SUPPLEMENTAL FIGURE LEGENDS

Supplemental Figure 1. Serial weights and food intake in control and 2-AAA treated animals.

Supplemental Figure 2. Insulin tolerance tests were performed after completion of chronic 2-AAA treatment in mice fed either the standard chow or the high-fat diet (n=12 per condition)

Supplemental Figure 3. BTC6 cells were incubated with 2-AAA at concentrations ranging from 0 to 100 µM for 24 hours as per **Figure 5A**, but in the presence of higher ambient glucose (5.0 mM).

Supplemental Figure 4. Representative dose-response studyusing isotope-labeled standard for 2-AAA in normal pooled human plasma is shown.The parent to product ion MRM transition used for 2-AAA-d3 was m/z 163 to m/z 119, while the MRM transition for endogenous 2-AAA was 160 to 116. Boxes represent mean data from calibration curves run at the beginning, middle, and end of each analytical batch of ~150 samples. The median concentration of the endogenous 2-AAA in the control samples as assessed by the LC-MS method is denoted with an arrow

(1.22μM).Peak areas were >2 orders of magnitude above the lower limit of quantitation (as defined as a discrete peak 10-fold greater than noise, lowest dose with a closed box) and fell well within the linear range of the dose-response relationship.

Supplemental Table 1: Metabolite profiling in individuals with and without incident diabetes (Framingham Heart Study). The 57 metabolites listed were detected in at least 70% of the study sample.

Metabolite	Paired T-statistic	P-value
2-aminoadipate	3.39	0.0009
quinolinate	2.53	0.0121
PEP	2.49	0.0138
UDP-galactose/UDP-glucose	2.42	0.0164
hippurate	-2.19	0.0294
F1P/F6P/G1P/G6P	2.24	0.0265
beta-hydroxybutyrate	-1.95	0.0529
UDP	1.91	0.0583
3-methyladipate	-1.85	0.0657
salicylurate	1.77	0.0780
isocitrate	1.61	0.11
alpha-glycerophosphate	1.58	0.12
kynurenine	1.56	0.12
hypoxanthine	-1.44	0.15
urate	1.43	0.15
glycodeoxycholate/glycochenodeoxycholate	1.36	0.18
glycocholate	1.31	0.19
4-pyridoxate	-1.26	0.21
phosphoglycerate	1.23	0.22
lactate	1.13	0.26
hydroxyphenylacetate	1.13	0.26
pantothenate	-1.09	0.28
adipate	-0.99	0.32
xanthurenate	0.96	0.34
fumarate/maleate	-0.91	0.36
indole-3-propionate	-0.90	0.37
alpha-ketoglutarate	-0.88	0.38
xanthine	0.78	0.44
citrate	-0.76	0.45
GDP	0.75	0.45
alpha-hydroxybutyrate	-0.74	0.46
GMP	0.73	0.46
indoxylsulfate	0.71	0.48
uridine	0.65	0.52

cystathionine	0.64	0.53
ribose-5-phosphate/ribulose-5-phosphate	0.63	0.53
pyruvate	0.56	0.57
sucrose	0.54	0.59
oxalate	-0.43	0.67
hyodeoxycholate/ursodeoxycholate/chenodeoxycholate/deoxycholate	0.41	0.68
suberate	-0.34	0.74
gentisate	0.30	0.76
aconitate	0.29	0.77
inositol	-0.29	0.77
inosine	0.26	0.79
taurocholate	-0.26	0.80
ADP	0.26	0.80
propionate	0.25	0.80
AMP	0.25	0.81
orotate	0.18	0.86
phosphocreatine	0.15	0.88
lactose	0.13	0.90
cAMP	-0.13	0.92
taurodeoxycholate/taurochenodeoxycholate	0.09	0.93
2-hydroxyglutarate	-0.09	0.93
malate	-0.08	0.94
sorbitol	0.04	0.97

Results are from paired t-tests (case minus control) for each variable.

Supplemental Table 2: Biochemical measures of glycemia in study samples

	Framingham Heart Study		Malmö Diet and Cancer Study	
	Cases (n=188)	**Matched Controls (n=188)**	**Cases (n=162)**	**Matched Controls (n=162)**
Fasting glucose, mg/dl	105 (14)	106 (12)	97 (13)	97 (11)
Hemoglobin A1c, %	5.5 (0.7)	5.4 (0.8)	-	-
Fasting insulin, uIU/ml	11.7 (11.4)	9.9 (9.6)	9.0 (6.0)	9.0 (6.0)
HOMA-IR	3.0 (2.8)	2.5 (2.6)	2.2 (1.4)	2.1 (1.7)
2-hour OGTT glucose, mg/dl	123 (44)	115 (39)	-	-
Prediabetes, %	79%	83%	47%	40%

Values are medians and IQR. Prediabetes is defined as hemoglobin A1c of 5.7 to 6.4% or fasting glucose of 100 to 125 mg/dl.

Supplemental Table 3: Relative risk of diabetes for individuals in the top quartile of 2-AAA and other metabolic predictors

	Case-control sample	**"Whole cohort" sample**
2-AAA	4.56 (1.93-10.75)	2.07 (1.31-3.28)
Insulin	1.76 (0.97-3.20)	2.49 (1.56-3.99)
Glucose	N/A	4.23 (2.16-8.40)
2-hour glucose (OGTT)	2.54 (1.30-5.00)	3.12 (1.98-4.92)
BMI	N/A	3.34 (1.91-5.84)
HbA1c	1.64 (0.74-3.61)	2.04 (1.25-3.34)

