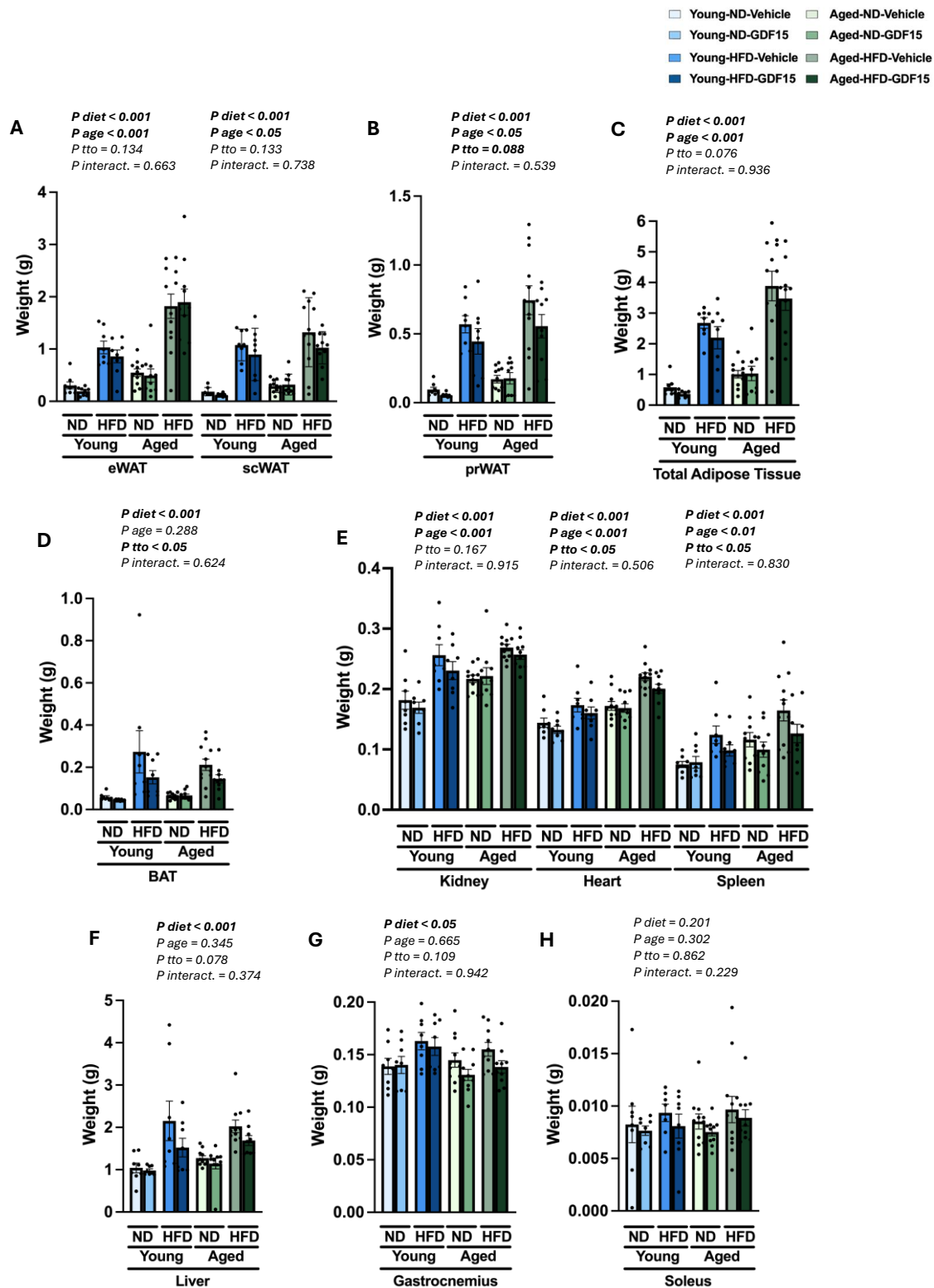


SUPPLEMENTARY DATA

GDF15 Induces Weight Loss with Diet- and Age-Dependent Metabolic Effects Across Tissues in Mice

