Supplemental Figures and Associated Legends

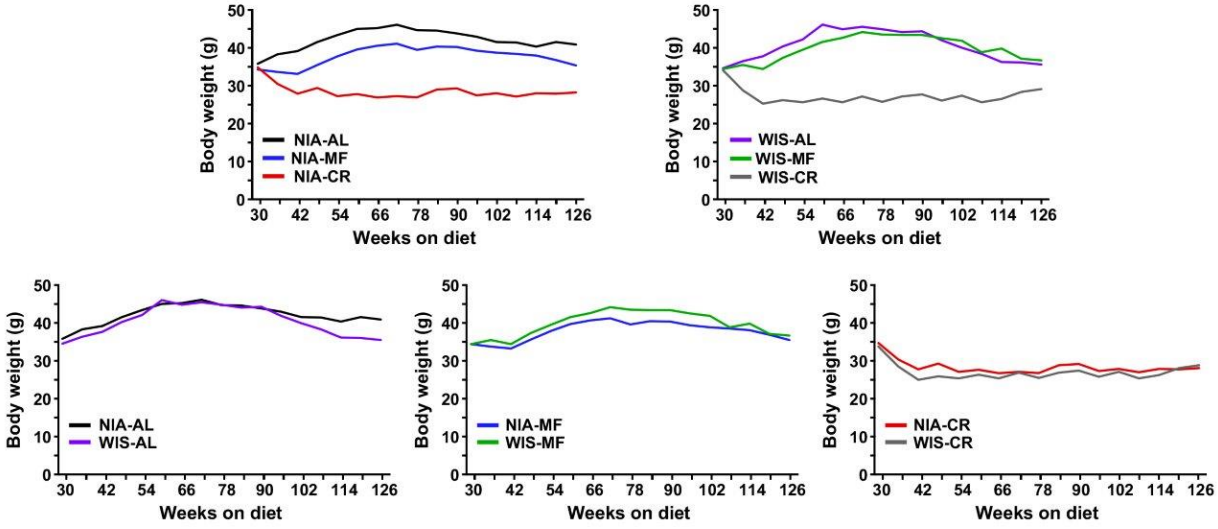

Figure S1. Bodyweight trajectories, **Related to Figure 1C**. Bodyweight trajectories for mice on NIA diet (upper, left panel) or WIS diet (upper right panel) for a period of 96 weeks. Lower panels depict bodyweight trajectories between NIA- and WIS-fed mice among the three feeding paradigms: AL (left panel), MF (middle panel) and CR (right panel).

