Supplemental Table S1: Clinical laboratory tests. Data are summarized by means with standard deviations. P-values compare means estimated by the general linear mixed regression model. YAG-0w, YAG-2w = YA before and after receiving 2w of GlyNAC supplementation. OAG-0w, OAG-2w, OAG-16w, and OAP-0w, OAP-2w, OAP-16w = OA before and after 2w and 16w of GlyNAC, or placebo supplementation.

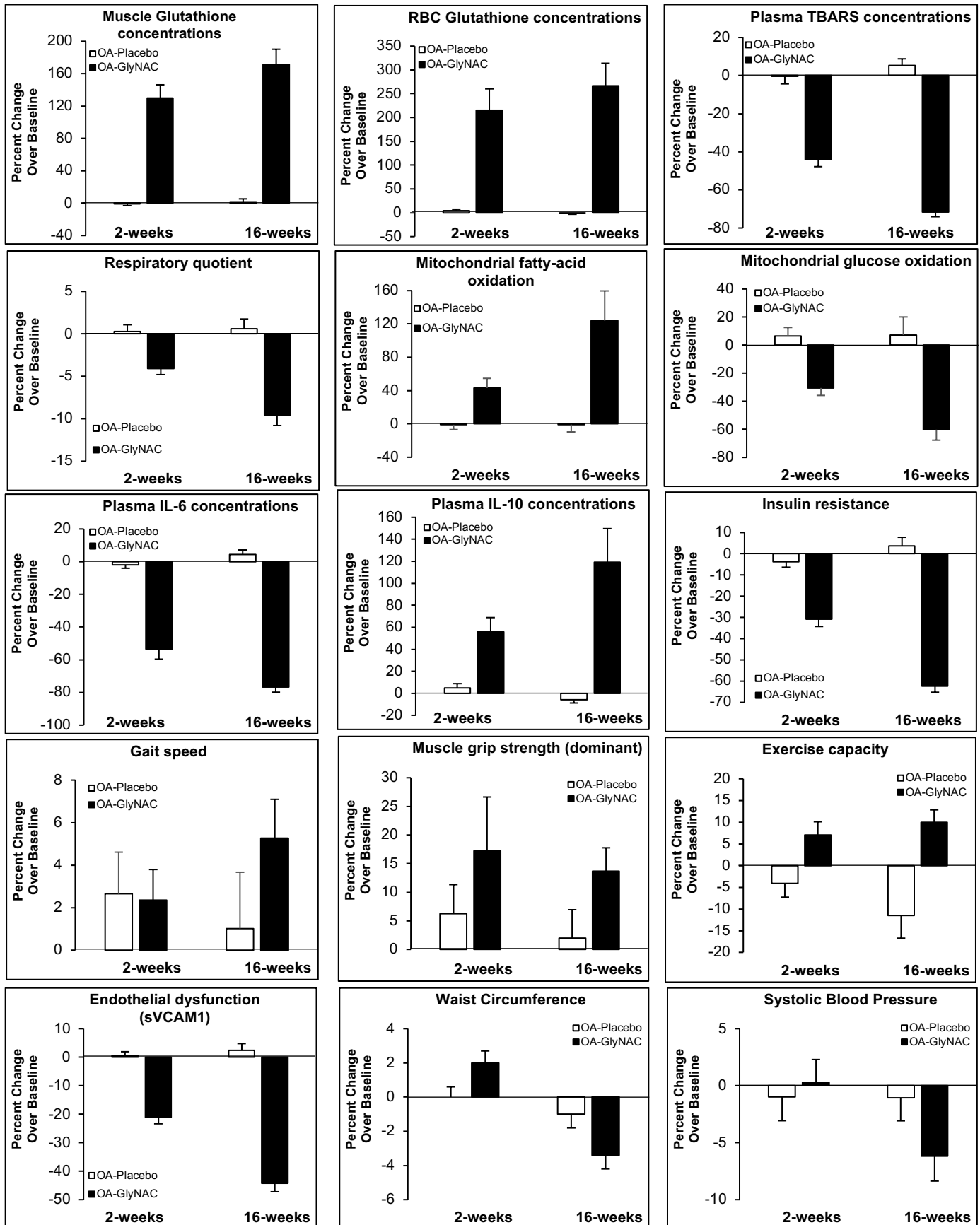| Parameters	YAG-0w (N=11)	YAG-2w (N=11)	OAG-0w *YA-0w v OAG-0w* (N=12)	OAG-2w (N=12)	OAG-16w *OAG-0w v OAG-16w; OAG-16w v YA-0w* (N=11)	OAP-0w *YA-0w v OAP-0w; OAP-0w v OAG-0w* (N=12)	OAP-2w (N=12)	OAP-16w *OAP-0w v OAP-16w* (N=12)
Hemoglobin (g/L)	13.7 ± 1.5	13.4 ± 1.5	14.7 ± 1.2 *P=0.47*	13.9 ± 0.8 *P=0.017*	14.0 ± 0.8 *P=0.17* *P>0.99*	14.0 ± 1.3 *P>0.99* *P=0.82*	13.5 ± 1.2 *P=0.23*	13.7 ± 1.2 *P>0.99*
Total protein (g/dl)	7.3 ± 0.3	7.1 ± 0.3	7.0 ± 0.4 *P=0.18*	6.9 ± 0.3 *P>0.99*	6.8 ± 0.4 *P>0.99* *P=0.052*	6.9 ± 0.2 *P=0.032* *P>0.99*	6.8 ± 0.4 *P>0.99*	6.8 ± 0.4 *P>0.99*