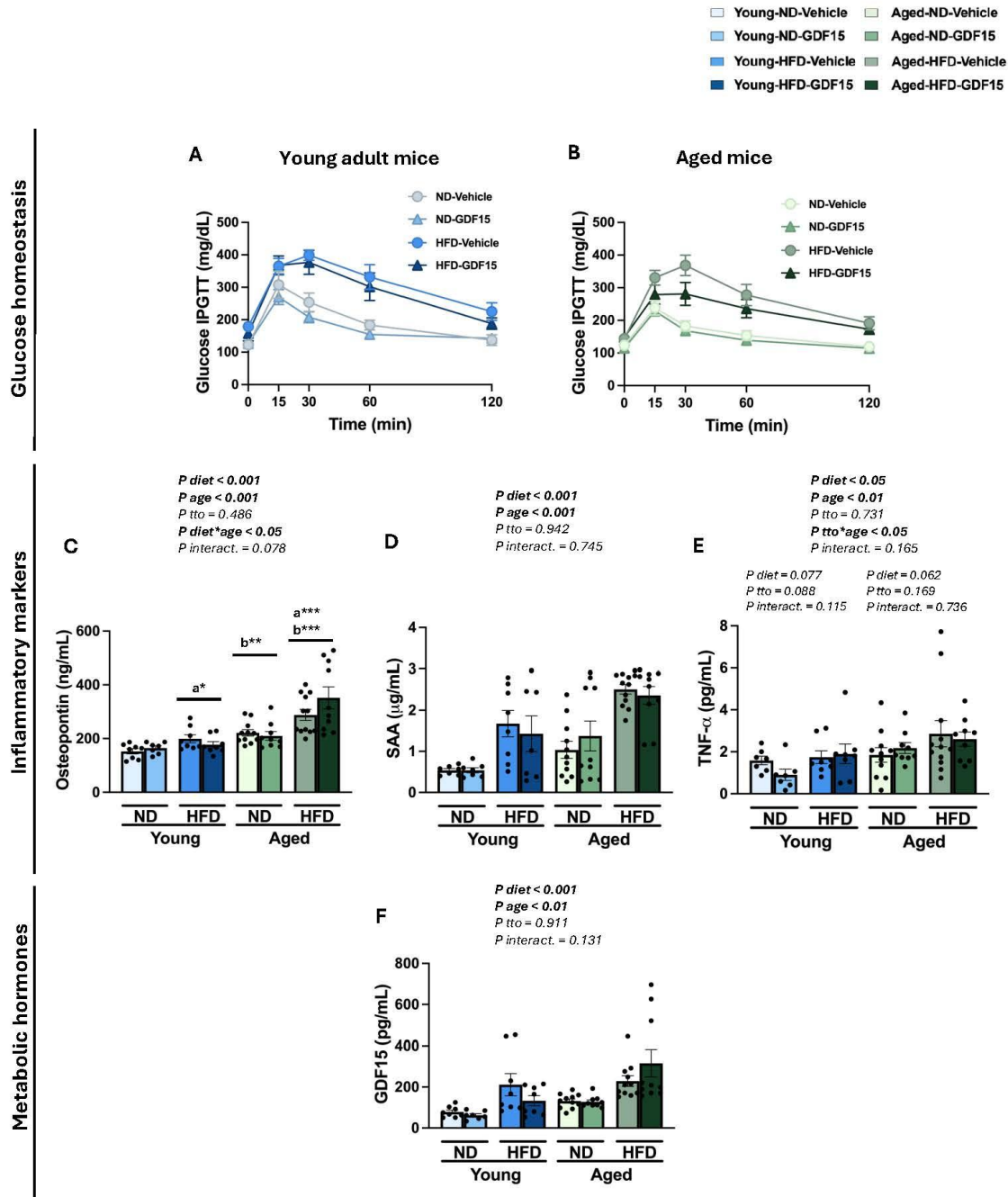
Laura Salmón-Gómez, Victoria Catalán, Beatriz Ramírez, Maite Aguas-Ayesa, Amaia Rodríguez, Sara Becerril, Gema Frühbeck, Javier Gómez-Ambrosi

SUPPLEMENTARY DATA



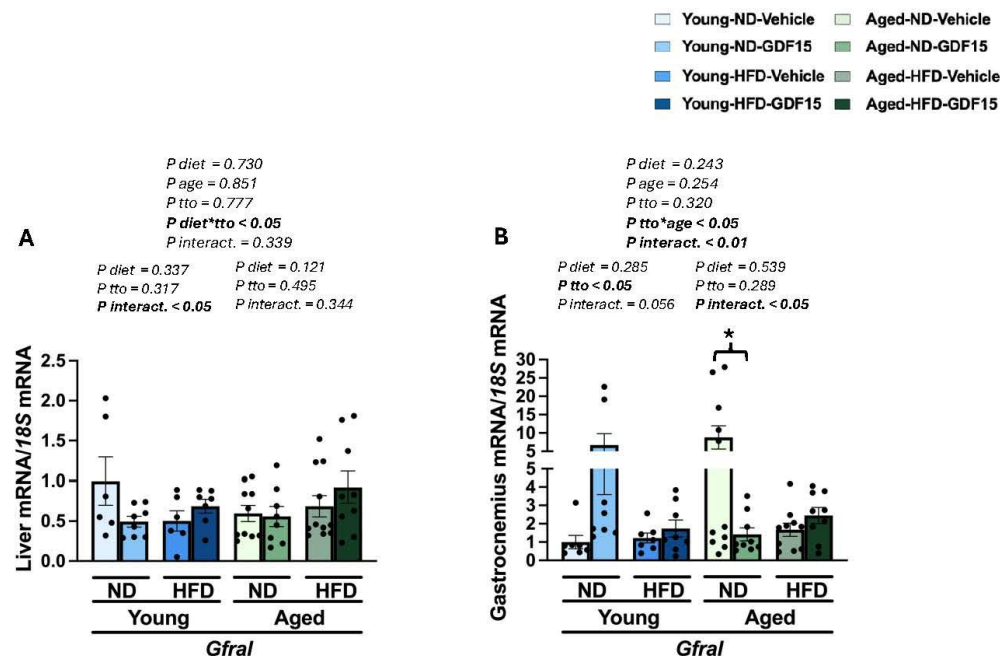
Supplementary Figure 1. Tissue weights of (A) epididimal white adipose tissue (eWAT) and subcutaneous white adipose tissue (scWAT), (B) perirenal white adipose tissue (prWAT), (C) total adipose tissue, (D) brown adipose tissue (BAT), (E) kidney, heart and spleen, (F) liver, (G) gastrocnemius muscle and (H) soleus muscle. Data are presented as the mean ± SEM. Exact sample sizes for each analysis are provided in Supplementary Table 3. Differences between groups were tested by three-way ANOVA. *P* values displayed at the top of each graph correspond to three-way ANOVA results.

