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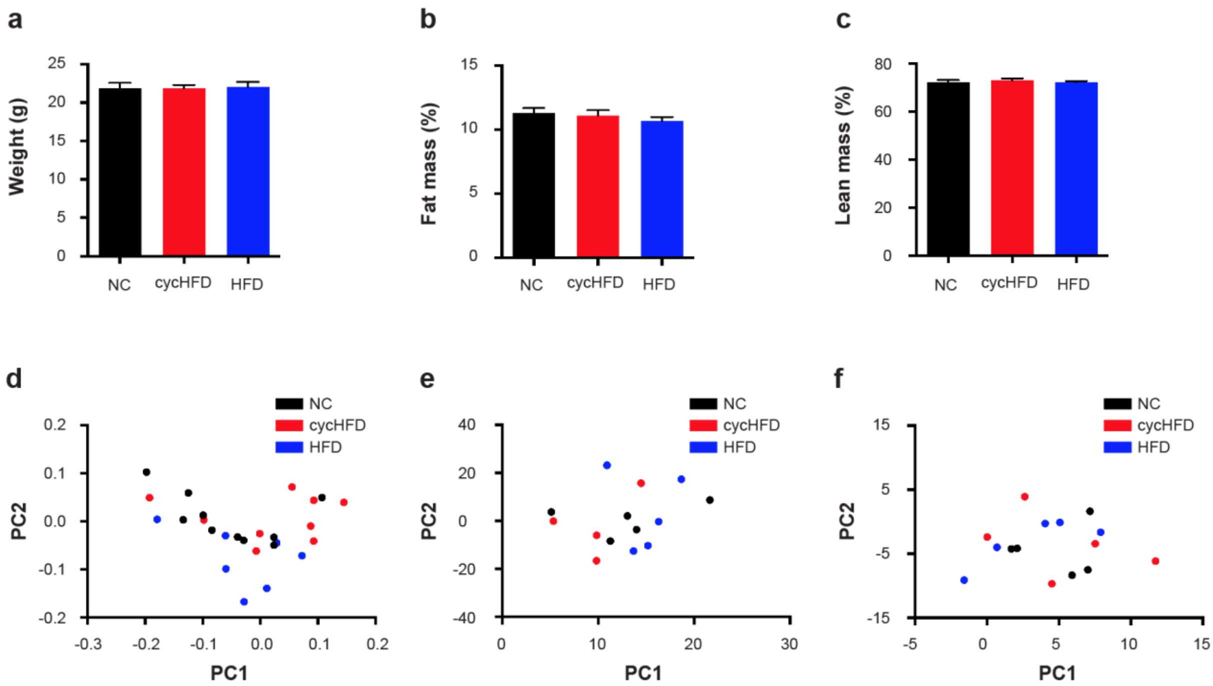
Experiments depicted in this study exclusively utilized wild-type C57Bl/6 mice. Colonized wild-type C57Bl/6 mice were obtained as littermates from a commercial source and acclimatized to the local vivarium for 2 weeks before the onset of each experiment. Mice for each experiment were purchased together and obtained through a single delivery. Before dietary interventions, mice were randomized to ensure that no incidental pre-diet differences in body weight, body fat content, or microbiome composition existed between the different groups (**Supplementary Figure 1**). Mice were initially exposed to HFD for 4 weeks (Fig. 3c, 5 weeks), followed by NC diet in the weight cycling group, until the weight of the NC control group was reached. Six independent repeats of this experimental scheme of the main phenotype appear in Fig. 1b, 1j, 1l, 5b, 6b, and Extended Data Fig. 10f. Three additional independent repetitions are provided in **Supplementary Figure 2**. Expectedly, the weight loss time period slightly differed between experiments, as did the time required to reach the HFD control weight after subsequent re-administration of HFD to the weight cycling group.