Albumin (mg/dl)	4.7 ± 0.2	4.7 ± 0.3	4.3 ± 0.3 *P=0.001*	4.3 ± 0.4 *P>0.99*	4.3 ± 0.3 *P>0.99* *P=0.003*	4.4 ± 0.2 *P=0.002* *P>0.99*	4.4 ± 0.2 *P>0.99*	4.3 ± 0.2 *P>0.99*
Total bilirubin (mg/dl)	0.7 ± 0.4	0.6 ± 0.3	0.5 ± 0.1 *P=0.29*	0.5 ± 0.1 *P>0.99*	0.4 ± 0.1 *P>0.99* *P=0.11*	0.6 ± 0.3 *P>0.99* *P>0.99*	0.5 ± 0.3 *P>0.99*	0.4 ± 0.3 *P=0.11*
Direct bilirubin (mg/dl)	0.2 ± 0.1	0.1 ± 0.1	0.1 ± 0.0 *P=0.38*	0.1 ± 0.0 *P>0.99*	0.1 ± 0.0 *P>0.99* *P=0.36*	0.1 ± 0.1 *P>0.99* *P>0.99*	0.1 ± 0.1 *P>0.99*	0.1 ± 0.1 *P>0.99*
Alkaline phosphatase (U/L)	51.4 ± 17.3	54.0 ± 15.5	67.3 ± 17.7 *P=0.17*	71.0 ± 16.0 *P=0.65*	72.2 ± 21.6 *P=0.14* *P=0.039*	72.4 ± 17.0 *P=0.045* *P>0.99*	70.1 ± 16.9 *P>0.99*	75.0 ± 17.2 *P>0.99*
Blood urea nitrogen (BUN) (mmol/L)	13.9 ± 4.1	14.1 ± 3.6	14.9 ± 4.1 *P>0.99*	17.8 ± 5.0 *P=0.013*	14.7 ± 4.8 *P>0.99* *P>0.99*	15.1 ± 3.6 *P>0.99* *P>0.99*	17.2 ± 3.7 *P=0.13*	16.6 ± 2.5 *P = 0.45*