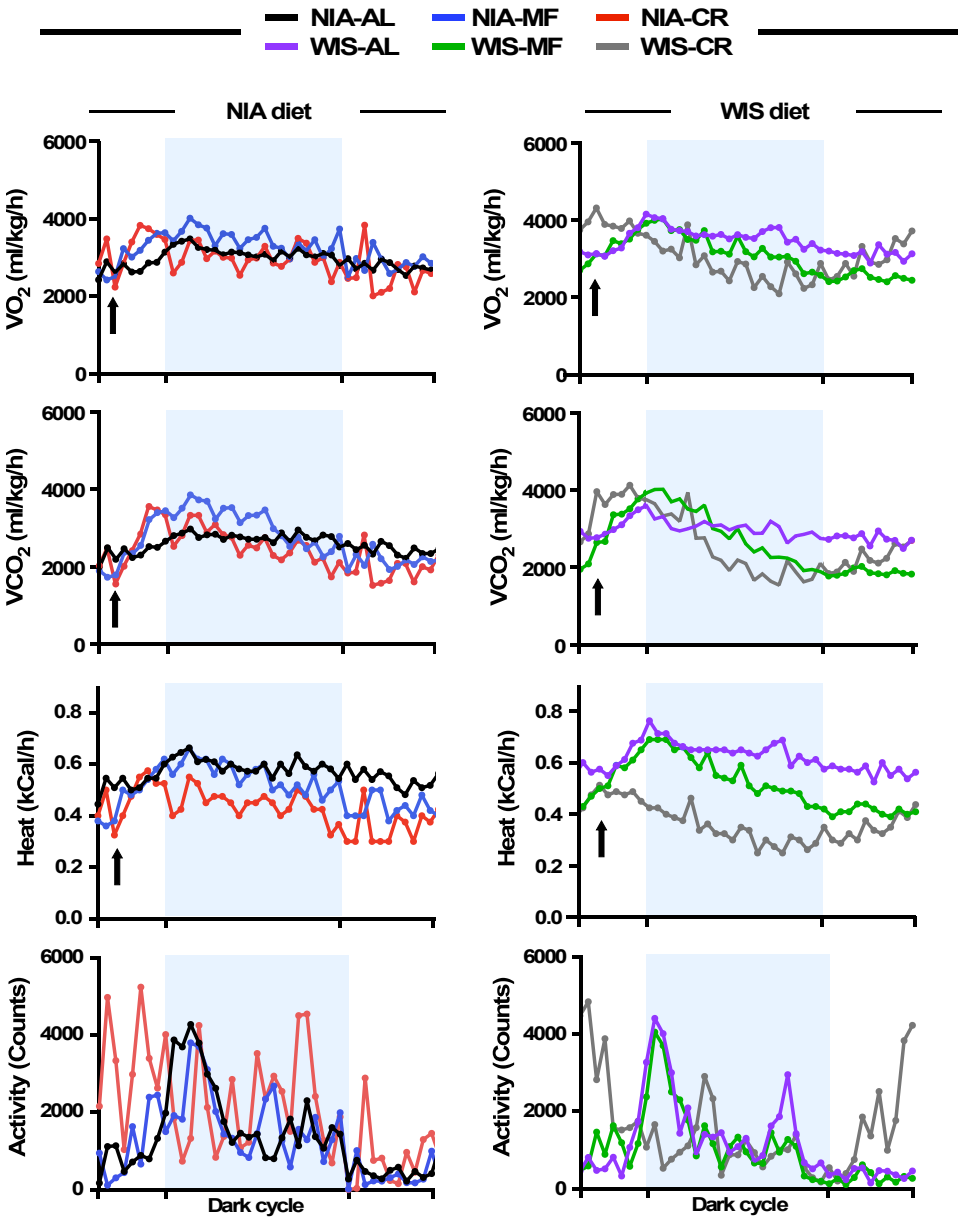

Figure S2. Metabolic assessments, **Related to Figure 1D**. At 41-42 months of age, mice were placed into metabolic cages to measure oxygen utilization (VO_2), carbon dioxide production (VCO_2), heat generation, and spontaneous activity as detailed in the STAR Methods. n=5-6 per group.

At meal time (3:00 PM), NIA-fed mice under CR showed rapid rise in VCO_2 and VO_2 and then followed trajectories similar as AL mice, while MF mice maintained larger VCO_2 and VO_2 values well in the dark cycle before returning to baseline levels (Fig. S2). Interestingly, the metabolism in WIS-fed mice under CR was more rapid at meal time but markedly decelerated at the onset of the dark cycle; falling well below the AL levels and consistent with fat fueling (Fig. S2). In MF mice on WIS diet, the VCO_2 and VO_2 values peaked at the onset of the dark cycle before slowly returning to baseline levels. Heat production rose in all groups of mice at meal time,

but followed different trajectories thereafter depending on the eating pattern and diet composition. For instance, mice under AL had the highest heat production at baseline, peaking at the onset of the dark cycle and remaining elevated throughout the night irrespective of diet type. Mice under MF exhibited sharp increase in heat production at meal time to reach levels comparable to those of AL mice. Note the faster rate of decline in heat production in WIS-fed mice than mice on the NIA diet at the onset of the dark cycle (Fig. S2). Diet composition had a profound impact on heat production in mice under CR especially when fed the WIS diet. Both MF and AL mice were most active at the onset of the dark cycle regardless of diet type. CR mice on the NIA diet appeared active at meal time and throughout the dark cycle whereas WIS-fed mice under CR were most active when anticipating meal time.

Table S1. Diet composition, **Related to Figure 1A.**

	NIA diet			WIS diet		
Ingredients	(% by weight)	% kcal	Sources	(% by weight)	% kcal	Sources
Protein	17.5	19.7	Soybean, fish meal	13.1	13.4	Lactalbumin
Sucrose	3.9	7.6		28.5	46.0	
Carbohydrate (other than sucrose)	48.3	55.0	Wheat, corn	32.72	16.3	Corn, dextrin
Fat	7.0	17.7	Soy, corn, fish oils	10.6	24.4	Corn oil
Fiber	6.7		Cellulose	5.0		Cellulose
Gross calculated caloric density (kCal/g)	3.418	100.0		3.927	100.0	

