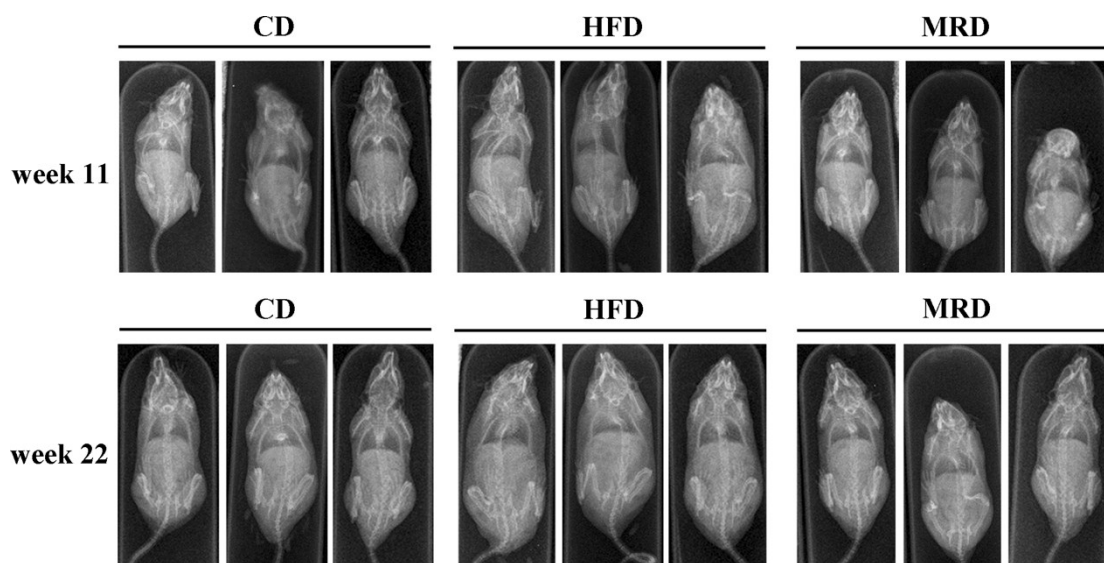


## 1 Supporting information

### 2 Supplemental Figure



3

4 **Fig. S1** Representative images of micro-CT scans obtained from the three randomly selected CD,

5 HFD and MRD mice at week 11 and week 22. CD, control diet group; HFD, high fat diet group;

6 MRD, high fat + methionine-restricted diet group. Related to Fig. 1C.

7

### 8 Supplemental Tables

9 **Table S1** The ingredients of the experimental diets (g/100 g of diet)

Ingredients	CD	HFD	MRD
L-arginine	1.12	1.12	1.12
L-histidine-HCl-H <sub>2</sub> O	0.33	0.33	0.33
L-isoleucine	0.82	0.82	0.82
L-leucine	1.11	1.11	1.11
L-lysine	1.44	1.44	1.44
L-methionine <sup>1</sup>	0.86	0.86	0.17

L-phenylalanine	1.16	1.16	1.16
L-threonine	0.82	0.82	0.82
L-tryptophan	0.18	0.18	0.18
L-valine	0.82	0.82	0.82
L-glutamic acid <sup>1</sup>	2.70	2.70	3.39
L-glycine	2.33	2.33	2.33
Corn starch	47.25	31.25	31.25
Maltodextrin	5.00	5.00	5.00
Dextrose	20.00	20.00	20.00
Cellulose	5.00	5.00	5.00
Lard	4.00	20.00	20.00
Mineral mix <sup>2</sup>	3.50	3.50	3.50
Vitamin mix <sup>2</sup>	1.00	1.00	1.00
Choline bitartrate	0.20	0.20	0.20

10 <sup>1</sup>When the methionine content in the diet was decreased, the glutamic acid content was increased

11 on an equal mass.

12 <sup>2</sup>Mineral mix and Vitamin mix were prepared based on the AIN-93 diet.

13

14 **Table S2** Sequences of primers used in quantitative real-time reverse transcription PCR

Gene symbol	Forward primer (5'–3')	Reverse primer (5'–3')
FAS	ATGCTGTGGATCTGGGCTGTC	CAGTTTCACGAACCCGCCTC
ACC1	GGCAGCAGTTACACCACATAC	TCATTACCTCAATCTCAGCATAGC

