boxes, whiskers, and outliers denote values as described for Fig. 1F. Wilcoxon matched-pair signed-rank tests (two tailed) were used to analyze each pairwise comparison within each group. A Mann-Whitney test was used to analyze differences between the W and U groups at the same time point. $*P < 0.05$, $**P < 0.01$, and $***P < 0.001$ [adjusted by the Benjamini-Hochberg procedure (*35*)]. (**D** and **E**) Changes in fecal concentrations of (D) acetic acid and (E) butyric acid. SCFAs were measured using gas chromatography, and amounts are expressed as milligrams per gram of dry feces (± SE). (**F** and **G**) Changes in (F) fecal water pH and (G) the glucagon-like peptide-1 (GLP-1) AUC in a meal tolerance test (± SE). For (D) to (G), two-way repeated-measures ANOVA with Tukey's post hoc test was used for intra- and intergroup comparisons. $*P < 0.05$, $**P < 0.01$, and $***P < 0.001$ for comparison with day 0; $\#P < 0.05$ for comparison with the U group at the same time point. $n = 27$ patients in the W group and 16 patients in the U group.

were largely consistent with the measured fecal SCFA content (Fig. 2, D and E, and fig. S10). Acetic acid concentrations were essentially similar in both groups throughout the study, increasing to day 28 and decreasing afterward to levels marginally higher than baseline (Fig. 2D), whereas butyric acid concentrations increased significantly only in the W group (Fig. 2E). Both groups had a significant reduction in fecal pH at day 28 (6.36 ± 0.11 versus 6.82 ± 0.07 at baseline for the W group and 6.21 ± 0.18 versus 6.79 ± 0.09 at baseline for the U group), and the pH remained at similar levels for the rest of the study (Fig. 2F). This pH change indicates increased SCFA production and an acidified gut lumen. Acetate and butyrate have been shown to improve glucose homeostasis by inducing gut production of glucagon-like peptide-1 (GLP-1) and peptide YY (PYY), which in turn stimulate insulin secretion (*21*–*24*). The trend of increased fecal acetate and butyrate concentrations in the W group coincided with a significantly greater postprandial GLP-1 area under the curve (AUC) (Fig. 2G) and a higher level of fasting PYY (fig. S10) for the W group than for the U group at the end of the intervention. This finding, together with the trend for the high-fiber intake to increase postprandial insulin (table S3), supports the notion of an SCFA-driven effect on the gut hormone-insulin secretion cascade that improves glucose regulation.

The different responses of SCFA-related functional genes to the high-fiber intervention prompted us to ask how individual bacteria that harbor the SCFA-producing genes respond to the increased availability of fermentable carbohydrates. From 180 bacterial CAGs that were shared by >20% of our samples, we assembled 154 high-quality draft genomes of prevalent bacteria (57% ± 11% total reads per sample were mapped) (table S5) that met at least five of the six reference genome criteria from the NIH Human Microbiome Project (www.hmpdacc.org/reference_genomes/finishing.php). These high-quality draft genomes of prevalent gut bacteria allowed us to examine compositional changes at the strain level, with functional annotation of each strain. We annotated 141 genomes as SCFA producers, as they harbored at least one of the key genes for SCFA production (table S6). Among those genomes, 79 belonged to bacterial strains that were nonresponders to the high-fiber intervention (i.e., they remained unchanged during the study); 47 belonged to negative responders (i.e., they were significantly reduced); and 15 belonged to positive responders (i.e., they were significantly promoted by the high-fiber diet) (table S6 and fig. S11). The enrichment of these 15 positive responders mostly peaked at day 28 (Fig. 3A) and remained stable afterward, consistent with the pattern we observed in the overall gut microbiota structure (Fig. 1F). These 15 strains are from three different phyla; some (e.g., Lachnospiraceae bacterium CAG0409 and Clostridiales bacterium CAG0023) are poorly characterized, whereas others are from well-known beneficial species. The response, however, was strain specific: only one of the six strains of *Faecalibacterium prausnitzii* was promoted (table S6). In the W group, all 15 positive responders harbored genes for acetate production, and 5 also possessed the capacity for butyrate production (Fig. 3B). In the U group, only 3 acetate producers among the 15 positive responders were promoted (Fig. 3C), which was likely a response to acarbose-induced starch delivery to the colon (*15*). These genome-level data were consistent with the enrichment of the acetic acid production pathways and a trend toward higher fecal acetate in both groups (Fig. 2, B and D). However, an effect of the high-fiber diet on promoting the butyrate production pathway and inducing butyrate production was observed only in the W group (Fig. 2, C and E). The 15 positive responders to the increased availability of diverse fermentable carbohydrates are the major active producers for SCFA production in the context of high-fiber intervention for T2DM. They are most likely the main drivers of the fiber-induced increase in SCFAs that contributes to improved host metabolic outcomes.