SUPPLEMENTARY DATA



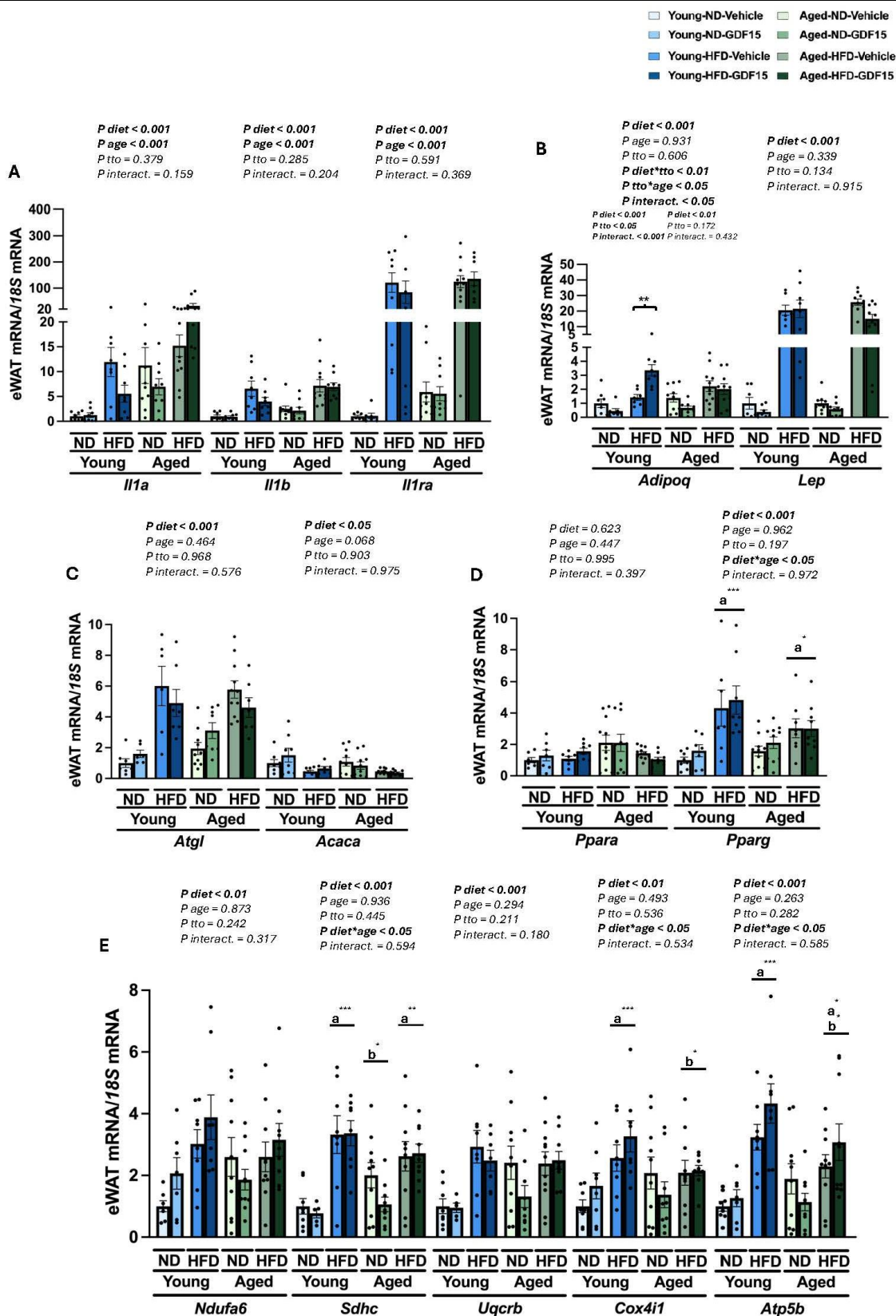
Supplementary Figure 2. Intraperitoneal glucose tolerance test (IPGTT) in (A) young and (B) old mice. Inflammatory markers: circulating levels of (C) osteopontin (OPN), (D) serum amyloid A (SAA) and (E) tumour necrosis factor α (TNF- α). Circulating concentrations of (F) growth differentiation factor 15 (GDF15). Data are presented as the mean $\pm$ SEM. Exact sample sizes for each analysis are provided in Supplementary Table 3. Differences between groups were tested by three- or two-way ANOVA followed by Student's *t*-tests when necessary. *P* values displayed at the top of each graph correspond to three-way ANOVA results, whereas the additional *P* values shown below correspond to subsequent two-way ANOVA analyses performed when significant interactions were detected in the three-way ANOVA. Only significant partial interactions between factors were represented. The letters indicate Student's *t*-test comparisons. a denotes HFD vs. ND comparisons within the same age group; b denotes young vs. old comparisons within the same type of diet. **P* < 0.05, ***P* < 0.01, ****P* < 0.001.