Outcome measure	YAG-0w (N=11)	YAG-2w (N=11)	OAG-0w YA-0w v OAG-0w (N=12)	OAG-2w (N=12)	OAG-16w OAG-0w v OAG-16w; OAG-16w v YA-0w (N=11)	OAP-0w YA-0w v OAP-0w; OAP-0w v OAG-0w (N=12)	OAP-2w (N=12)	OAP-16w OAP-0w v OAP-16w; (N=12)
Estimated glomerular filtration rate (eGFR)	95.0 ± 14.3	101.5 ± 19.1	77.2 ± 15.8 *P=0.030*	75.0 ± 17.7 *P>0.99*	76.3 ± 16.0 *P>0.99* *P=0.026*	77.2 ± 11.3 *P=0.030* *P>0.99*	76.3 ± 10.0 *P>0.99*	80.4 ± 11.1 *P>0.99*
Plasma total cholesterol (LDLc) (mg/dL)	175.4 ± 26.6	168.3 ± 24.3	194.9 ± 34.6 *P=0.73*	195.7 ± 66.2	196.2 ± 45.2 *P>0.99* *P=0.67*	201.0 ± 26.3 *P=0.36* *P>0.99*	195.5 ± 26.3	196.2 ± 29.8 *P>0.99* *P=0.73*
Plasma triglycerides (mg/dL)	77.3 ± 28.7	75.0 ± 25.3	169.0 ± 92.5 *P=0.012*	150.7 ± 65.5	141.7 ± 74.4 *P=0.089* *P=0.103*	120.3 ± 48.1 *P=0.45* *P=0.34*	135.3 ± 63.4	115.8 ± 29.4 *P=0.70* *P=0.45*
Plasma HDL-cholesterol (HDLc) (mg/dL)	56.9 ± 17.0	54.9 ± 17.1	50.3 ± 23.4 *P>0.99*	40.5 ± 10.6	51.7 ± 26.2 *P>0.99* *P>0.99*	57.6 ± 17.4 *P>0.99* *P>0.99*	53.7 ± 15.6	56.9 ± 16.5 *P>0.99* *P>0.99*
Plasma LDL-cholesterol (mg/dL)	103.0 ± 24.9	98.3 ± 23.3	116.8 ± 31.9 *P>0.99*	108.4 ± 33.3	116.2 ± 30.6 *P>0.99* *P>0.99*	119.4 ± 23.7 *P>0.99* *P>0.99*	110.4 ± 20.0	113.8 ± 29.0 *P>0.99* *P>0.99*
Plasma non-HDL-cholesterol (mg/dL)	118.5 ± 25.7	113.4 ± 25.7	144.7 ± 32.8 *P=0.28*	155.2 ± 65.2	144.5 ± 37.0 *P>0.99* *P=0.27*	143.4 ± 28.7 *P=0.30* *P>0.99*	141.8 ± 32.7	139.3 ± 32.4 *P>0.99* *P=0.63*
LDLc/HDLc ratio	2.0 ± 0.8	2.0 ± 0.8	2.5 ± 0.9 *P>0.99*	2.7 ± 0.7	2.4 ± 1.0 *P>0.99* *P>0.99*	2.3 ± 1.0 *P>0.99* *P>0.99*	2.3 ± 0.9	2.3 ± 1.1 *P>0.99* *P>0.99*
Plasma thyroid stimulating hormone (TSH, mIU/L)	2.3 ± 1.3	1.8 ± 0.7	2.7 ± 1.6 *P>0.99*	2.4 ± 1.4 *P>0.99*	2.3 ± 1.3 *P>0.99* *P>0.99*	2.7 ± 1.4 *P>0.99* *P>0.99*	2.6 ± 1.3	2.6 ± 1.0 *P>0.99*