SCD1	TCATCCCATCGCCTGCTCTACCC	TGGTGTAGGCGAGTGGCGGAA
SREBP1c	TCTGGAGACATCGCAAACAAG	AGGTGGCGGATGAGGTTC
HSL	AGACCACATCGCCCACA	CCTTTATTGTCAGCTTCTTCAAGG
PPAR $\alpha$	ATGGAGACCTTGTGTATGG	ATCTGGATGGTTGCTCTG
CPT1	TCAAGCCAGACGAAGAACATC	TGGTAGGAGAGCAGCACCTT
CYP7A1	GCCTCTGAAGAAGTGAATGG	GCCTCCTTGATGATGCTATC
LPL	GGGAGTTTGGCTCCAGAGTTT	TGTGTCTTCAGGGGTCCTTAG
FMO3	GGAACCAGGAATATGGAAG	GGTGACCTTCTGAGCTACAT
CBS	CCAGGCACCTGTGGTCAAC	GGTCTCGTGATTGGATCTGCT
CSE	TTCCTGCCTAGTTTCCAGCAT	GGAAGTCCTGCTTAAATGTGGTG
$\beta$ -actin	GGGTCAGAAGGACTCCTATG	GTAACAATGCCATGTTCAAT

15 FAS, fatty acid synthase; ACC1, acetyl CoA carboxylase 1; SCD1, stearyl-coenzyme A  
16 desaturase 1; SREBP1c, sterol regulatory element-binding protein-1c; HSL,  
17 hormone sensitive lipase; PPAR $\alpha$ , peroxisome proliferator-activated receptor  $\alpha$ ; CPT1, carnitine  
18 palmitoyltransferase 1; CYP7A1, cholesterol 7 $\alpha$ -hydroxylase; LPL, lipoprotein lipase; FMO3,  
19 flavin monooxygenase 3; CBS, cystathionine- $\beta$ -synthase; CSE, cystathionine- $\gamma$ -lyase.

20

21 **Table S3** Systemic endogenous metabolites of mice in liver (related to Fig. 3)

Keys	Metabolites	Moieties	$\delta^1\text{H}$ (ppm) and multiplicity
1	Cholesterol	CH <sub>3</sub>	0.84(s)
2	Lipids	CH <sub>3</sub> , CH <sub>2</sub> , CH <sub>2</sub> CH <sub>2</sub> CO, CH <sub>2</sub> C=C, CH <sub>2</sub> CO,	0.88(t), 1.28(m), 1.56(m), 2.01(m), 2.23(m), 2.76(m), 5.31(m)

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		C=CCH <sub>2</sub> C=C, CH=CH	
3	Leucine	αCH, δCH <sub>3</sub> , δCH <sub>3</sub>	3.72(t), 0.91(d), 0.96(d)
4	Isoleucine	γCH <sub>3</sub> , δCH <sub>3</sub>	1.01(d), 0.94(t)
5	Valine	αCH <sub>3</sub> , βCH, γCH <sub>3</sub>	3.61(d), 2.26(m), 0.99(d), 1.04(d)
6	β-Hydroxybutyrate	γCH <sub>3</sub>	1.20(d)
7	Lactate	αCH, βCH <sub>3</sub>	1.33(d), 4.11(q)
8	Threonine	αCH, βCH, γCH <sub>3</sub>	1.32(d), 4.25(m), 3.58(d)
9	Alanine	αCH, βCH <sub>3</sub>	1.48(d), 3.77(q)
10	Acetate	CH <sub>2</sub> -C=O	1.92(s)
11	Lysine	δCH <sub>2</sub> , βCH <sub>2</sub> , εCH <sub>2</sub> , αCH	1.75(m), 1.91(m), 3.03(t), 3.76(t)
12	Glutamate	αCH, βCH <sub>2</sub> , γCH <sub>2</sub>	2.06(m), 2.34(m), 3.75(m)
13	Glutamine	αCH, βCH <sub>2</sub> , γCH <sub>2</sub>	2.15(m), 2.45(m), 3.68(t)
14	Acetoacetate	CH <sub>3</sub>	2.29(s)
15	Pyruvate	CH <sub>3</sub>	2.36(s)
16	Succinate	α,βCH <sub>2</sub>	2.41(s)
17	GSH	βCH <sub>2</sub> , γCH <sub>2</sub> , CH, αCH, αCH <sub>2</sub>	2.16(m), 2.55(m), 2.95(m), 3.78(m)
18	GSSG	βCH <sub>2</sub> , γCH <sub>2</sub> , CH, αCH, αCH <sub>2</sub>	2.17(m), 2.52(m), 2.98(m), 3.78(m)
19	Methionine	αCH, βCH <sub>2</sub> , γCH <sub>2</sub> , S-CH <sub>3</sub>	2.14(s), 2.16(m), 3.87(t), 2.65(t)
20	Malate	CH <sub>2</sub> , CH-OH	2.67(dd), 4.29(dd)
21	Aspartate	βCH <sub>2</sub> , αCH	2.69(dd), 2.83(dd)
22	Dimethylamine	CH <sub>3</sub>	2.73(s)
23	Sarcosine	CH <sub>3</sub> , CH <sub>2</sub>	2.76(s), 3.65(s)

