

**Supplementary Table 1.** Summary of randomized controlled trials (RCTs) conducted in Asia evaluating the effects of dietary interventions on gut microbiota composition and metabolic health outcomes.

Author(s), Year, Country	Study Design and Population	Dietary Exposure	Microbiota Outcomes	Metabolic Health Outcomes	Key Findings	Study Limitations
Chen et al., 2023, China (9)	Randomized, open-label, parallel-group clinical trial; 17 adults with T2DM	8-week high-fiber diet (whole grains, prebiotics, traditional Chinese medicinal foods) vs. standard diet	Increased abundance of <i>Lactobacillus</i> , <i>Bifidobacterium</i> , <i>Akkermansia</i> , <i>Bacteroides</i> , <i>Ruminococcus</i> , <i>Blautia</i> ; decreased <i>Klebsiella</i> , <i>Desulfovibrio</i> , <i>Proteobacteria</i> ; increased richness and diversity	Improved glucose homeostasis (lower HbA1c, FBG); better lipid profiles (lower TC, TG, LDL-C, higher HDL-C); decreased inflammatory markers (IL-1b, IL-6, MCP-1, TNF-a); improved mood (lower HAMA, HAMD scores)	High-fiber diet enhanced gut microbiota composition and diversity, improved metabolic markers, reduced systemic inflammation, and alleviated depression/anxiety symptoms	Small sample size, open-label design, short intervention duration, lack of long-term follow-up
Feng et al., 2022, China (10)	Randomized, double-blind, placebo-controlled clinical trial; 90 adults with T2D	1.5 g of white common bean extract (WCBE) with a-amylase inhibitor activity taken before meals vs. placebo (maltodextrin) for 4 months	Enrichment of SCFA-producers: <i>Bifidobacterium</i> , <i>Faecalibacterium</i> , <i>Anaerostipes</i> , <i>Adlercreutzia</i> ; decrease in opportunistic pathogens: <i>Klebsiella</i> , <i>Cronobacter</i> , <i>Citrobacter</i> , <i>Weissella</i>	Significant reduction in HbA1c, improved postprandial glucose, steady HOMA-IR, improved HDL-C, and GGT; alleviation of diabetic vasculopathy and peripheral neuropathy (TCSS, baPWV, SNCV)	WCBE improved glycemic control and diabetic complications via gut microbiota modulation and enzymatic inhibition; potential prebiotic anti-diabetic agent	Small sample size, short intervention, no SCFA measurements, limited mechanistic insights, used 16S rRNA instead of metagenomics
Fu et al., 2025, China (11)	Series of nutritional n-of-1 trials; 30 young adults (22-34 years); cross-over HC and LC diets over 72 days; validated in 1219 middle-aged adults	High-carbohydrate (65-75%E) vs. low-carbohydrate (15-25%E) diets; isocaloric with 15%E from protein	Intra- and inter-individual personalized gut microbiota dynamics; 67 species responsive to HC, 83 to LC; creation of carb-sensitivity score from 10 key species	Under HC: higher PC3 scores correlated with worse MPG, MAGE, and TAR; score validated to correlate with HbA1c and fasting glucose in habitual HC diet group	HC diet effects on glycemic sensitivity modulated by personal gut microbiota; carb-sensitivity score predicts glycemic control; supports personalized dietary recommendations	Short trial duration, only healthy young adults in n-of-1 trials, complex gut-microbiota-diet interactions, observational validation cohort
Guo et al., 2021, China (12)	Randomized clinical trial: 39 adults with metabolic syndrome (30-50 years)	8-week 2-day intermittent fasting (75% energy restriction on two nonconsecutive days/week) vs. control diet	Altered gut microbial composition (↑ <i>Roseburia</i> , <i>Ruminococcaceae</i> ; ↓ <i>Acidobacteria</i> bacterium); increased SCFAs; decreased LPS; shifts in carbohydrate metabolism genes	↓ weight, BMI, fat mass, insulin, HOMA-IR, TGs, leptin, MDA; ↑ adiponectin, total nitrate; ↓ sCD40L, ADMA; no change in TMAO	2-day IF improved cardiometabolic risk factors and gut microbiota profiles; enhanced SCFA production and endothelial function; beneficial microbial functional shifts	Small sample size, short intervention, no mechanistic inference, limited to specific age and region
Huang et al., 2022, China (13)	Randomized, double-blind, placebo-controlled trial; 136 adults on atypical antipsychotics for schizophrenia or bipolar disorder	12-week supplementation with probiotics ( <i>Lactobacillus</i> , <i>Bifidobacterium</i> , <i>Enterococcus</i> ) and dietary fiber vs. probiotics only, fiber only, or placebo	Increased α-diversity and species richness; ↑ <i>Bacteroidetes</i> , ↓ <i>Firmicutes</i> ; ↑ <i>Bacteroides</i> <i>thetaiotaomicron</i> , <i>B. uniformis</i> , <i>Parabacteroides</i> <i>goldsteinii</i> ; associated with metabolic benefits	↓ weight, BMI, insulin, insulin resistance index (IRI), and cholesterol; probiotics+fiber group had -2.36 kg weight change vs. +2.63 kg in placebo	Probiotics and fiber combination reversed antipsychotic-induced weight gain and improved metabolic markers; synergy stronger than individual components	Short duration, no long-term follow-up, regional limitation, small stool sample for microbiota analysis, self-reported behaviors