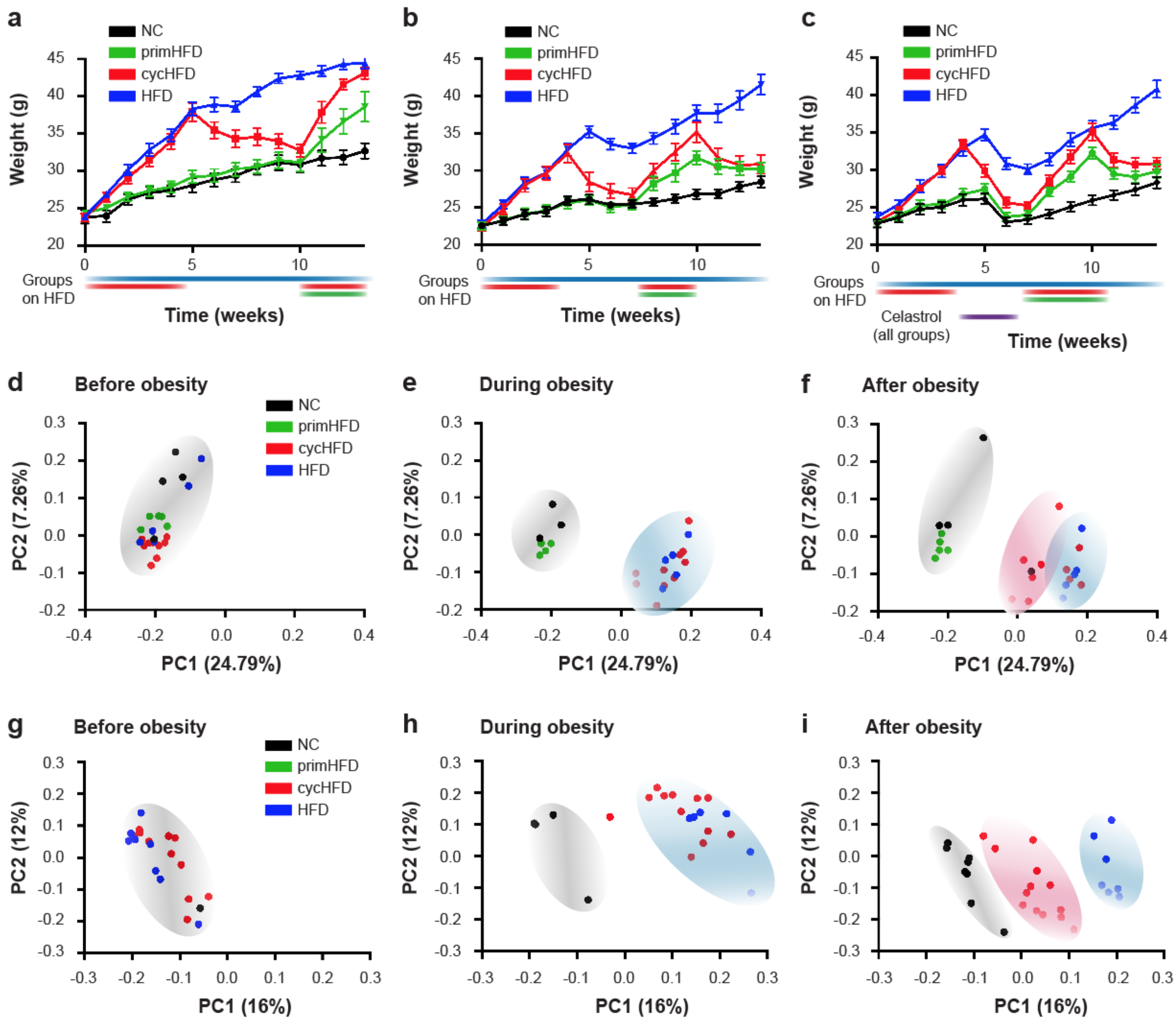
Metabolic abnormalities induced by 4 weeks of high-fat feeding in this study were significant in comparison to normal chow controls, similarly to an 8 week HFD protocol (**Supplementary Figure 3**).