Outcome measure	YAG-0w (N=11)	YAG-2w (N=11)	OAG-0w YA-0w v OAG-0w (N=12)	OAG-2w (N=12)	OAG-16w OAG-0w v OAG-16w; OAG-16w v YA-0w (N=11)	OAP-0w YA-0w v OAP-0w; OAP-0w v OAG-0w (N=12)	OAP-2w (N=12)	OAP-16w OAP-0w v OAP-16w; (N=12)
Plasma free thyroxine (FT4, ng/L)	1.2 ± 0.2	1.2 ± 0.2	1.0 ± 0.2 *P=0.13*	1.1 ± 0.1 *P>0.99*	1.1 ± 0.2 *P>0.99* *P=0.48*	1.0 ± 0.1 *P=0.089* *P>0.99*	1.1 ± 0.2 *P>0.99*	1.1 ± 0.1 *P>0.99*
Glycosylated hemoglobin (HbA1c, %)	5.3 ± 0.2	-	5.8 ± 0.2 *P<0.001*	-	-	5.6 ± 0.3 *P=0.03*	-	

Supplemental Table S2: Monitored blood labs. Data are summarized by means with standard deviations. P-values compare means estimated by the general linear mixed regression model. 2w, 4w, 8w, 12w, 16w refer to weeks after receiving supplements. P = compared to 0w.

	0w	2w	4w	8w	12w	16w
Alanine transaminase (ALT; U/L)						
YAG (N=11)	17.1 ± 5.8	16.5 ± 5.9 *P>0.99*	-	-	-	-
OAG (N=12 for 0w, 2w; N=11 for 4w, 8w, 12w, 16w)	24.6 ± 9.6	25.1 ± 10.2 *P>0.99*	25.5 ± 11.4 *P>0.99*	23.2 ± 13.8 *P>0.99*	24.9 ± 18.6 *P>0.99*	25.2 ± 19.3 *P>0.99*
OAP (N=12)	23.0 ± 9.0	23.8 ± 10.1 *P>0.99*	22.1± 7.5 *P>0.99*	23.1 ± 7.6 *P>0.99*	20.8 ± 4.2 *P>0.99*	24.9 ± 8.3 *P>0.99*
Aspartate transaminase (AST; U/L)						
YAG (N=11)	18.3 ± 8.2	20.1 ± 10.2 *P>0.99*	-	-	-	-
OAG (N=12 for 0w, 2w; N=11 for 4w, 8w, 12w, 16w)	21.9 ± 3.8	23.9 ± 7.4 *P>0.99*	21.3 ± 7.1 *P>0.99*	20.5 ± 6.6 *P>0.99*	22.6 ± 8.9 *P>0.99*	25.2 ± 9.6 *P>0.99*
OAP (N=12)	24.2 ± 6.3	23.9 ± 8.2 *P>0.99*	19.9 ± 8.2 *P=0.27*	20.0 ± 6.2 *P=0.38*	20.1 ± 6.8 *P>0.99*	23.4 ± 9.5 *P>0.99*
Creatinine (mg/dl)						
YAG (N=11)	0.9 ± 0.2	0.8 ± 0.2 *P=0.44*	-	-	-	-
OAG (N=12 for 0w, 2w; N=11 for 4w, 8w, 12w, 16w)	0.9 ± 0.2	0.9 ± 0.2 *P>0.99*	0.9 ± 0.2 *P>0.99*	1.0 ± 0.3 *P>0.99*	1.0 ± 0.3 *P>0.99*	0.9 ± 0.2 *P>0.99*
OAP (N=12)	0.8 ± 0.2	0.9 ± 0.2 *P>0.99*	0.9 ± 0.2 *P=0.10*	0.9 ± 0.2 *P>0.99*	0.8 ± 0.1 *P>0.99*	0.8 ± 0.1 *P>0.99*

Supplemental Figure S1: Effect of GlyNAC supplementation of age-associated defects

Supplemental Figure S2: Response of aging hallmarks in older adults to supplementation with GlyNAC

Aging hallmarks	Effect of GlyNAC
Mitochondrial impairment	Improves
Dysregulated nutrient sensing	Improves
Altered intercellular communication	Improves
Genomic instability	Improves
Loss of proteostasis	Improves
Cellular senescence	Improves
Stem cell exhaustion	Improves
Telomere shortening	Not tested
Epigenetic alterations	Not tested