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Rustanti et al., 2022, Indonesia (14)	Randomized, double-blind, placebo-controlled trial; 40 T2D women (aged 20-50); 11-week intervention	1 g/day skim milk powder containing 10 <sup>10</sup> CFU/g L. plantarum Dad-13 vs. skim milk placebo	↑ L. plantarum in probiotic group (qPCR); no change in Bifidobacterium, Prevotella, SCFA, or alpha/beta diversity; some genus-level shifts (↑ Faecalibacterium, Collinsella, Succinivibrio)	↓ HbA1c in the probiotic group; no change in fasting blood sugar or total cholesterol; ↑ defecation frequency; no change in weight or blood pressure	L. plantarum Dad-13 reduced HbA1c and modulated specific gut bacteria (e.g., Faecalibacterium) despite no effect on SCFA or diversity; beneficial correlations observed with microbiota and inflammation	Small sample, short duration, incomplete blood sample data due to COVID-19, modest dietary control, no long-term follow-up
Kavyani et al., 2021, Iran (15)	Randomized, double-blind, placebo-controlled clinical trial; 44 NAFLD patients; 12-week intervention	20g/day Camelina sativa oil (CSO) + 10g/day resistant dextrin vs. 20g/day CSO + maltodextrin; all on -500 kcal/day diet	Modulation inferred through reduction in metabolic endotoxemia (LPS), enhancement of antioxidant markers (SOD, TAC); no direct microbiota sequencing data	↓ insulin, HOMA-IR, hs-CRP, LPS endotoxin, cortisol, GHQ, DASS scores; ↑ TAC and SOD; no effect on FPG, QUICKI, uric acid, catalase, 8-iso-PGF2α	CSO and resistant dextrin co-supplementation improved metabolic, oxidative, and mental health biomarkers in NAFLD patients; supports targeting gut-liver-brain axis	No gut microbiota composition or SCFA data; no arms for individual components; short duration; regional cohort
Roshanravan et al., 2017, Iran (16)	Randomized, double-blind, placebo-controlled trial; 60 adults with T2D; 45-day intervention	Group A: 600 mg/day sodium butyrate; Group B: 10 g/day inulin; Group C: combination; Group D: placebo	Inferred effects; expected ↑ Bifidobacterium, F. prausnitzii, Akkermansia via SCFA enhancement; mechanisms include GPR41/43 activation	↓ FBS and waist-hip ratio in Group C; ↓ waist circumference in Groups B and C; ↑ GLP-1 in Groups A and C vs placebo; no significant lipid changes	Combined inulin + butyrate improved GLP-1 levels, FBS, and anthropometric measures; supports synergy in metabolic control in T2DM	Short duration, small sample size, no direct SCFA or endotoxin measurement, non-significant intergroup glycemia differences
Roshanravan et al., 2017, Iran (16)	Randomized, double-blind, placebo-controlled trial; 60 overweight/obese adults with T2D	Group A: 600 mg/day sodium butyrate; Group B: 10 g/day inulin; Group C: both; Group D: placebo; 45-day intervention	↑ A. muciniphila abundance in Groups A and B; non-significant ↑ in Group C; inferred effects via 16S rRNA qPCR	↓ TNF-α mRNA, hs-CRP, MDA, and diastolic BP in Groups A, B, C; systolic BP unchanged; no SCFA or endotoxin data	Inulin and butyrate enhanced A. muciniphila and reduced inflammation and oxidative stress; supported Ang II pathway modulation	No SCFA or endotoxin data; modest sample; short duration; results need validation in larger and longer trials
Salamat S et al., 2024, Iran (17)	Randomized, double-blind, placebo-controlled trial; 96 obese adults; 12-week intervention	Group A: vitamin D; Group B: multi-strain probiotic (B. lactis, B. longum, L. acidophilus, L. reuteri, L. fermentum); Group C: both; Group D: placebo	↑ Lactobacillus, Bifidobacterium, Firmicutes; ↓ Proteobacteria and Bacteroidetes; more pronounced changes in combined group	↓ weight, BMI, WC, insulin, HOMA-IR, TG, CRP; ↑ HDL-C and QUICKI; strongest effects in the combined group	Combined vitamin D and probiotics supplementation synergistically improved anthropometric, glycemic, lipid, and inflammatory markers	No SCFA data, no microbiota diversity measures, reliance on 16S qPCR, short intervention
Reshef et al., 2024, Israel (18)	Randomized, double-blind, placebo-controlled pilot trial; 19 adults with NAFLD and metabolic syndrome	16 g/day inulin-type fructans (ITFs) vs. isocaloric maltodextrin placebo for 12 weeks; stable weight maintained	↑ Bifidobacterium abundance in a prebiotic group; no significant change in alpha diversity or other microbial taxa	No significant changes in liver fat content (H1MRS), liver enzymes, metabolic markers (e.g., glucose, insulin, HOMA-IR), or inflammatory markers (CRP, FGF-19, LPS-BP)	Prebiotics increased Bifidobacterium but did not improve liver fat or metabolic/inflammatory markers without weight loss	Small sample size, pilot design, short duration, no change in lifestyle, single prebiotic type tested