The immunoblot source data for Fig. 6l is provided in **Supplementary Figure 4**.

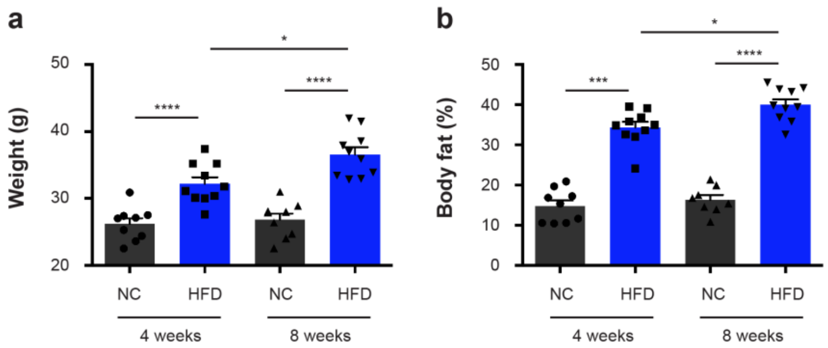
Information about bacterial species and their flavonoid-metabolizing genes is provided in **Supplementary Table 1**. The composition of the different rodent diets used in this study is provided in **Supplementary Tables 2 and 3**. **Supplementary Table 4** shows the chromatographic conditions for apigenin and naringenin separation.



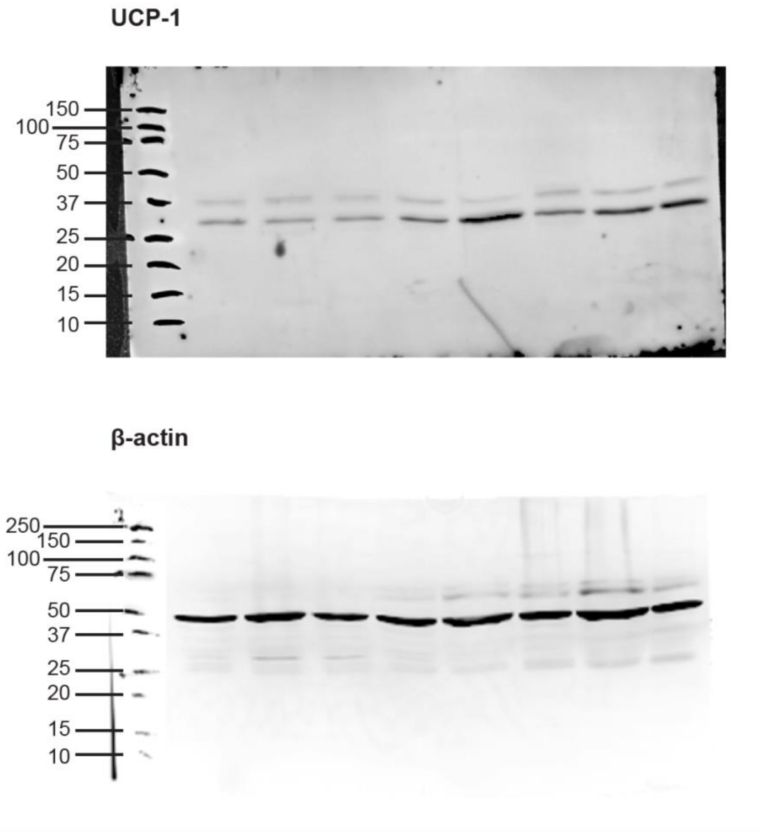
Supplementary Figure 1 | Metabolic and microbiota parameters before dietary intervention. a-c, Weights (**a**), body fat (**b**) and lean mass (**c**) before administration of diet. **d**, PCoA of fecal microbiota before administration of diet. **e, f**, PCA of KEGG genes (**e**) and gene modules (**f**) before administration of diet.



