Table 5: Overview of KD-Induced Microbiota Changes in Non-cancer Studies

Study Citation	Purpose	Design	N	Diet	Length	KD-induced Microbiota Compositional Changes	Additional Notes	Sequencing Type
(34)	To understand how KDs affect the gut microbiome and the downstream consequences for host metabolism and immunity	Inpatient crossover study in overweight or class I obese non-diabetic men	n=17	BD: 35%:15%:50% [fat:protein:CHO], KD: 80%:15%5%	8 weeks (4 weeks BD, 4 weeks KD)	Phyla: ↑ Bacteroidetes, ↓ Firmicutes, ↓ Actinobacteria Genera: 19 genera changed significantly (FDR < 0.05, DESeq2), ↓ Bifidobacterium showed the greatest depletion	No significant differences in SCFA levels or bacterial load. Significant overall separation in fecal metabolite profiles between KD and BD.	16S, metaG
(35)	To examine how the fecal microbiome is affected by KD in children with epilepsy	Children with therapy-resistant inoperable epilepsy or a diagnosis of a neurometabolic disorder served as the experimental group. One parent per trial served as a "control" and followed normal intake of a standard western diet.	n=12	KD: 4:1 [fat:protein+CHO] in 7 children, 3.5:1 [fat:protein+CHO] in 2 children, 3:1 [fat:protein+CHO] in 3 children	3 months	Phyla: ↑ Bacteroidetes, ↑ Proteobacteria (notably Eschericha coli) ↓ Firmicutes (notably Eubacterium rectale), ↓ Actinobacteria Genera: ↓ Bifidobacterium (overall 15.8% → 3.9%), ↓ Eubacterium rectale (2.5% → 0.5%), ↓ Dialister (2.2% → 0.4%), ↑ Escherichia (3.1% → 8.5%), ↑ Eggerthella	Patients had a non-significant change in alpha diversity on KD. Beta diversity and PCA revealed KD patient samples became more functionally and taxonomically distinct after 3 months.	metaG
(38)	To investigate if MMKD can beneficially alter the gut microbiome and SCFA production and whether the changes are associated with improvements in Alzheimer's disease biomarkers	Randomized, double-blind, crossover study in older adults at risk for Alzheimer's Disease	n=17	MMKD: 60-65%:30-35%:<10%, AAHD: 15-20%, 20-30%,55-65%	18 weeks (6 weeks MMKD, 6 weeks AAHD, 6 week washout)	Phyla: No signifcant changes in the dominant phyla (Firmicutes, Bacteroidetes, Proteobacteria), ↑ Tenericutes (slight), Genera/Family: ↓ Bifidobacterium (signifcant reduce), ↑ Akkermansia, ↑Slackia, ↑ Enterobacteriaceae, ↓ Lachnobacterium	Changes in fecal levels of organic acids: ↑ Butyrate, ↓ Acetate	16S
(37)	To assess how KD affects metabolic biomarkers, gut microbiota composition, and fecal short-chain fatty acid levels in overweight or obese women	Single-arm study in women aged 20-65 years with a BMI of > 25 kg/m2	n=15	KD: >70% of energy from fats, 1 g/kg protein, <20 g CHO	6 weeks	Phyla: ↑ Firmicutes (65.8% → 92.6%), ↑ Protetobacteria (1.2% → 1.4%), ↑ Tenericutes (0.2% → 0.3%), ↓ Bacteroidetes (25.7% → 4.2%), ↓ Actinobacteria Genera: ↑ Oscillibacter (p = 0.022), ↑	SCFA production (acetate, propionate, butyrate) decreased significantly, Alpha diversity (Chao1, Shannon, inverse Simpson) showed a trend toward reduction, but was not statistically significant,	16S

						Blautia (p = 0.031), ↑ Akkermansia, ↑ Lactobacillus, ↓ Prevotella (p = 0.025), ↓ Bifidobacterium, ↓ Coprococcus	Beta-diversity decreased significantly.	
(36)	To examine the effects of KD therapy on intestinal microbiota composition in children with refractory epilepsy and bacterial biomarkers	Single-arm study in children with monthly seizures and therapy with ≥ 2 antiepileptic drugs	n=20	KD: 4:1 [fat:protein+CHO]	6 months	Phyla: ↑ Bacteroidetes, ↓ Firmicutes, ↓ Actinobacteria, Proteobacteria was unchanged Genera/Family/Order: ↑ Bacteroides, ↑ Bacteroidia, ↓ Clostridiales, ↓ Clostridia, ↓ Ruminococcaceae, ↓ Faecalibacterium	Non-significant reduction in alpha diversity. Significant difference in beta-diversity (ANOSIM R=0.447, p=0.001). ↑ uric acid, ↑ free fatty acids, ↑ cholesterol, ↑ triglycerides, ↑ LDL, ↓ HDL, ↓ total bilirubin	16S

KD=ketogenic diet

MMKD = modified mediterranean ketogenic diet

SCFA = short-chain fatty acid

PCA = principal component analysis

FDR = false discovery rate

BMI = body mass index