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Goto et al., 2022, Japan (19)	Randomized, double-blind, controlled cross-over trial; 19 Japanese adults	4-week barley (22g with 138g multi-grain rice) vs. control (150g multi-grain rice) with a 4-week washout	Increased Anaerostipes, Blautia, and Agathobacter; no significant SCFA level changes; no Prevotella/Bacteroides correlation with glucose tolerance	Improvement in glucose tolerance in those with impaired baseline; barley moderated glucose tolerance towards a healthier state	Barley improved glucose tolerance in subjects with initially poor glycemic control; Anaerostipes increase consistently correlated with glucose tolerance improvement	Small sample, some control fiber overlap, short duration, limited SCFA metabolite resolution, 16S rRNA limitations
Kanazawa et al., 2021, Japan (20)	Randomized, double-blind, placebo-controlled trial; 88 obese adults with T2D; 24-week intervention	Daily synbiotic (LcS, BbrY, and 7.5g GOS) vs. control; intervention dose was 3.0 g probiotic powder + 7.5 g GOS	↑ Bifidobacterium adolescentis, B. pseudocatenulatum, total lactobacilli; ↑ Actinobacteriota; ↓ Bacteroidota, Fusobacteriota, Proteobacteria; ↑ acetic and butyric acids	No significant difference in IL-6, hs-CRP, LBP, glucose, HbA1c, BMI, or lipid levels between groups	Synbiotic supplementation enhanced gut microbial profiles and SCFA levels but did not significantly impact inflammation or glycemic control in obese T2DM patients	Short-term intervention, regional population, and changes in microbial composition not mirrored by systemic metabolic outcomes
Chaiyasut et al., 2021, Thailand (21)	Randomized, double-blind, placebo-controlled clinical trial; 72 Thai obese adults (36 synbiotic, 36 placebo)	12-week supplementation with synbiotic (L. paracasei, B. longum, B. breve, inulin, fructooligosaccharide) vs. placebo	Significant increase in SCFAs (butyric, propionic, acetic, lactic acids); reduced lactulose, QA, indole; improved lactulose/mannitol ratio	Reduced body weight, BMI, body fat, waist circumference, LDL, IL-6, IL-1β, TNF-α, LPS, zonulin, hsCRP, IgA; improved HDL-C	Synbiotic supplementation improved obesity-related parameters and inflammation markers more effectively than placebo	Short duration; limited generalizability; lacked long-term follow-up; no direct microbiota diversity analysis
Chaiyasut et al., 2023, Thailand (22)	Randomized, double-blind, placebo-controlled clinical trial; 40 T2D (20 probiotic, 20 placebo)	12-week supplementation with Bifidobacterium breve (50 × 10 <sup>9</sup> CFU/day) vs. placebo (corn starch)	Significant reductions in Streptococcus, Butyricoccus, and Eubacterium hallii; increased diversity metrics (Simpson evenness); no significant beta-diversity changes	Reduced body weight, body fat, fasting blood sugar (FBS), and HbA1c in the probiotic group; improved HDL and LDL	B. breve supplementation helped prevent the worsening of metabolic parameters and improved microbiota composition in T2DM patients	Small sample size, single strain used, no dietary control, short study duration, limited metagenomic data
Bellikci-Koyu et al., 2019, Turkey (23)	Parallel-group, randomized, controlled study; 22 adults with metabolic syndrome (12 kefir, 10 control)	180 mL/day kefir vs. unfermented milk for 12 weeks	Significant increase in Actinobacteria in the kefir group; no significant change in Bacteroidetes, Proteobacteria, or Verrucomicrobia; no overall changes in diversity	Reduction in fasting insulin, HOMA-IR, TNF-α, IFN-γ, systolic and diastolic blood pressure; effects not significantly different from control	Kefir had modest favorable effects on metabolic parameters and increased Actinobacteria but no significant microbiota shifts compared to control	Small sample size, short duration, no significant between-group differences, limited microbiota changes, lack of SCFA analysis

**Supplementary Table 2.** Overview of RCTs conducted in Europe assessing the effects of dietary interventions on gut microbiota and metabolic health outcomes

Author(s), Year, Country	Study Design and Population	Dietary Exposure	Microbiota Outcomes	Metabolic Health Outcomes	Key Findings	Study Limitations	Country	Continent
Horvath et al., 2020, Austria (24)	Randomized, double-blind, placebo-controlled pilot study; 26 patients with diabetes	6-month daily supplementation with multi-species synbiotic (EcologicBarrier + OmniLogic Plus) vs. placebo	No significant changes in diversity or overall taxa; <i>L. brevis</i> detected only in the intervention group during/post-intervention; linked to better outcomes	No change in glucose metabolism; reduction in hip circumference, serum zonulin, and lipoprotein(a); improved neutrophil function and physical functioning (QoL)	Synbiotics did not alter glucose metabolism but improved gut permeability, inflammation markers, and physical QoL; <i>L. brevis</i> presence correlated with improvements	Small sample, short duration, high dropout rate, imbalance in sex distribution, and pilot nature limit generalizability	Austria	Europe
Salazar et al., 2015, Belgium/Spain (25)	Randomized, double-blind, placebo-controlled, parallel trial; 30 obese women; 3-month intervention	16 g/day inulin-type fructans (ITF) vs. maltodextrin placebo	↑ <i>Bifidobacterium longum</i> , <i>B. pseudocatenulatum</i> , <i>B. adolescentis</i> ; a negative correlation between <i>B. longum</i> and serum LPS	↓ fecal SCFA (acetate, propionate); SCFA positively correlated with BMI, fasting insulin, HOMA-IR, HbA1c	ITF increased specific <i>Bifidobacterium</i> spp. and reduced fecal SCFA, suggesting prebiotics could counteract obesity-linked endotoxemia and metabolic risk	Small sample, only women, fecal SCFA may not fully reflect systemic SCFA production or absorption	Belgium/ Spain	Europe
Cicero et al., 2020, Italy (26)	Randomized, double-blind, placebo-controlled, parallel-group clinical trial; 60 elderly patients with metabolic syndrome	60-day supplementation with synbiotic formula ( <i>L. plantarum</i> PBS067, <i>L. acidophilus</i> PBS066, <i>L. reuteri</i> PBS072, inulin, FOS) vs. placebo	Microbiota not directly profiled; expected modulation based on strain functionality; improved EQ-5D VAS scores suggesting systemic effects	Reduced waist circumference, fasting insulin, FPG, TC, LDL-C, non-HDL-C, TG, hsCRP, TNF-alpha; increased HDL-C; reduced MetS prevalence	Synbiotic treatment significantly improved multiple metabolic and inflammatory markers, reduced MetS prevalence, and improved perceived health	No direct microbiota analysis, short duration, limited biomarkers, no fat mass measurement	Italy	Europe
Roberta Barone Lumaga et al., 2024, Italy (27)	Randomized, crossover, double-blind controlled trial; 38 healthy adults	30-day consumption of sourdough-leavened whole-grain bread vs. brewer's yeast-leavened bread	No major differences in global microbiota composition; ↑ Actinobacteriota and Firmicutes; ↑ <i>Bifidobacterium</i> and <i>Blautia</i> spp.; ↓ <i>Akkermansia</i> spp. (only significant in some analyses)	No significant change in glycemia, insulin sensitivity, or inflammatory markers; ↑ gastrointestinal well-being scores	Sourdough bread improved subjective gastrointestinal symptoms and slightly altered beneficial microbiota (e.g., <i>Bifidobacterium</i> , <i>Blautia</i> ) without systemic metabolic changes	A healthy population may limit generalizability; short duration; small sample size; minor microbiota effects	Italy	Europe