Supplementary Figure 2 | Enhanced secondary weight gain and incomplete microbiota recovery after dieting. a-c, Weight curves of weight cycling mice and controls. In (**c**), all groups were treated with celastrol during the weight loss period. **d-i**, PCoA plots of fecal microbiota from the indicated groups before the onset of the experiment (**d, g**), after 4 weeks of HFD (**e, h**), and upon weight normalization in the weight cycling group (**f, i**).



Supplementary Figure 3 | Comparison of different durations of HFD. Body weight (**a**) and body fat content (**b**) after 4 and 8 weeks of HFD feeding.



Supplementary Figure 4 | Immunoblot source data for Fig. 6l. The right four lanes are from antibiotics-treated mice, the left four lanes from controls.

Supplementary Table 1 | Flavonoid-metabolizing bacteria. The table lists bacterial species found in the metagenomic data set which encode for the indicated KEGG genes involved in flavonoid metabolism.

Name	KEGG Gene
Bacilli|Lactobacillales|Streptococcaceae|Lactococcus|Lactococcus lactis|A76	K13082
Bacilli|Lactobacillales|Streptococcaceae|Lactococcus|Lactococcus lactis|A76	K00660
Bacilli|Lactobacillales|Streptococcaceae|Lactococcus|Lactococcus lactis|CV56	K13082
Bacilli|Lactobacillales|Streptococcaceae|Lactococcus|Lactococcus lactis|CV56	K00660
Bacilli|Lactobacillales|Streptococcaceae|Lactococcus|Lactococcus lactis|Il1403	K13082
Bacilli|Lactobacillales|Streptococcaceae|Lactococcus|Lactococcus lactis|Il1403	K00660
Bacilli|Lactobacillales|Streptococcaceae|Lactococcus|Lactococcus lactis|IO-1	K13082
Bacilli|Lactobacillales|Streptococcaceae|Lactococcus|Lactococcus lactis|IO-1	K00660
Bacilli|Lactobacillales|Streptococcaceae|Lactococcus|Lactococcus lactis|KF147	K13082
Bacilli|Lactobacillales|Streptococcaceae|Lactococcus|Lactococcus lactis|KF147	K00660
Bacilli|Lactobacillales|Streptococcaceae|Lactococcus|Lactococcus lactis|KLDS 4.0325	K13082
Bacilli|Lactobacillales|Streptococcaceae|Lactococcus|Lactococcus lactis|KLDS 4.0325	K00660
Bacilli|Lactobacillales|Streptococcaceae|Lactococcus|Lactococcus lactis|KW2	K13082
Bacilli|Lactobacillales|Streptococcaceae|Lactococcus|Lactococcus lactis|KW2	K00660
Bacilli|Lactobacillales|Streptococcaceae|Lactococcus|Lactococcus lactis|MG1363	K13082
Bacilli|Lactobacillales|Streptococcaceae|Lactococcus|Lactococcus lactis|MG1363	K00660
Bacilli|Lactobacillales|Streptococcaceae|Lactococcus|Lactococcus lactis|NZ9000	K13082
Bacilli|Lactobacillales|Streptococcaceae|Lactococcus|Lactococcus lactis|NZ9000	K00660
Bacilli|Lactobacillales|Streptococcaceae|Lactococcus|Lactococcus lactis|SK11	K13082
Bacilli|Lactobacillales|Streptococcaceae|Lactococcus|Lactococcus lactis|SK11	K00660
Bacilli|Lactobacillales|Streptococcaceae|Lactococcus|Lactococcus lactis|UC509.9	K13082
Bacilli|Lactobacillales|Streptococcaceae|Lactococcus|Lactococcus lactis|UC509.9	K00660
Bacteroidia|Bacteroidales|Bacteroidaceae|Bacteroides|Bacteroides xylanisolvens|XB1A	K13082
Bacteroidia|Bacteroidales|Porphyromonadaceae|Parabacteroides|Parabacteroides distasonis|ATCC 8503	K00660

Supplementary Table 2 | Normal chow diet (Teklad 2018).