We then explored the relationships among these 15 positive responders and other members of the gut ecosystem. In the W group, correlation analysis revealed that each of the 15 positive responders had at least one significant inverse correlation with the negative responders (Fig. 3B and table S7). Similarly, the positive and negative responders in the U group were inversely correlated (Fig. 3C and table S7). Higher genetic capacity for using starch, inulin, and arabinoxylan (fig. S12); more efficient energy and SCFA production from the same amount of fermentable substrates; and greater tolerance to a low

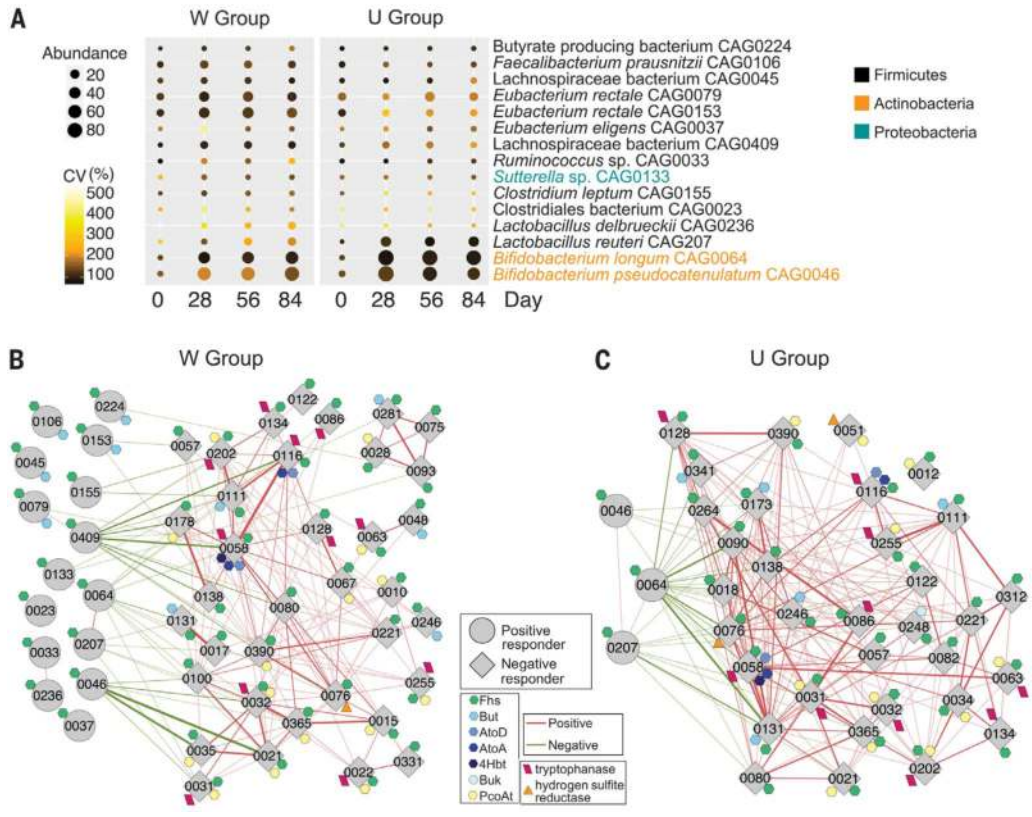

Fig. 3. A high-fiber diet selectively promotes a group of SCFA producers as the major active producers. (**A**) Time-course changes in the abundance of the active producers. The sizes and colors of the circles indicate the average abundance and the coefficient of variance (CV) of the abundance of the strains, respectively. Network plots highlight correlations between positive and negative responders at all time points in (**B**) the W group and (**C**) the U group. The correlation coefficients between CAGs were calculated using the method described by Bland and Altman (*36*). Lines between nodes represent correlations between the connected nodes, with linewidth indicating the correlation magnitude. For clarity, only lines corresponding to correlations with magnitudes of >0.4 were drawn. Fhs, formate-tetrahydrofolate ligase; But, butyryl-CoA:acetate CoA transferase; AtoA, acetoacetate CoA transferase alpha subunits; AtoD, acetoacetate CoA transferase beta subunits; 4Hbt, butyryl-CoA:4-hydroxybutyrate CoA transferase; Buk, butyrate kinase; PcoAt, propionate CoA-transferase/propionyl-CoA:succinate-CoA transferase.

gut luminal pH may explain why these 15 positive responders have a competitive edge over other potential SCFA producers (*25*, *26*). A well-known example is *Bifidobacterium* spp., which, via their "bifid shunt" pathway, are able to produce more adenosine triphosphate and acetate with a given amount of carbohydrates (*25*). For the negative responders, a preference for using animal carbohydrates and a lower tolerance for an acidified gut environment may partially explain why they were outcompeted in response to the high-fiber diet. For example, >20% of CAZy genes in *Bacteroides* spp. are associated with mucin metabolism (fig. S12), and many of these bacteria are known to be less tolerant to lower pH (*26*). Some negative responders also harbor genes that encode tryptophanase or hydrogen sulfite reductase, which are involved in producing metabolically detrimental indole and hydrogen sulfide, respectively (Fig. 3, B and C). The physiological relevance of the decline of these bacteria is supported by reduced gene abundance in the indole and hydrogen sulfide production pathways and reduced fecal amounts of these metabolites (fig. S13). Such changes may contribute to improved host glucose homeostasis, given the known inhibitory effects of these metabolites on GLP-1 and/or PYY production (*27*–*29*). Our data thus support a possible role for these positive responders in structuring a healthier gut ecosystem via production of SCFAs, which modify the gut environment to inhibit the detrimental bacteria, from carbohydrate fermentation. When these SCFA producers are maintained at a certain population level, their metabolic activities create environmental conditions—e.g., lower gut luminal pH, higher concentration of butyrate, and a stronger "competitive exclusion" effect (*26*, *30*, *31*)—that inhibit pathogenic or detrimental gut bacteria and support optimal host health (*26*).