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Meslier et al., 2020, Italy/France/Denmark (28)	RCT: 82 overweight/obese adults with low fruit/vegetable intake and sedentary lifestyle	8-week isocaloric Mediterranean diet (MD) tailored to habitual energy intake vs. control diet	↑ <i>F. prausnitzii</i> , <i>Roseburia</i> , <i>Lachnospiraceae</i> ; ↓ <i>R. torques</i> , <i>R. gnavus</i> , <i>B. wadsworthia</i> ; ↑ gene richness linked to ↓ inflammation	↓ total, LDL, HDL cholesterol; ↓ faecal bile acids and BCFAs; ↑ insulin sensitivity in high-adherence individuals	MD improved lipid profile, reduced inflammation, altered microbiota and metabolome (↑ SCFA producers, ↓ proteolytic fermentation); effects tied to adherence level	No change in primary SCFAs; modest cholesterol reduction; limited power for stratified subgroup findings	Italy/France/Denmark	Europe
Van der Beek et al., 2018, Netherlands (29)	Double-blind, randomized, placebo-controlled cross-over trial; 14 overweight/obese men	Single 24 g dose of inulin (0.5 g labeled with <sup>13</sup> C) vs. 24 g maltodextrin placebo in a high-fat milkshake	↑ plasma <sup>13</sup> C-labeled SCFAs (acetate, propionate, butyrate) and <sup>13</sup> CO <sub>2</sub> from 2 h post-intake; no change in satiety hormones or fecal SCFA	↑ early-phase fat oxidation; ↓ early postprandial glucose and insulin; ↑ plasma acetate (late); ↓ plasma FFAs (late); no appetite/satiety change	Inulin improved substrate metabolism via SCFA production and lower glycemic index, increasing fat oxidation and reducing insulin and FFA responses	Short duration, acute study, small sample, limited to overweight males, no long-term or microbiota compositional data	Netherlands	Europe
Van Trijp et al., 2021, Netherlands (30)	Randomized, double-blind, controlled, parallel trial; 37 middle-aged overweight/obese adults; 12-week intervention	98 g/day whole grain wheat (WGW) vs. refined wheat (RW); matched for macronutrients except for fiber (WGW: 17.6 g/day, RW: 7.2 g/day)	WGW ↑ <i>Ruminococcaceae_UCC-014</i> , <i>Ruminiclostridium_9</i> , <i>Ruminococcaceae_NK4A214_group</i> , predicted butyrate fermentation; RW ↓ SCFA fermentation capacity	WGW prevented liver fat increase; RW ↑ intrahepatic triglycerides; WGW ↓ serum amyloid A, ↑ β-hydroxybutyrate; RW had negative trends on liver markers	WGW improved gut microbial fermentation potential (butyrate) and stabilized liver fat; RW reduced microbial diversity and worsened hepatic outcomes	No fecal SCFA quantification, small sample, predictive metagenomics (PICRUSt2), subtle microbiota changes not all significant after correction	Netherlands	Europe
Canfora et al., 2022, The Netherlands (31)	Double-blind, placebo-controlled, randomized cross-over studies; lean (n=12) and prediabetic overweight/obese (n=12) men	One-day supplementation with INU+RS, INU, PLA; and BG+RS, BG, PLA (all isocaloric); RS = resistant starch, INU = long-chain inulin, BG = beta glucan	Individual-specific shifts: INU+RS changed microbiota more than BG+RS; no consistent changes in diversity; INU+RS showed more effect in lean individuals	In lean: INU+RS increased butyrate, breath H <sub>2</sub> , energy expenditure, carb oxidation, PYY, and improved insulin sensitivity. In prediabetics, only acetate increased, no metabolic improvements	INU+RS improves distal colonic fermentation and metabolic parameters in lean individuals but not in prediabetics. BG+RS had a minor effect. Effects are phenotype- and fiber-specific	Short intervention duration, male-only participants, non-significant primary outcome (plasma acetate), SCFA dynamics complex, no long-term data	Netherlands	Europe