SUPPLEMENTARY DATA



Supplementary Figure 3. Relative mRNA expression of GDF15 receptor *Gfral* in (A) liver and (B) gastrocnemius muscle. Data are presented as the mean ± SEM. Exact sample sizes for each analysis are provided in Supplementary Table 3. Differences between groups were tested by three- or two-way ANOVA followed by t-student tests when necessary. *P* values displayed at the top of each graph correspond to three-way ANOVA results, whereas the additional *P* values shown below correspond to subsequent two-way ANOVA analyses performed when significant interactions were detected in the three-way ANOVA. Only significant partial interactions between factors were represented. The asterisks indicate Student's *t*-test comparisons. **P* < 0.05.

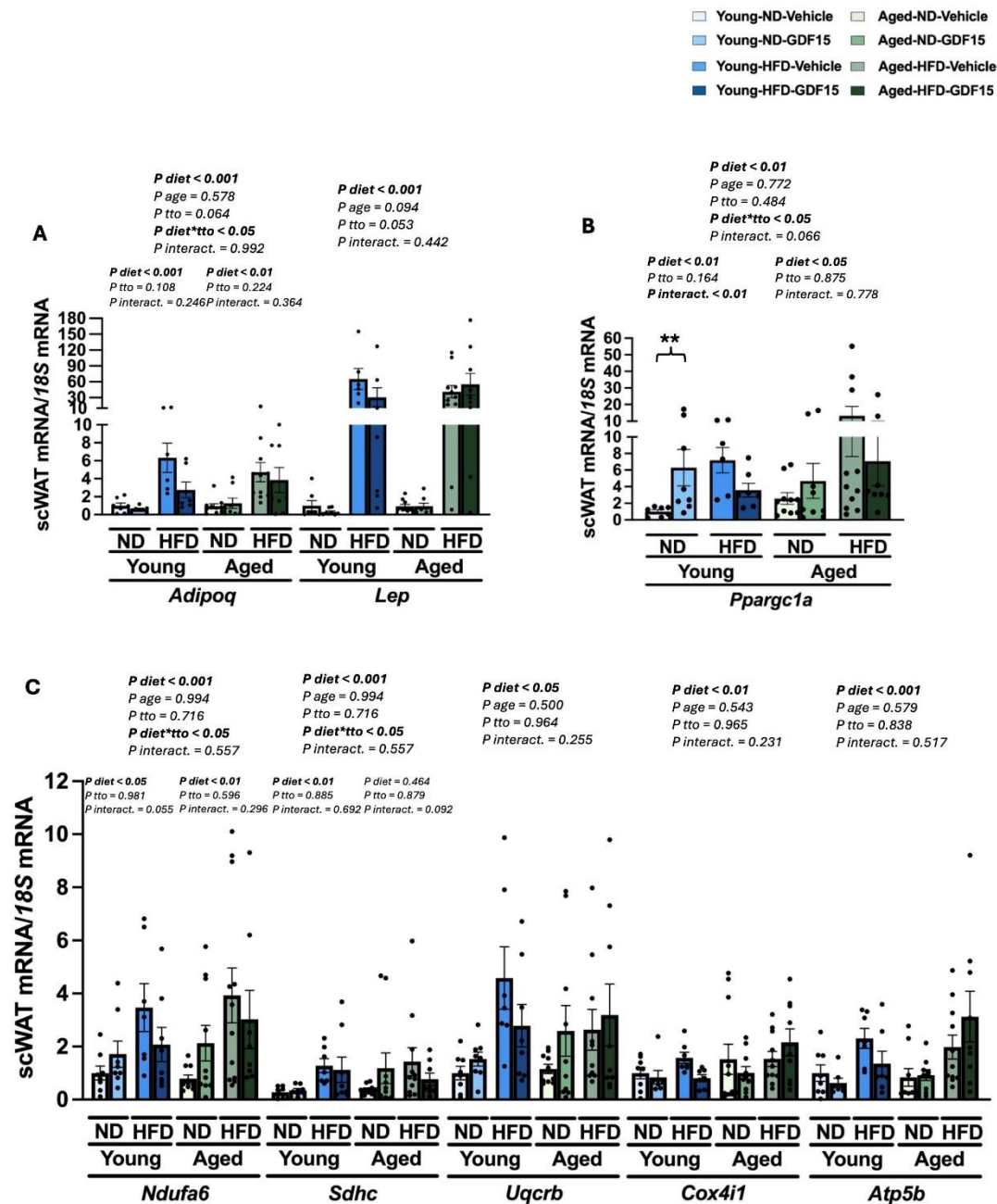
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SUPPLEMENTARY DATA