Table S2. Two-way ANOVA analyses of the indicated measures, **Related to Figure 1.**

	Average time to eat 2 replicates		Food consumed (kCal/day)		Average bodyweight over 116 weeks	
	F (DFn, DFd)	P value	F (DFn, DFd)	P value	F (DFn, DFd)	P value
Feeding regimen	F (1, 122) = 258.4	<0.0001	F (2, 72) = 139.7	<0.0001	F (2, 336) = 322.5	<0.0001
Diet type	F (1, 122) = 35.46	<0.0001	F (1, 72) = 115.5	<0.0001	F (1, 336) = 0.197	0.6575
Interaction	F (1, 122) = 0.0429	0.8363	F (2, 72) = 10.86	<0.0001	F (2, 336) = 7.037	0.0010

	Insulin		3-h FBG		HOMA-IR	
	F (DFn, DFd)	P value	F (DFn, DFd)	P value	F (DFn, DFd)	P value
Feeding regimen	F (2, 30) = 13.29	<0.0001	F (2, 41) = 6.72	0.0030	F (2, 30) = 22.81	<0.0001
Diet type	F (1, 30) = 1.989	0.1688	F (1, 41) = 0.0594	0.8086	F (1, 30) = 2.49	0.1250
Interaction	F (2, 30) = 0.0735	0.9293	F (2, 41) = 1.117	0.3370	F (2, 30) = 0.0532	0.9483

	β-hydroxybutyrate	
	F (DFn, DFd)	P value
Feeding regimen	F (2, 33) = 66.44	<0.0001
Diet type	F (1, 33) = 15.06	0.0005
Interaction	F (2, 33) = 14.81	<0.0001

Table S3. Lifespan statistics associated with the Kaplan-Meier survival curves for mice on the indicated feeding regimen and diet, **Related to Figures 2A-2C**.

Diet	Feeding		Lifespan analysis				
		n	Mean	25%	Median	75%	LogRank
NIA	AL	45	105.7 ± 3.6	88.6	103.7	120.4	<0.001
	MF	40	121.1 ± 3.6	107	122.9	134.9	
	CR	59	140.6 ± 3.1	121	140.1	160	
WIS	AL	44	106.8 ± 3.1	92	108.3	115.8	<0.001
	MF	41	118.5 ± 3.7	102.5	115.9	126.5	
	CR	62	136.2 ± 3.0	125.9	136.6	156.9	
Combined NIA+WIS	AL	89	107.6 ± 2.4	92	107	121	<0.001
	MF	81	119.8 ± 2.6	105.9	121.7	134.9	
	CR	12	138.5 ± 2.1	124	140.1	159	

LogRank test (Holm-Sidak method) was used. As there was no significant difference within feeding paradigms across diets (i.e. no significant difference in survival curves between NIA-AL and WIS-AL groups), diets were combined together to become a 'combined diet group'. AL, *ad libitum;* MF, Meal-fed; CR, 30% calorie restriction.

Table S4. LogRank test with multiple comparisons (Holm-Sidak method), **Related to Figures 2A-2C.**

Comparisons	**Statistic**	***P* Value**
NIA-AL vs. NIA-CR	44.338	8.29E-11
NIA-MF vs. NIA-CR	15.856	0.000137
NIA-AL vs. NIA-MF	6.176	0.0130
WIS-AL vs. WIS-CR	45.230	1.75E-11
WIS-MF vs. WIS-CR	14.774	0.000121
WIS-AL vs. WIS-MF	5.739	0.0166
NIA-AL vs. WIS-AL	0.00446	0.947
NIA-MF vs. WIS-MF	0.0188	0.891
NIA-CR vs. WIS-CR	1.553	0.213

Table S5. Kaplan-Meier survival curves were compared using LogRank test (Holm-Sidak method), **Related to Figures 2A-2C.**

	AL vs MF		AL vs CR		MF vs CR	
Diet type	Statistic	*P* value	Statistic	*P* value	Statistic	*P* value
Combined NIA+WIS	6.9	0.0015	80.1	6.60E-20	38.5	<0.0001

Table S6. Blinded histopathological analysis of tissues collected at death as scored by board certified veterinary pathologists, **Related to Figure 3.**