In regard to the relationship with host disease phenotypes, seven positive responders in the W group showed at least one significant correlation with clinical parameters (Fig. 4A). Lachnospiraceae bacterium CAG0409 showed negative correlations with 13 clinical parameters in the W group. However, this bacterium was a nonresponder to acarbose and showed no correlations with any clinical parameters in the U group. The acetate-producing *Bifidobacterium pseudocatenulatum* was one of the most significantly promoted SCFA producers in this study. Inoculation with *B. pseudocatenulatum* strain C95 significantly reduced weight gain, body fat, fasting glucose, and insulin resistance; improved the postprandial glycemic response; and increased the cecum acetate content in mice with high-fat diet–induced obesity (Fig. 4B and fig. S14). In a separate gnotobiotic mouse cohort that received the baseline gut microbiota from a participant in the W group, a similar effect of *B. pseudocatenulatum* C95 inoculation in lowering the fasting blood glucose level was observed (fig. S15). To further understand how the positive responders affect host metabolic health as a group, we derived an active SCFA producer (ASP) index based on the abundance and diversity [Heip evenness (*32*)] of the 15 high-fiber–promoted SCFA producers (fig. S16). The ASP index was higher for the W group throughout the study, mirroring better clinical outcomes, and followed similar temporal trajectories for the W and U groups (Fig. 4C); that is, it increased from baseline and plateaued from day 28 onward despite continued decrease in HbA1c over the course of the intervention (Fig. 1A). The ASP index was negatively correlated with HbA1c when the data points at baseline and the end of the intervention were analyzed together (Fig. 4D). This relationship between the ASP index and HbA1c was also observed in another independent trial (designated QIDONG) in which a T2DM cohort received a similar high-fiber intervention (table S8 and fig. S17). These findings confirm the physiological importance of this group of SCFA producers in T2DM, at least in the context of largely similar regimens of fermentable carbohydrate supplementation. The ASP index reached a plateau at day 28 and remained unchanged throughout the rest of the intervention. When plotting the ASP index at baseline and day 28 with HbA1c at baseline and day 84, we observed a significant negative correlation similar to that observed with day 84 as the end point for the ASP index, indicating that changes in this group of bacteria at an early time point (day 28) may be informative for later (day 84) treatment outcomes (Fig. 4E).