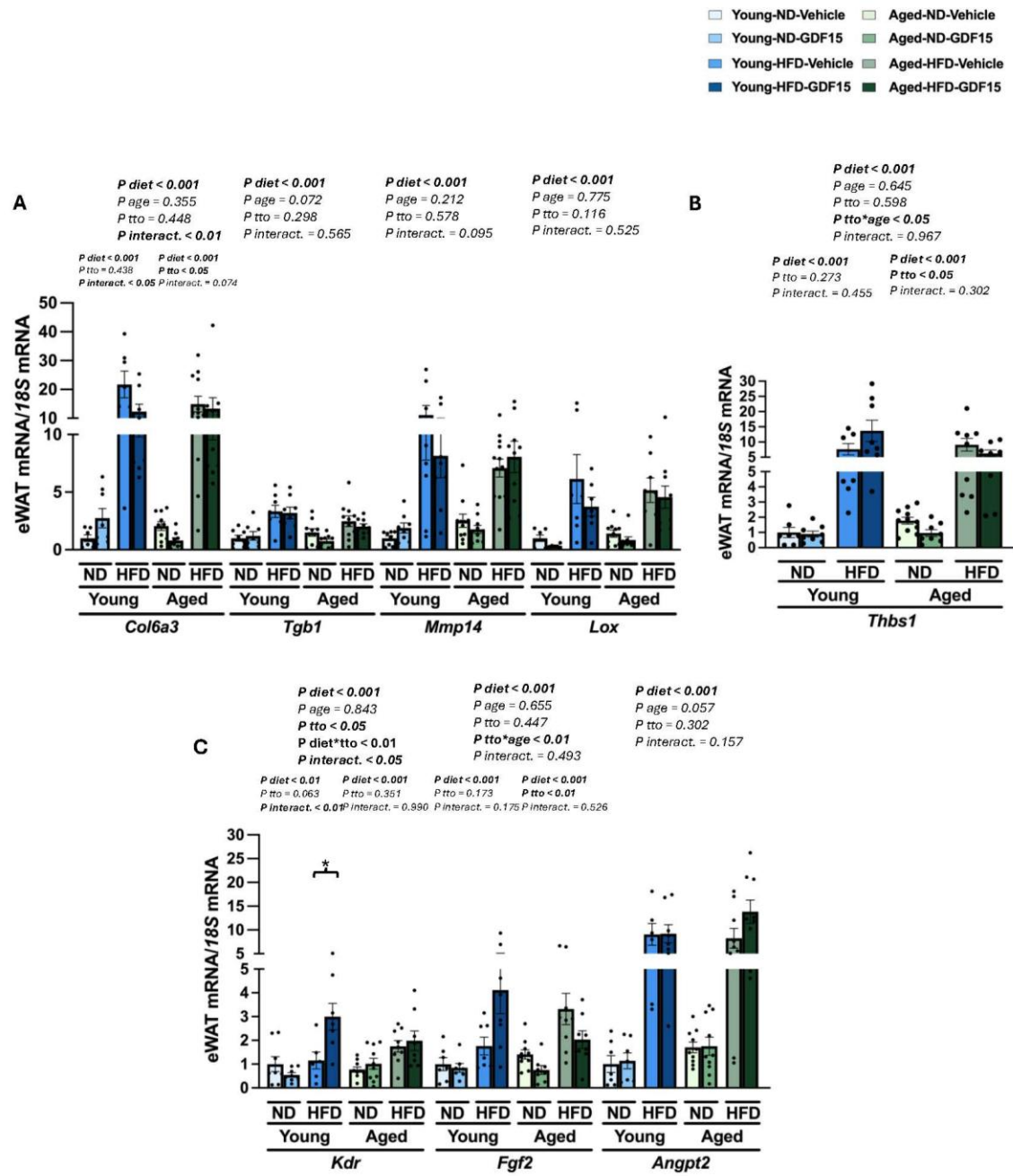
Supplementary Figure 4. Relative mRNA expression of selected genes in epididimal white adipose tissue (eWAT) **(A)** *Il1a*, *Il1b* and *Il1ra*; **(B)** *Adipoq* and *Lep*; **(C)** *Atgl* and *Acaca*; **(D)** *Ppara* and *Pparg*; **(E)** *Ndufa6*, *Sdhc*, *Uqcrb*, *Cox4i1* and *Atp5b*. Data are presented as the mean $\pm$ SEM. Exact sample sizes for each analysis are provided in Supplementary Table 3. Differences between groups were tested by three- or two-way ANOVA followed by t-student tests when necessary. *P* values displayed at the top of each graph correspond to three-way ANOVA results, whereas the additional *P* values shown below correspond to subsequent two-way ANOVA analyses performed when significant interactions were detected in the three-way ANOVA. Only partial significant interactions between factors were represented. The letters and asterisks indicate Student's t-test comparisons. a denotes HFD vs. ND comparisons within the same age group; b denotes young vs. old comparisons within the same type of diet. **P* < 0.05, ***P* < 0.01, ****P* < 0.001.