		NIA diet			WIS diet		
Feeding paradigm		AL	MF	CR	AL	MF	CR
Mean age at necropsy (weeks)		104 ± 0.3	117 ± 0.4	132 ± 0.2	110 ± 0.4	115 ± 0.3	135 ± 0.2
N scored (% of total study mice)		33 (73.3)	31 (77.5)	42 (71.2)	28 (63.6)	30 (73.2)	41 (66.1)
Heart	Overall no pathology, n (%)	9 (27.3)	17 (54.8)	18 (42.9)	18 (64.3)	18 (60.0)	22 (53.7)
	Mineralization	3 (1.7 ± 0.7)	1 (1)	1 (1)	0 (0)	1 (1)	2 (1.0 ± 0)
	Degeneration	1 (1)	0 (0)	0 (0)	1 (1)	1 (1)	1 (3)
	Amyloid	21 (2.9 ± 0.25)	13 (2.8 ± 0.3)	22 (2.7 ± 0.2)	8 (2.9 ± 0.4)	9 (2.4 ± 0.4)	15 (3.1 ± 0.3)
	Hemangiosarcoma	0 (0)	0 (0)	0 (0)	1 (4)	0 (0)	0 (0)
	Necrosis	0 (0)	0 (0)	1 (1)	0 (0)	1 (1)	1 (1)
	Suppurative inflammation	0 (0)	1 (3)	0 (0)	0 (0)	0 (0)	1 (1)
	Thrombosis	2 (3 ± 1)	0 (0)	2 (1.5 ± 0.5)	0 (0)	2 (2.0 ± 0)	2 (2.0 ± 0)
	Lymphoma	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Liver	Overall no pathology, n (%)	11 (33.3)	5 (16.1)	6 (14.3)	5 (17.9)	5 (16.7)	5 (12.2)
	Mineralization	2 (1.5 ± 0.5)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Amyloid	11 (1.5 ± 0.2)	8 (1.9 ± 0.1)	18 (1.6 ± 0.2)	5 (1.6 ± 0.2)	2 (1.5 ± 0.5)	9 (1.9 ± 0.3)
	Hemisarcoma	3 (3.7 ± 0.9)	1 (4)	0 (0)	4 (3.0 ± 0.7)	1 (5)	1 (5)
	Hepatocellular carcinoma	2 (2 ± 0)	3 (2.0 ± 0.6)	0 (0)	6 (3.2 ± 0.4)	3 (3.3 ± 0.7)	4 (3.3 ± 0.3)
	Hyperplasia	0 (0)	0 (0)	2 (3.5 ± 0.5)	0 (0)	1 (2)	0 (0)
	Lipidosis	0 (0)	1 (1)	0 (0)	3 (2.7 ± 0.3)	6 (2.7 ± 0.3)	0 (0)
	Hepatoadenoma	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Necrosis	0 (0)	1 (2)	1 (1)	1 (1)	1 (3)	1 (3)
	Cyst	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)
	Lymphocytic infiltration	2 (1 ± 0)	3 (1.0 ± 0)	3 (1.0 ± 0)	3 (1.0 ± 0)	4 (1.0 ± 0)	4 (1.3 ± 0.3)
	Lymphoma	6 (2.2 ± 0.5)	11 (2.7 ± 0.4)	16 (2.7 ± 0.2)	8 (1.8 ± 0.3)	12 (2.5 ± 0.3)	20 (2.5 ± 0.2)
Kidney	Overall no pathology, n (%)	1 (3.03)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Mineralization	12 (1.1 ± 0.1)	7 (1.0 ± 0)	16 (1.1 ± 0.1)	14 (1.0 ± 0)	15 (1.1 ± 0.1)	19 (1.4 ± 0.3)
	Degeneration	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Amyloid	13 (4.4 ± 0.2)	9 (4.0 ± 0.4)	19 (3.8 ± 0.3)	8 (3.8 ± 0.4)	4 (2.8 ± 0.9)	18 (3.2 ± 0.4)
	Glomerulonephritis	32 (3.0 ± 0.3)	31 (2.5 ± 0.2)	41 (2.9 ± 0.2)	27 (2.8 ± 0.2)	30 (2.8 ± 0.2)	41 (2.8 ± 0.2)
	Hydronephritis	1 (4)	1 (4)	0 (0)	0 (0)	1 (2)	0 (0)
	Necrosis	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)
	Adenoma	1 (4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Cyst	1 (1)	0 (0)	0 (0)	0 (0)	1 (1)	3 (2.0 ± 0.6)
	Carcinoma	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	1 (4)