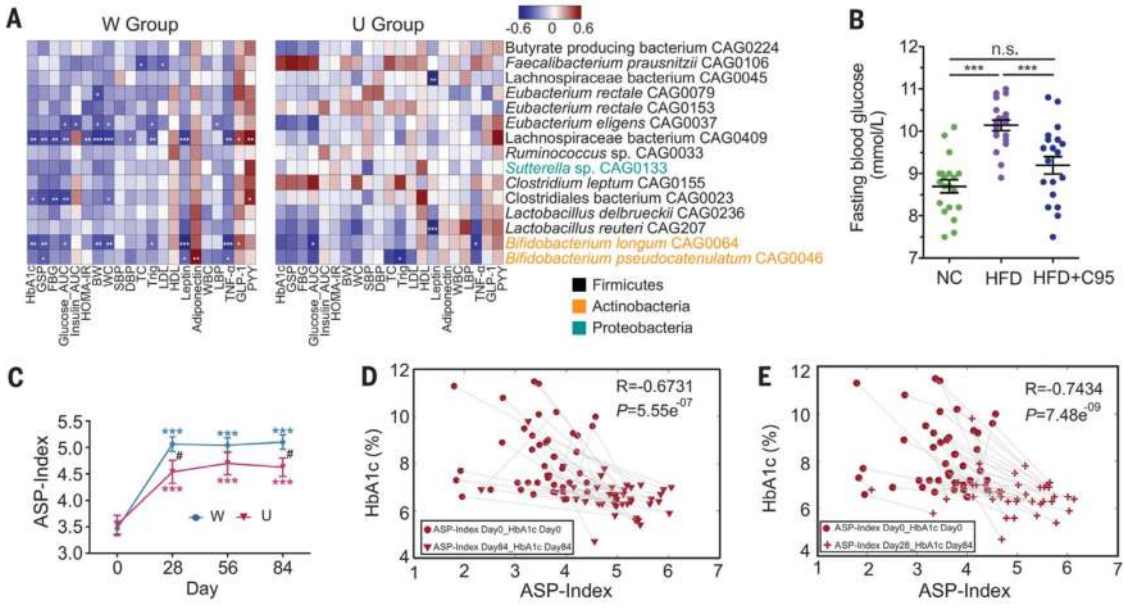

Fig. 4. The group of active producers for SCFA production correlates with metabolic outcomes in participants with T2DM. (**A**) In the heat map, asterisks denote correlations between the abundance of individual active SCFA producers and clinical outcomes. GSP, glycated serum protein; FBG, fasting blood glucose; HOMA-IR, (fasting glucose level × fasting insulin level)/22.5; BW, body weight; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; Trig, triglycerides; LDL, low-density lipoprotein; HDL, high-density lipoprotein; WBC, white blood cell count; LBP, lipopolysaccharide-binding protein; TNF-α, tumor necrosis factor–α. $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$. (**B**) *B. pseudocatenulatum* C95 alleviates high-fat diet–induced dysregulation of glucose homeostasis in mice. Data are presented as the means ± SEM (n = 19 to 20 mice for each group). NC, normal chow diet; HFD, high-fat diet; HFD+C95, high-fat diet with *B. pseudocatenulatum* C95. Data were analyzed using one-way ANOVA followed by Tukey's post hoc test. $^{***}P < 0.001$; n.s., not significant. (**C**) Time-course changes in the ASP index $\left[\ln\left(\text{Heipevenness} \times 10^{10} \times \sum_{i=1}^{15} A_i\right)\right]$, where A_i is the abundance of active SCFA producer i. (**D**) Correlation between the ASP index (day 0 and day 84) and HbA1c (day 0 and day 84). n = 43 patients. R, correlation coefficient. (**E**) Correlation between the ASP index (day 0 and day 28) and HbA1c (day 0 and day 84). n = 43 patients. The correlation coefficients in (A), (D), and (E) were calculated using the method described by Bland and Altman (*36*).

The bloom of the positive responders preceded the physiologically relevant reduction in HbA1c. Such temporal difference, i.e., the gut microbiota quickly responding and reaching a plateau while the host metabolism "played catch-up" with new inputs from the gut ecosystem, not only implies a causative relationship between fiber-induced changes in gut microbiota and improvement of host metabolic health but also provides a critical time window early in the intervention that may inform the eventual effectiveness of microbiome-targeted dietary interventions.

In this study, we identified a group of acetate- and butyrate-producing bacterial strains that were selectively promoted by increased availability of diverse fermentable carbohydrates in the form of dietary fibers. These positive responders are likely the key players for maintaining the mutualistic relationship between the gut microbiota and the human host; promoting this active group of SCFA producers not only enhanced a beneficial function but also maintained a gut environment that keeps detrimental bacteria at bay.