SUPPLEMENTARY DATA



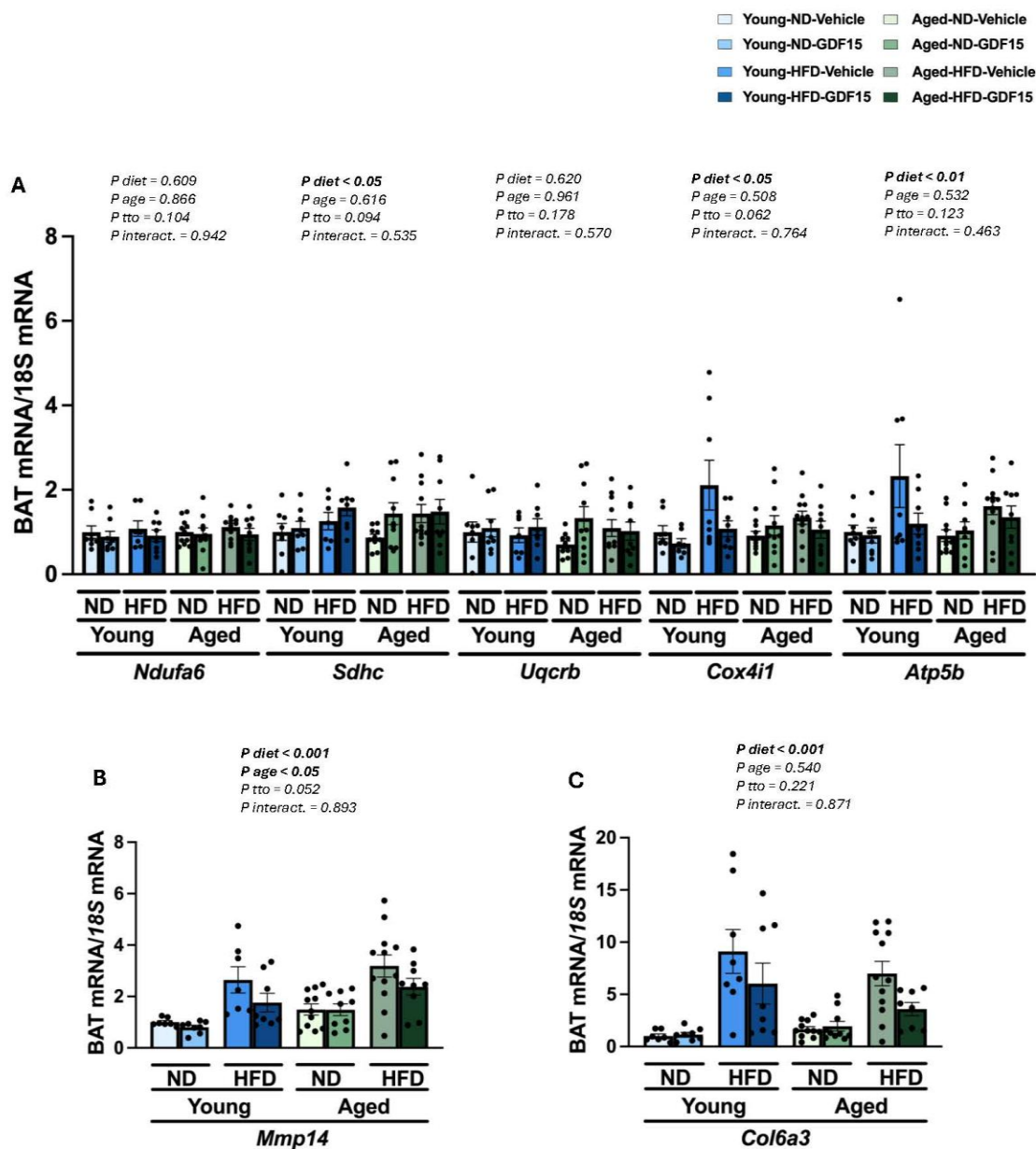
Supplementary Figure 5. Relative mRNA expression of selected genes in subcutaneous white adipose tissue (scWAT) (A) *Adipoq* and *Lep*; (B) *Ppargc1a*; (C) *Ndufa6*, *Sdhc*, *Uqcrb*, *Cox4i1* and *Atp5b*. Data are presented as the mean ± SEM. Exact sample sizes for each analysis are provided in Supplementary Table 3. Differences between groups were tested by three- or two-way ANOVA followed by t-student tests when necessary. *P* values displayed at the top of each graph correspond to three-way ANOVA results, whereas the additional *P* values shown below correspond to subsequent two-way ANOVA analyses performed when significant interactions were detected in the three-way ANOVA. Only partial significant interactions between factors were represented. The asterisks indicate Student's *t*-test comparisons. ***P* < 0.01.