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Author(s), Year, Country	Study Design and Population	Dietary Exposure	Microbiota Outcomes	Metabolic Health Outcomes	Key Findings	Study Limitations	Country	Continent
P.F. de Groot et al., 2017, The Netherlands (32)	Review article summarizing RCTs and other studies on FMT in metabolic syndrome	Not applicable directly; FMT rather than diet manipulation; mentions high-fat diets and fiber indirectly	Changes in microbial diversity, presence of butyrate-producing bacteria, Firmicutes/Bacteroidetes ratio, Akkermansia muciphila	Improved insulin sensitivity, reduced hepatic steatosis, improved glucose and lipid metabolism, reduced blood pressure in animal models	FMT from lean donors can improve insulin sensitivity in metabolic syndrome patients; microbiota plays a role in metabolic syndrome pathology	Single human RCT with small sample; effects temporary; variable response based on host-microbiota; logistical and safety concerns with FMT	Netherlands	Europe
Comanys et al., 2022, Spain (33)	Randomized, double-blind, placebo-controlled trial; 120 abdominally obese adults	12-week daily intake of 50g enriched seafood sticks (SIAP2: <i>B. animalis</i> subsp. <i>lactis</i> CECT 8145, 1.7g inulin, 370mg omega-3) vs. placebo	Decreased alpha-diversity; changes in Lachnospiraceae, Ruminococcaceae, Prevotella, Faecalibacterium, and Roseburia; LEfSE biomarkers enriched post-intervention	Reduced insulin (-5.25 mg/dL), HOMA-IR (-1.33), and pulse pressure (-4.69 mmHg in women); reduced TG increase post-meal in the acute phase	Enriched seafood sticks reduced CMD risk factors via microbiota modulation; benefits observed in insulin sensitivity and postprandial TG	No change in visceral fat, lower omega-3 dosage, no microbiota change link in men, short duration, no fat mass analysis	Spain	Europe
Galié et al., 2021, Spain (34)	Randomized, controlled, cross-over trial; 38 adults with Metabolic Syndrome	2-month Mediterranean Diet vs. habitual diet + 50 g/day mixed nuts (crossover with 1-month washout)	MedDiet increased Lachnospiraceae NK4A136, Ruminococcaceae; nuts increased Roseburia, Oxalobacter; decreased Ruminococcaceae UCG014, Lactococcus; minimal alpha/beta-diversity changes	MedDiet decreased glucose, insulin, and HOMA-IR vs. nuts; fecal metabolite changes included higher acetate and malate, lower bile acids, and cadaverine	MedDiet is more effective than nuts in improving insulin resistance and modulating microbiota; Lachnospiraceae NK4A136 is linked to better metabolic profiles and bile acid changes	Small sample size, short duration, unblinded design, high interindividual microbiota variability, 16S rRNA limits resolution	Spain	Europe
Galié et al., 2021, Spain (34)	Randomized, controlled, cross-over dietary-intervention trial; 44 adults with Metabolic Syndrome	2-month Mediterranean Diet vs. non-MedDiet + 50 g/day mixed nuts, with 1-month washout	Two clusters of microbial genera (e.g., Lachnospiraceae, Ruminococcaceae, Christensenellaceae) correlated with plasma metabolite changes; no significant diversity shifts	Decreases in glucose, insulin, HOMA-IR with MedDiet vs. nuts; specific plasma metabolites linked to improved insulin resistance	MedDiet induced a distinct plasma metabolomic profile and insulin resistance improvements linked to specific microbiota clusters; highlights diet-metabolite-microbiota interplay	Small sample size, unblinded design, high inter-individual microbiota variability, 16S rRNA limitations for species resolution	Spain	Europe

**Supplementary Table 2.** Overview of RCTs conducted in Europe assessing the effects of dietary interventions on gut microbiota and metabolic health outcomes

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Gomez-Perez A et al., 2023, Spain (7)	Sub-analysis of the PREDIMED-Plus trial: 297 overweight/obese adults with metabolic syndrome from Spain	Mediterranean diet with lifestyle intervention (energy-restricted diet and physical activity); 1-year follow-up	Decreased Proteobacteria and Enterobacteriaceae; increased Oscillospira, Coprococcus, and Lachnospira in improved HSI group; altered profiles in FIB-4 tertiles including Bifidobacterium, Sutterella, Faecalibacterium	HSI and FIB-4 indexes improved in subsets; associated with BMI, glucose, HbA1c, ALT, GGT; steatosis/fibrosis biomarker response linked to microbiota shifts	Mediterranean diet-induced lifestyle changes modulate gut microbiota and liver disease biomarkers (HSI, FIB-4); suggests microbiota as a potential biomarker in NAFLD management	NAFLD/NASH not biopsy-confirmed; all participants received dietary advice, population-specific effects, limited generalizability	Spain	Europe
Mateo-Gallego et al., 2021, Spain (35)	Randomized, double-blind, cross-over pilot study: 14 adults with T2DM or prediabetes and overweight/obesity	10-week modified alcohol-free beer (16.5g isomaltulos, 5.28g resistant maltodextrin/day) vs. regular alcohol-free beer	↑ Parabacteroides (Porphyomonadaceae); enhanced metabolic pathways (e.g., N-glycan, LPS, ubiquinone biosynthesis); ↓ Bacteroides (trend)	↓ glucose, HOMA-IR with modified beer; both interventions ↓ BMI; no significant changes in HbA1c, insulin, cholesterol, CRP	Modified beer improved insulin resistance and modulated microbiota (↑ Parabacteroides); metabolic benefits potentially mediated by microbiota shifts	Small sample, pilot design, short duration, limited generalizability, potential confounders like physical activity and metformin use	Spain	Europe
Iversen et al., 2022, Sweden (36)	Randomized controlled 12-week weight loss trial; 242 overweight adults; hypocaloric rye vs. refined wheat diet	High-fiber rye cereal products (30g fiber/day) vs. refined wheat products (8g fiber/day)	↑ Agathobacter, Haemophilus, UCG-003; ↓ Ruminococcus torques, Eubacterium ventriosum, Anaerofilum, Anaerotruncus, Holdemania; ↑ plasma butyrate	Greater weight/fat loss in rye group; ↓ CRP; modest ↑ plasma butyrate; no change in glucose, insulin, HDL, LDL, TG	Rye improved weight loss, reduced CRP, and increased butyrate-producing microbes; microbiota changes linked to inflammation and SCFA profile	No pre-run-in microbiota, confounding by weight loss, 16S rRNA resolution, cereal source confounded with fiber dose	Sweden	Europe
Marungruang et al., 2018, Sweden (37)	Randomized, controlled, parallel 8-week intervention; 47 overweight/obese adults aged 51-72	A multi-functional diet (MFD) rich in fiber, polyphenol, omega-3s, soy, and nuts vs. control diet matched to Nordic guidelines but without 'active' components	↑ Prevotella copri (LEfSE); Faecalibacterium negatively associated with BP, Treponema positively associated; no α/β-diversity changes	↓ LDL (-34%), total cholesterol (-26%), triglycerides (-16%), ApoB/ApoA1 and LDL/HDL ratios; ↓ Reynold's cardiovascular risk score (-36%)	MFD improved cardiometabolic markers with minor gut microbiota shifts; specific taxa like P. copri and Faecalibacterium were linked to improved risk markers	Small shifts in microbiota despite high fiber, baseline microbiota variation, short duration, and healthy comparator diet may have dampened contrast	Sweden	Europe