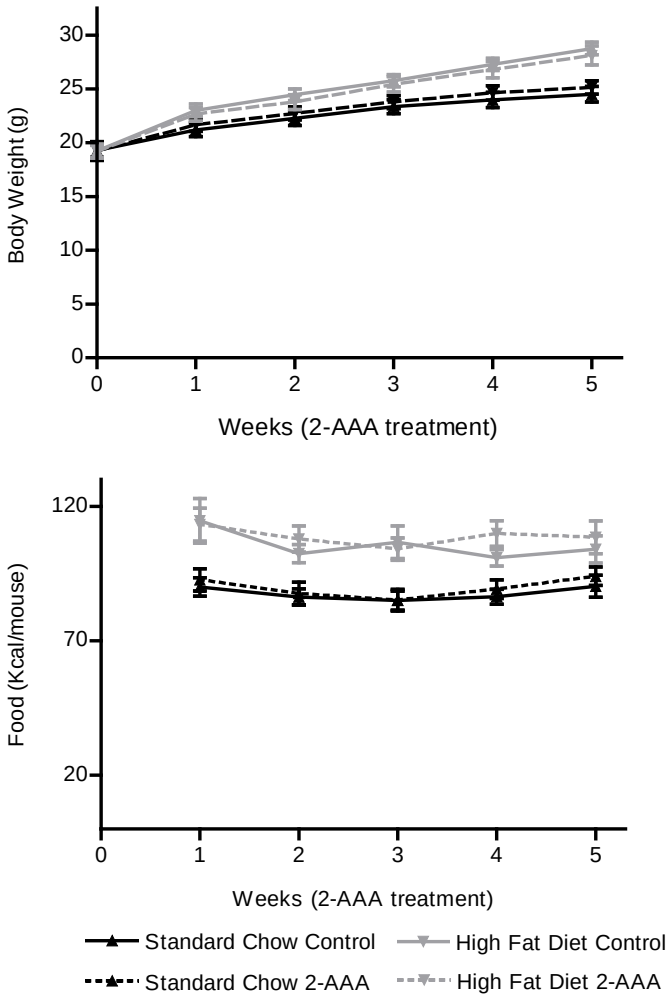
Values shown are odds ratios (case-control sample) or hazard ratios (whole cohort sample) from age- and sex-adjusted regression models. 95% confidence intervals are shown in the parentheses.

N/A: not analyzed in the case-control sample because individuals were matched according to fasting glucose and BMI.

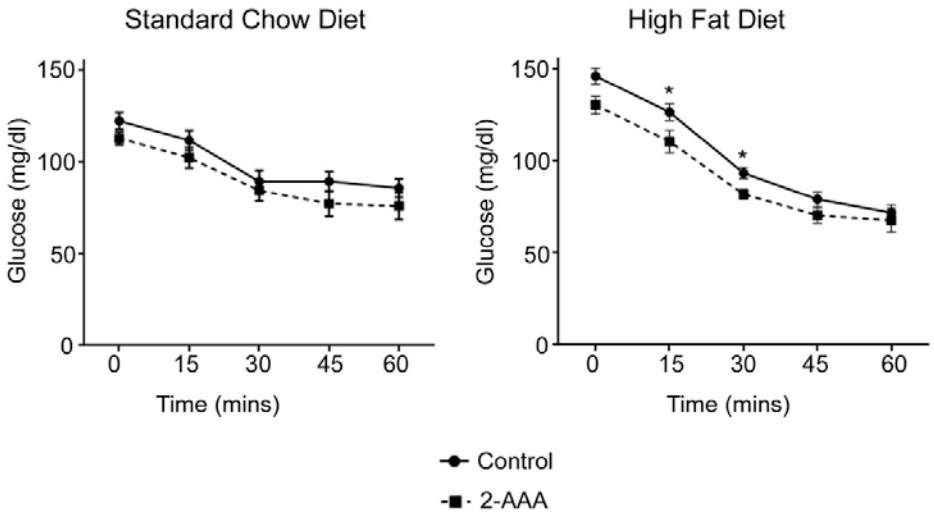
Supplemental Table 4: Distribution of 2-AAAconcentrations. To estimate normative values for 2-AAA, we selected a healthy reference sample comprised of individuals from the Framingham Offspring Cohort who met the following criteria: no prior cardiovascular disease, no hypertension, BMI less than 30 kg/m^2, no valvular heart disease, and estimated glomerular filtration rate >60 (n=819). The mean age in the reference sample was 52 years, and 57% were female. Absolute quantitation for 2-AAA was performed using an isotope-labeled reference compound. The full distribution of 2-AAA values in the reference sample is shown below. The mean for the cases was 1.55 μM; the mean for the controls was 1.40 μM.

Quantile	**2-AAA level (μM)**
0% (Minimum)	0.42
10%	0.76
25% Q1	0.96
50% (Median)	1.22
75% Q3	1.53
90%	1.93
100% (Maximum)	8.77

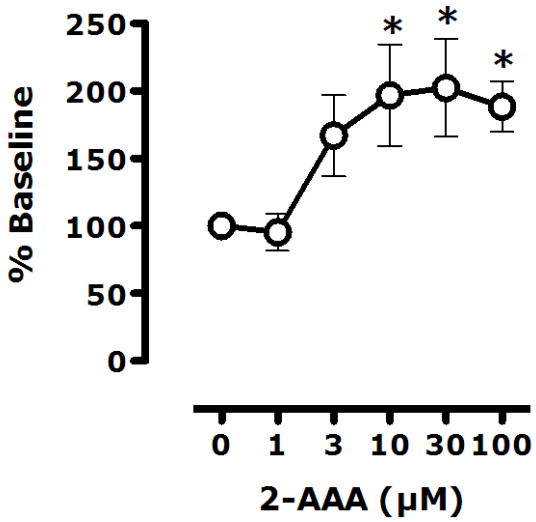
Supplemental Figure 1



Supplemental Figure 2



Supplemental Figure 3



Supplemental Figure 4