Despite the increased availability of fermentable carbohydrates of diverse physicochemical structures, only a small number of bacteria with the genetic capacity for producing SCFAs were able to take advantage of this new resource and become the dominant positive responders. Such a group of species that "exploit the same class of environmental resources in a similar way" may be considered a "guild" in ecology (*33*). Members of a guild do not necessarily share taxonomic similarity, but they co-occur when adapting to the changing environment. In our case, the 15 positive responders are from three different phyla, but they act as a guild to augment deficient SCFA production from the gut ecosystem by responding to increased fermentable carbohydrate availability in similar ways. When they are considered as a functional group, the abundance and evenness of this guild of SCFA producers correlate with host clinical outcomes. Such guild-based analysis offers a more ecologically relevant way to reduce the dimensionality of microbiome data sets than the conventional taxon-based analysis and facilitates the identification of functionally important members of gut microbiota in human health and disease.

Our study suggests that chronic diseases such as T2DM may be a consequence of the loss of or deficiency in a beneficial function(s), such as SCFA production from carbohydrate fermentation, in the gut ecosystem. In ecological terms, the production of SCFAs from carbohydrate fermentation, which is needed to maintain human health, can be considered an "ecosystem service" provided by the gut microbiota to human hosts (*34*). Restoring or enhancing the lost or deficient function by reestablishing the functionally active ecological populations as ecosystem service providers (ESPs) is the key to a healthier microbiota, which can help alleviate disease phenotypes. Targeted promotion of the active SCFA producers as ESPs via personalized nutrition may present a novel ecological approach for manipulating the gut microbiota to manage T2DM and potentially other dysbiosis-related diseases.

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SUPPLEMENTARY MATERIALS

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Gut bacteria selectively promoted by dietary fibers alleviate type 2 diabetes

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