**Supplementary Table 2.** Overview of RCTs conducted in Europe assessing the effects of dietary interventions on gut microbiota and metabolic health outcomes

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Chambers et al., 2019, UK (38)	Randomized, double-blind, placebo-controlled trial; 18 adults with biopsy-confirmed NAFLD	20 g/day inulin-propionate ester (IPE, 14.6 g inulin + 5.4 g propionate) vs. 20 g/day inulin; 42-day intervention	Not directly reported; SCFA data show IPE ↓ fasting butyrate; proposed ↑ colonic propionate:acetate ratio inhibits hepatic DNL	IHCL ↑ with inulin but not IPE; HOMA-IR worsened with inulin, stable with IPE; no change in weight or physical activity	Inulin ↑ liver fat in weight-stable NAFLD patients; IPE prevented this, likely via propionate-mediated DNL inhibition; acetate excess may promote steatosis	Small sample, short duration, metabolic variability, no direct microbiota or hepatic gene expression data	UK	Europe

*Note. This table highlights the types of interventions, microbiota responses, clinical effects, and study limitations across European populations.*

**Supplementary Table 3.** Summary of RCTs conducted in the Americas (North, Central, and South America) evaluating dietary interventions and their effects on gut microbiota and metabolic health.

Author(s), Year, Country	Study Design and Population	Dietary Exposure	Microbiota Outcomes	Metabolic Health Outcomes	Key Findings	Study Limitations	Country	Continent
Santamarina et al., 2024, Brazil (39)	Double-blind, RTC; 41 overweight adults; 180-day intervention	NSupple (prebiotics + minerals) and NSupple_Silybum (same + silymarin)	NSupple_Silybum: ↑ Bacteroidetes, Bacteroides, Prevotella, Alistipes onderdonkii, ↓ F/B ratio, ↓ Roseburia, Blautia obeum, Dorea, Coprococcus; Faecalibacterium linked to sleep quality; Bilophila linked to QoL	↓ WC-mid (both), ↓ WHR, WHtR (NSupple_Silybum), ↓ C-RP, cortisol, TNF-α (NSupple_Silybum); ↑ HbA1c and glycemia (NSupple); ↓ AST/ALT ratio	NSupple_Silybum improved inflammation, anthropometric, and sleep via microbiota modulation (notably Bacteroidetes, Faecalibacterium, Alistipes); synergistic effects across blend components	No placebo, small sample size, no fecal metabolomics; compositional vs. functional microbiome changes not deeply probed	Brazil	America
Santamarina et al., 2025, Brazil (40)	Double-blind, RCT; 77 overweight adults	90-day supplementation with NSupple (prebiotics, β-glucans, minerals) or NSupple_Silybum (NSupple + silymarin)	NSupple: ↑ Faecalibacterium, Lactobacillus, Lentisphaerae; ↓ Coprococcus eutactus, R. bromii. NSupple_Silybu: ↓ Adlercreutzia, Sutterella, Blautia obeum; ↓ F/B ratio in both groups	↓ weight, WC, WHtR, LDL, non-HDL, total cholesterol; ↓ cortisol and inflammatory markers (IL-6/IL-10, TNF-α/IL-10 ratios); improved sleep scores (ESS, PSQI)	Nutraceuticals reshaped microbiota, improved metabolic and inflammatory markers, and enhanced sleep; NSupple_Silybum showed stronger lipid and inflammatory benefits	No silymarin detection in plasma, high dropout, unclear mechanism specificity, limited SCFA data, healthy population baseline	Brazil	America
Escouto et al., 2023, Brazil/Canada (41)	Randomized, double-blind, placebo-controlled trial; 48 adults with histology-confirmed NASH; 6-month intervention	Daily probiotics: 1 billion CFU Lactobacillus acidophilus + 1 billion CFU Bifidobacterium lactis vs. placebo	No significant shifts in gut microbiota; Mitsuoella was overrepresented in the probiotic group, but baseline imbalance noted	↓ APRI score (fibrosis marker); no significant changes in AST, ALT, CRP, IL-6, TNF-α, leptin, lipid profile, or HOMA-IR	Probiotics modestly reduced APRI score but did not significantly affect liver enzymes, inflammation, or gut microbiota composition in NASH	Small sample, short duration, baseline fibrosis heterogeneity, frequent metformin/statin/antibiotic use, modest microbiota sequencing yield	Brazil/Canada	America
Agrinier et al., 2024, Canada (42)	Randomized, double-blind, placebo-controlled cross-over trial; 30 adults with overweight and hypertriglyceridemia	1.5 g/day of Camu-camu (polyphenol-rich supplement) vs. placebo for 12 weeks	Increased abundance of Enterococcus, Lactobacillus, Lactococcus, and Pediococcus pentosaceus; Decreased Adlercreutzia, Intestinibacter, Shuttleworthia; Functional changes in fermentation and metabolic pathways	15.85% relative decrease in liver fat vs. placebo, reduced plasma AST and ALT levels; no significant change in body weight or glucose homeostasis	Camu-camu supplementation reduces hepatic steatosis and improves liver injury markers in overweight individuals, with gut microbiota alterations suggesting prebiotic-like effects	Limited sample size due to COVID-19; no liver biopsies; short duration; no significant changes in glucose homeostasis observed	Canada	America

**Supplementary Table 3.** Summary of RCTs conducted in the Americas (North, Central, and South America) evaluating dietary interventions and their effects on gut microbiota and metabolic health.