SUPPLEMENTARY DATA



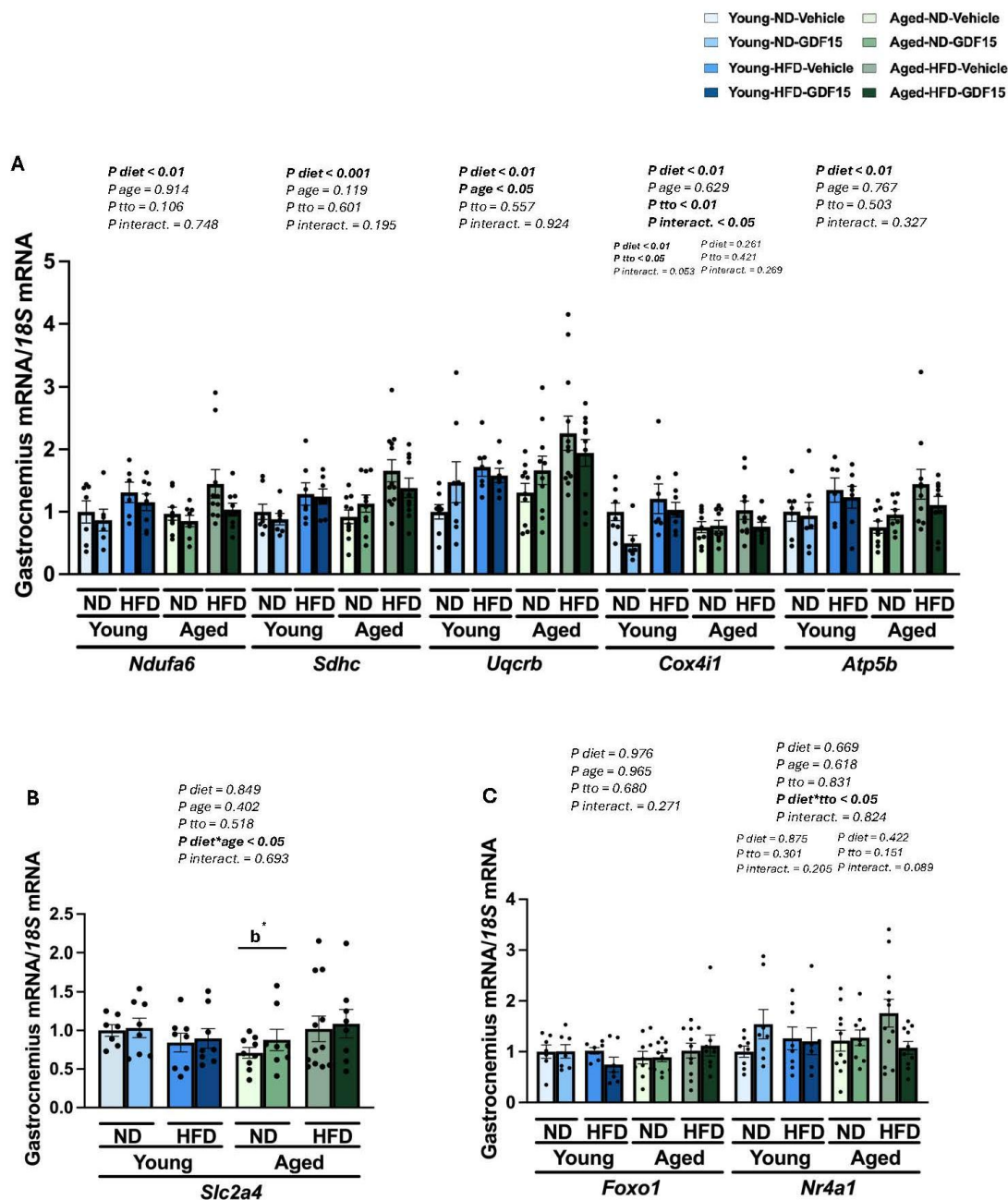
Supplementary Figure 6. Relative mRNA expression of selected genes in epididymal white adipose tissue (eWAT) (A) *Col6a3*, *Tgfb1*, *Mmp14* and *Lox*; (B) *Thbs1*; (C) *Kdr*, *Fgf2* and *Angpt2*. Data are presented as the mean $\pm$ SEM. Exact sample sizes for each analysis are provided in Supplementary Table 3. Differences between groups were tested by three- or two-way ANOVA followed by t-student tests when necessary. *P* values displayed at the top of each graph correspond to three-way ANOVA results, whereas the additional *P* values shown below correspond to subsequent two-way ANOVA analyses performed when significant interactions were detected in the three-way ANOVA. Only partial significant interactions between factors were represented. The letters indicate Student's t-test comparisons. a denotes HFD vs. ND comparisons within the same age group; b denotes young vs. old comparisons within the same type of diet. **P* < 0.05.