	Lymphocytic infiltration	12 (1.2 ± 0.1)	9 (1.0 ± 0)	10 (1.2 ± 0.1)	9 (1.2 ± 0.1)	13 (1.3 ± 0.1)	11 (1.0 ± 0)
	Suppurative inflammation	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (3)
	Lymphoma	3 (2.3 ± 0.3)	3 (2.7 ± 1.2)	1 (2)	6 (2.3 ± 0.2)	6 (1.5 ± 0.2)	3 (1.3 ± 0.3)
Spleen	Overall no pathology, n (%)	12 (36.4)	11 (35.5)	15 (35.7)	15 (53.6)	21 (70.0)	20 (48.8)
	Mineralization	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Degeneration	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Amyloid	14 (4.5 ± 0.3)	11 (4.5 ± 0.4)	21 (4.6 ± 0.2)	5 (4.2 ± 0.4)	1 (5)	13 (3.8 ± 0.4)
	Hemisarcoma	4 (4 ± 0.4)	0 (0)	1 (1)	3 (4.0 ± 0.6)	1 (5)	1 (4)
	Hyperplasia	0 (0)	1 (3)	0 (0)	0 (0)	0 (0)	0 (0)
	Necrosis	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Carcinoma	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Lymphocytic infiltration	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Suppurative inflammation	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Lymphoma	4 (2.5 ± 0.6)	6 (2.2 ± 0.6)	5 (2.4 ± 0.7)	5 (1.6 ± 0.2)	7 (1.1 ± 0.1)	6 (1.8 ± 0.3)
Lung	Overall no pathology, n (%)	10 (30.3)	12 (38.7)	10 (23.8)	6 (21.4)	8 (26.7)	7 (17.1)
	Mineralization	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Congestion	0 (0)	0 (0)	1 (3)	0 (0)	0 (0)	0 (0)
	Amyloid	1 (1)	1 (1)	2 (1.5 ± 0.5)	1 (1)	2 (1.5 ± 0.5)	1 (2)
	Thrombosis	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	1 (1)
	Hyperplasia	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Alveolar/bronchiolar carcinoma	1 (5)	0 (0)	0 (0)	1 (4)	3 (1.7 ± 0.7)	0 (0)
	Edema	1 (4)	0 (0)	0 (0)	1 (3)	0 (0)	0 (0)
	Necrosis	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Alveolar/bronchiolar adenoma	5 (1.2 ± 0.2)	6 (1.8 ± 0.2)	8 (1.6 ± 0.4)	4 (2.0 ± 0.2)	7 (1.6 ± 0.2)	6 (1.3 ± 0.2)
	Alveolar proteinosis	2 (3 ± 2)	1 (2)	0 (0)	1 (3)	0 (0)	0 (0)
	Lymphocytic infiltration	14 (1.3 ± 0.1)	10 (1.7 ± 0.2)	19 (1.1 ± 0.1)	13 (1.4 ± 0.2)	10 (1.2 ± 0.1)	16 (1.2 ± 0.1)
	Suppurative inflammation	0 (0)	0 (0)	0 (0)	0 (0)	2 (1.5 ± 0.5)	0 (0)
	Lymphoma	5 (2.4 ± 0.4)	8 (2.1 ± 0.3)	11 (2.2 ± 0.3)	6 (2.3 ± 0.3)	8 (2.3 ± 0.4)	13 (2.7 ± 0.2)
Pancreas	Overall no pathology, n (%)	23 (69.7)	26 (83.9)	30 (71.4)	23 (82.1)	27 (90.0)	32 (78.0)
	Mineralization	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Amyloid	7 (1.1 ± 0.1)	3 (1.0 ± 0)	9 (1.6 ± 0.2)	5 (1.6 ± 0.2)	1 (1)	8 (1.9 ± 0.4)
	Lymphocytic infiltration	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)
	Suppurative inflammation	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Lymphoma	0 (0)	1 (1)	2 (1.5 ± 0.5)	0 (0)	1 (1)	1 (2)
Lymph nodes	Overall no pathology, n (%)	17 (51.1)	20 (64.5)	24 (57.1)	16 (57.1)	21 (70.0)	25 (61.0)

	Mineralization	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Amyloid	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
	Lymphocytic infiltration	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Suppurative inflammation	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Lymphoma	4 (3.5 ± 1.0)	9 (3.0 ± 0.4)	5 (3.8 ± 0.2)	5 (2.6 ± 1.0)	9 (1.8 ± 0.3)	12 (1.8 ± 0.4)