Author(s), Year, Country	Study Design and Population	Dietary Exposure	Microbiota Outcomes	Metabolic Health Outcomes	Key Findings	Study Limitations	Country	Continent
Lambert et al., 2015, Canada (43)	Double-blind, placebo-controlled, parallel-group RCT; 60 adults with NAFLD; 6-month intervention	16 g/day Synergy1 (oligofructose-enriched inulin) vs. isocaloric maltodextrin placebo combined with 10% weight loss goal via dietitian support	Shotgun sequencing of gut microbiota; VOC profiling; analysis of fecal endotoxin and satiety hormones; modulation expected via increased Bifidobacterium	Primary: reduction in hepatic injury and liver fat (FibroScan, FibroTest, MRI); Secondary: improved glucose tolerance, body composition, appetite, inflammatory markers	The protocol aimed to test whether prebiotics improve hepatic outcomes in NAFLD beyond diet-induced weight loss alone; focus on microbiota-mediated mechanisms	Study protocol; clinical trial in progress; future results pending for efficacy conclusions	Canada	America
Mayengbam et al., 2018, Canada (44)	Double-blind, placebo-controlled, 12-week clinical trial; 53 overweight/obese adults	15 g/day yellow pea fiber in wafer form vs. isocaloric placebo wafer	↑ Lachnospira in PF group; ↓ Actinomycetaceae, ↑ Barnesiellaceae; ↓ alpha diversity; correlations with SCFAs and bile acids	↓ weight correlated with ↑ Lachnospira higher acetate, lower isovalerate, and bile acids (cholate, deoxycholate, total BAs) in the PF group	Pea fiber-modulated gut microbiota increased SCFA production, reduced harmful bile acids, and improved body weight and metabolite profile	No direct link between fiber and systemic metabolic markers, limited SCFA profiling; diversity measures paradoxically declined	Canada	America
Medina-Vera et al., 2019, Mexico (45)	Randomized, double-blind, placebo-controlled trial; 81 adults with T2D; 3-month intervention	Dietary portfolio (DP): reduced-energy diet + functional foods (inulin, chia, soy protein, dehydrated nopal, polyphenols); placebo matched for kcal/fluor	↓ Prevotella copri; ↑ Faecalibacterium prausnitzii, Akkermansia muciniphila, Bifidobacterium longum; ↑ alpha diversity; changes occurred independently of medications	↓ glucose AUC, triglycerides, total and LDL cholesterol, FFAs, HbA1c, CRP; ↑ plasma antioxidant activity; ↓ metabolic endotoxemia (LPS)	Functional food-based dietary intervention significantly reshaped gut microbiota and improved glycemic, lipid, inflammatory, and endotoxemia markers in T2D	Moderate dropout, 3-month duration, limited metabolomic profiling, interactions with medications not deeply analyzed	Mexico	America
Frias et al., 2023, USA (46)	Double-blind, randomized, placebo-controlled trial with an open-label diet-only arm; 192 adults with T2D	12-week fibre-enriched formula (resistant starch + oat beta-glucan) vs. fibre-absent placebo or dietary advice	Significant increase in butyrate-producing bacteria (Roseburia feces, Anaerostipes hadrus); small beta-diversity shifts; no significant alpha-diversity changes	Reduction in HbA1c (-0.36% vs. +0.30% in placebo), improved diabetes distress score (cT2-DDAS), improved HRQoL (WHO-5, ROSS), mild weight and blood pressure reduction	Fiber-enriched formula improved HbA1c and quality of life in T2D patients; gut microbiota modulation with increased butyrate producers; well-tolerated	Short duration, high dropout rates, self-reported inclusion criteria, modest metabolic effect size, unquantified butyrate levels	USA	America

**Supplementary Table 3.** Summary of RCTs conducted in the Americas (North, Central, and South America) evaluating dietary interventions and their effects on gut microbiota and metabolic health.

Author(s), Year, Country	Study Design and Population	Dietary Exposure	Microbiota Outcomes	Metabolic Health Outcomes	Key Findings	Study Limitations	Country	Continent
Hill et al., 2022, USA (47)	Randomized, controlled trial: 28 caregivers and 18 children in low-resource households	10-week high-fiber dietary intervention including weekly education, produce harvesting, cooking demos, and counseling vs. written materials only	Altered bile acid metabolizing organisms; increased Bifidobacterium, Subdoligranulum; correlated with HEI and sterol metabolite excretion; dyad microbial response overlap	Improved Healthy Eating Index (HEI), reduced energy intake and BP; enhanced LCA and cholesterol excretion; increased microbial taxa associated with reduced BP	Multifaceted lifestyle intervention improved diet quality, BP, and sterol elimination via shared gut microbiota responses in caregiver-child dyads	Small sample size, optional fecal sample donation, potential self-report bias, short duration	USA	America
Hughes et al., 2021, USA (48)	Randomized, double-blind, placebo-controlled, cross-over trial; 30 healthy adults (40-65 years)	1-week consumption of RS2-enriched wheat rolls vs. wild-type wheat; cross-over design with a 2-week washout	↑ Ruminococcus, Gemmiger, Faecalibacterium, Roseburia, Bifidobacterium; ↓ Shannon diversity and Chao1 richness; ↑ breath hydrogen and methane	↓ postprandial glucose and insulin iAUC and peaks; no change in fasting glucose, insulin, or HOMA-IR; ↑ butyrate correlated with fermentation indices	RS2 wheat lowered postprandial glycemia and altered gut microbiota favoring fermentation; butyrate-producing taxa linked to glycemic response	Short duration, small sample, no change in fasting metrics, 16S rRNA sequencing limits resolution	USA	America
Mitchell et al., 2021, USA (49)	Randomized, double-blind, placebo-controlled feeding trial; 24 adults at elevated risk for T2D	10 g/day chicory root inulin vs. 10 g/day maltodextrin for 6 weeks under controlled diet	↑ Bifidobacteria copy number; no change in intestinal permeability or endotoxin concentration	↓ fasting insulin and HOMA-IR in the inulin group (attenuated after baseline adjustment); no change in peripheral insulin sensitivity	Inulin increased Bifidobacteria but did not improve peripheral insulin sensitivity or intestinal barrier markers in adults at risk for T2D	Small sample size, baseline insulin imbalance, relatively healthy cohort, limited microbiota profiling, proof-of-concept design	USA	America
Mohr AE et al., 2024, USA (50)	RCT; 41 overweight/obese adults; 8-week intervention comparing intermittent fasting with protein pacing (IF-P) vs. continuous caloric restriction (CR)	IF-P: ~35% protein diet with meal replacements + intermittent fasting (1-2 days/week); CR: calorie-matched, heart-healthy diet (~21% protein)	IF-P ↑ Christensenellaceae, Rikenellaceae, Marvinbryantia; ↓ Butyricoccus, Eubacterium ventriosum, Agathobacter; enhanced Bray-Curtis dissimilarity vs. CR	IF-P group had significantly more weight/fat loss, improved body composition, ↑ cytokines (IL-4, IL-6, IL-8, IL-13); distinct plasma metabolomic profiles	IF-P diet led to stronger microbiome remodeling and metabolic improvements vs. CR; differential cytokine and metabolite responses with potential for precision nutrition	Small sample size, 8-week duration, exploratory multi-omics, effects of protein intake, and meal format not isolated	USA	America