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24	TMA	CH <sub>3</sub>	2.88(s)
25	Dimethylglycine	CH <sub>3</sub>	2.93(s)
26	Creatine	N-CH <sub>3</sub> , CH <sub>2</sub>	3.03(s), 3.93(s)
27	Creatinine	CH <sub>3</sub> , CH <sub>2</sub>	3.06(s), 4.03(s)
28	Tyrosine	βCH <sub>2</sub> , 2,6-CH, 3,5-CH	3.06(dd), 3.15(dd), 6.90(d), 7.19(d)
29	Ethanolamine	CH <sub>2</sub> -NH <sub>2</sub> , CH <sub>2</sub> -OH	3.18(t), 3.83(t)
30	Choline	N-(CH <sub>3</sub> ) <sub>3</sub> , αCH <sub>2</sub> , βCH <sub>2</sub>	3.2(s), 4.05(t), 3.51(t)
31	Phosphocholine	N-(CH <sub>3</sub> ) <sub>3</sub> , βCH <sub>2</sub> , αCH <sub>2</sub>	3.23(s)
32	GPC	N-(CH <sub>3</sub> ) <sub>3</sub> , O-CH <sub>2</sub> , N-CH	3.24(s)
33	Taurine	N-CH <sub>2</sub> , S-CH <sub>2</sub>	3.26(t), 3.41(t)
34	TMAO	CH <sub>3</sub>	3.27(s)
35	Betaine	CH <sub>3</sub> , CH <sub>2</sub>	3.28(s), 3.90(s)
36	Myo-Inositol	5-CH, 4,6-CH, 2-CH	3.30(t), 3.63(t), 4.06(t)
37	Proline	βCH <sub>2</sub> , γCH <sub>2</sub> , δCH <sub>2</sub>	2.02-2.33(m), 2.00(m), 3.34(t)
38	Methanol	CH <sub>3</sub>	3.36(s)
39	Glycine	CH <sub>2</sub>	3.56(s)
40	AMP	5-CH <sub>2</sub> , 4-CH, 3-CH, 2-CH, 1- CH, 8-CH	4.04(m), 4.36(m), 4.51(m), 4.81(m), 6.15(d), 8.27(s), 8.61(s)
41	Inosine	3-CH, 1-CH, 8-CH, 2-CH	4.44(dd), 6.11(d), 8.24(s), 8.35(s)
42	β-Glucose	1-CH, 2-CH, 3-CH, 4-CH, 5- CH, 6-CH	4.65(d), 3.25(dd), 3.46(dd), 3.40(dd), 3.47(dd), 3.74(dd), 3.90(dd)
43	α-Glucose	1-CH, 2-CH, 3-CH, 4-CH, 5-	5.25(d), 3.54(dd), 3.71(dd), 3.42(dd),

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		CH, 6-CH <sub>2</sub>	3.83(dd), 3.78(dd)
44	Unsaturated lipids	=C-CH <sub>2</sub> -C=, -CH=CH-	5.19(m), 5.31(m)
45	Allantoin	CH	5.40(s)
46	Glycogen	1-CH, 2-CH, 3-CH, 4-CH, 5- CH, 6-CH <sub>2</sub>	5.41(m), 3.42(m), 3.60(m), 3.72(m), 3.86(m)
47	Uracil	CH, N-CH	7.54(d), 5.81(d)
48	Xanthine	2-CH, 1-CH	5.86 (d), 4.73 (m)
49	Uridine	N-CH, C-CH, CH <sub>2</sub>	7.88(d), 5.90(d), 3.92(dd)
50	Fumarate	CH, CH <sub>3</sub>	6.53(s)
51	Histidine	αCH, βCH <sub>2</sub>	7.88(s), 7.09(s)
52	Phenylalanine	2,6-CH, 3,5-CH, 4-CH	7.32(m), 7.42(m), 7.37(m)
53	Hypoxanthine	N-CH, CH	8.19(s), 8.22(s)
54	IMP	2-CH, 8-CH, 1-CH, 4-CH, 3- CH, CH <sub>2</sub>	8.57(s), 8.24(s), 6.15(d), 4.52(dd), 4.37(m), 4.03(m)
55	Formate	CH	8.46(s)
56	Nicotinate	5-CH, 4-CH, 6-CH, 2-CH, 5- CH, NH-CH <sub>2</sub>	7.60(dd), 8.26(d), 8.71(d), 8.95(s), 4.01(s)

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22 s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; m, multiplet; GSH, reduced

23 glutathione; GSSG, oxidized glutathione; GPC, glycerophosphorylcholine; TMA, trimethylamine;

24 TMAO, trimethylamine-N-oxide; AMP, adenosine 5'-monophosphate; IMP, inosine 5'-

25 monophosphate.