Macronutrients		Fatty acids	
Protein	18.6 %	C16:0 Palmitic	0.7 %
Fat	6.2 %	C18:0 Stearic	0.2 %
Carbohydrate	44.2 %	C18:1ω9 Oleic	1.2 %
Crude Fiber	3.5 %	C18:2ω6 Linoleic	3.1 %
Neutral Detergent Fiber	14.7 %	C18:3ω3 Linolenic	0.3 %
Ash	5.3 %	Total Saturated	0.9 %
Calories from protein	24 %	Total Monounsaturated	1.3 %
Calories from fat	18 %	Total Polyunsaturated	3.4 %
Calories from Carbohydrate	58 %	Cholesterol	-

		Vitamins	
Calcium	1.0 %	Vitamin A	15.0 IU/g
Phosphorus	0.7 %	Vitamin D3	1.5 IU/g
Sodium	0.2 %	Vitamin E	110 IU/g
Potassium	0.6 %	Vitamin K3	50 mg/kg
Chloride	0.4 %	Vitamin B1	17 mg/kg
Magnesium	0.2 %	Vitamin B2	15 mg/kg
Zinc	70 %	Niacin	70 mg/kg
Manganese	100 mg/kg	Vitamin B6	18 mg/kg
Copper	15 mg/kg	Pantothenic acid	33 mg/kg
Iodine	6 mg/kg	Vitamin B12	0.08 mg/kg
Iron	200 mg/kg	Biotin	0.4 mg/kg
Selenium	0.23 mg/kg	Folate	4 mg/kg
		Choline	1200 mg/kg

Amino acids			
Aspartic Acid	1.4 %	Valine	0.9 %
Glutamic Acid	3.4 %	Phenylalanine	1.0 %
Alanine	1.1 %	Tyrosine	0.6 %
Glycine	0.8 %	Methionine	0.4 %
Threonine	0.7 %	Cystine	0.3 %
Proline	1.6 %	Lysine	0.9 %
Serine	1.1 %	Histidine	0.4 %
Leucine	1.8 %	Arginine	1.0 %
Isoleucine	0.8 %	Tryptophan	0.2 %

Supplementary Table 3 | High-fat diet (Open Source Diets D12492).

Nutrients	g %	kcal %
Protein	26.2	20
Carbohydrate	26.3	20
Fat	34.9	60

Ingredients	g	kcal	Ingredients	g	kcal
Casein, 80 Mesh	200	800	**Mineral Mix, S10026**	10	0
L-Cystein	3	12	**DiCalcium Phosphate**	13	0
Maltodextrin 10	125	500	**Calcium Carbonate**	5.5	0
Sucrose	68.8	275.2	**Potassium Citrate**	16.5	0
Cellulose, BW200	50	0	**Vitamin Mix, V10001**	10	40
Soybean Oil	25	225	**Choline Bitartrate**	2	0
Lard	245	2205	**FD&C Blue Dye #1**	0.05	0
			Total	773.85	4057

Supplementary Table 4 | Chromatographic conditions for apigenin and naringenin separation.

Composition A: 5 %ACN + 0.1% formic acid

Composition B: 100% ACN + 0.1% formic acid

Time	% A	% B
0	100	0
22	72	28
22.5	60	40
23	0	100
24.5	0	100
25	100	0
26	100	0

MS parameters, MRM transitions and retention times for apigenin and naringenin

Analyte	ESI	Cone(V)	Transitions	Collision Energy (eV)	RT (min)
Naringenin	+	35	273.1 > 150.0	20	19.39
			273.1 > 147.0	24	
Apigenin	+	53	271.1 > 153.0	29	19.71
			271.1 > 91.1	38	