**Supplementary Table 3.** Summary of RCTs conducted in the Americas (North, Central, and South America) evaluating dietary interventions and their effects on gut microbiota and metabolic health.

Author(s), Year, Country	Study Design and Population	Dietary Exposure	Microbiota Outcomes	Metabolic Health Outcomes	Key Findings	Study Limitations	Country	Continent
Zhang et al., 2023, USA (51)	Randomized cross-over trial; 48 obese patients with a history of colorectal neoplasia; 8-week bean intervention	1 cup/day of cooked navy beans added to the usual diet	↑ alpha diversity, Faecalibacterium, Bifidobacterium, Eubacterium, Odoribacter; ↓ Collinsella, Roseburia, Streptococcus; shifts reversed post-intervention	↑ pipecolic acid, SAM, trigonelline; ↓ indole derivative; ↑ FGF-19; ↓ IL10ra, TRANCE, CD8A, PD-L1, CXCL1; no change in lipoproteins	Navy beans modulated gut microbiota, metabolites, and inflammation markers in high-risk patients, even without broader dietary changes	No placebo, moderate sample size, modest duration, no sustained effects without continued intake	USA	America

*Note: Studies span diverse populations and interventions, offering region-specific insights into diet–microbiota–metabolism interactions.*

**Supplementary Table 4.** Overview of RTCs conducted in multinational, European-Asian, and Australian cohorts assessing dietary interventions, gut microbiota modulation, and metabolic health outcomes.

Author(s), Year, Country	Study Design and Population	Dietary Exposure	Microbiota Outcomes	Metabolic Health Outcomes	Key Findings	Study Limitations	Country	Continent
Aldubayan et al., 2023, Denmark and Saudi Arabia (52)	Randomized, double-blind, placebo-controlled trial; 100 adults with obesity, 82 completed, aged 18-65	High-fiber (~38g/d) plant-based diet, with or without 20g/d of inulin-type fructans (ITF) for 10 weeks	Reduced microbial diversity in the ITF group; increased Bifidobacterium and Faecalibacterium prausnitzii; reduced Lachnospiraceae, Erysipelotrichaceae, Coriobacteriaceae	Weight loss, improved glucose, and lipid profiles in all; ITF group showed attenuated benefits: higher insulin, HOMA-IR, reduced HDL-C, elevated IL-10, MCP-1, TNF- $\alpha$	A plant-based diet improved weight and metabolic markers; added ITF altered microbiota, but reduced some benefits; no predictive value of baseline P/B ratio for weight loss	No SCFA flux data, short duration, no analysis of SCFA production, limited diversity insights, individualized responses to prebiotics	Denmark and Saudi Arabia	Europe/Asia
Gao et al., 2024, Multinational (8)	RCT from the DIRECT-PLUS Trial; 284 adults randomized to Healthy Dietary Guidelines (HDG), MedDiet, or Green-MedDiet; 18-month follow-up	Mediterranean diet interventions vs. HDG; Green-MedDiet included walnuts, green tea, and Mankai	Gut microbiome significantly modified secondary bile acid pool; species like R. gnavus, R. torques, and B. longum influenced bile acid metabolism; shotgun metagenomics used	Baseline levels of 14 fecal bile acids predicted BMI and lipid responses; MedDiet effect stronger with low 12-DHCA and TCA; modulated triglycerides, TC/HDLc, LDLc	Gut bile acid profile modifies MedDiet effects on cardiometabolic risk; bile acid-microbiota interactions offer biomarkers for personalized nutrition	Male-dominated sample, high-risk cohort, observational BA associations, absence of fecal SCFA data	Multinational	
Choo et al., 2021, Australia (53)	Randomized, controlled, parallel-group trial: 69 overweight/obese adults with elevated fasting blood glucose	56 g/day of almonds vs. isocaloric biscuit snack for 8 weeks	Increased richness, evenness, and diversity; elevated abundance of Ruminococcaceae family (Ruminiclostridium, NK4A214, UCG-003); no SCFA changes	Decreased fecal pH and moisture; no changes in intestinal permeability, SCFA levels, or glycemic regulation	Almonds altered microbiota with increased beneficial taxa and reduced fecal pH and moisture, but did not affect SCFAs or metabolic parameters	16S rRNA sequencing limits resolution; no shotgun metagenomics; fecal samples may not reflect total gut; no data on broader fermentation products; antibiotic use not excluded	Australia	Australia

Note: These studies encompass diverse geographical contexts and offer comparative insights across various regions.