SUPPLEMENTARY DATA



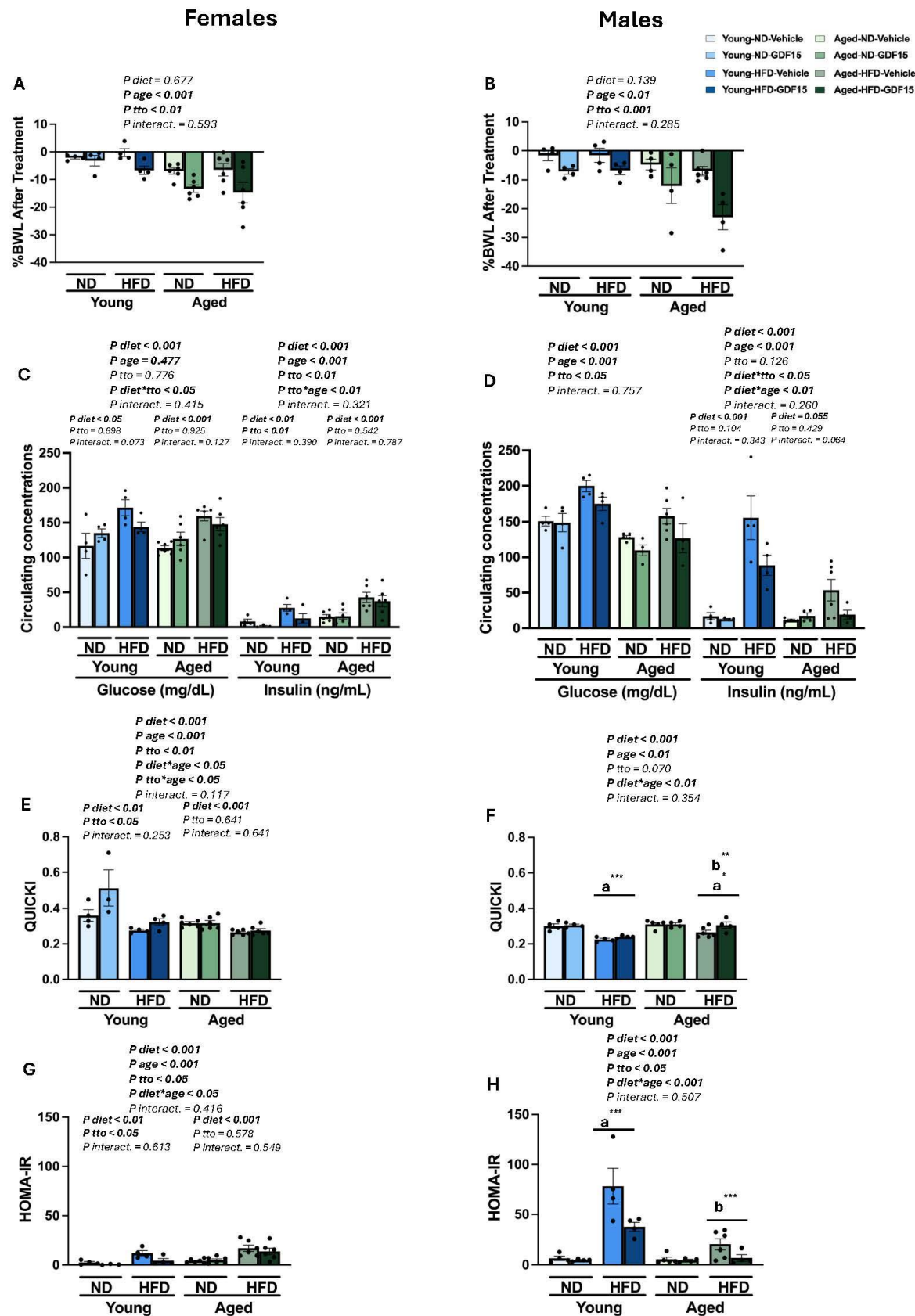
Supplementary Figure 7. Relative mRNA expresión of (A) *Ndufa6*, *Sdhc*, *Uqcrrb*, *Cox4i1* and *Atp5b*; (B) *Mmp14* and (C) *Col6a3* in brown adipose tissue (BAT). Data are presented as the mean ± SEM. Exact sample sizes for each analysis are provided in Supplementary Table 3. Differences between groups were tested by three-way ANOVA.

SUPPLEMENTARY DATA



Supplementary Figure 8. Relative mRNA expression of (A) *Ndufa6*, *Sdhc*, *Uqcrb*, *Cox4i1* and *Atp5b*; (B) *Glut4* and (C) *Foxo1* and *Nr4a1* in gastrocnemius muscle. Data are presented as the mean ± SEM. Exact sample sizes for each analysis are provided in Supplementary Table 3. Differences between groups were tested by three- or two-way ANOVA followed by t-student tests when necessary. *P* values displayed at the top of each graph correspond to three-way ANOVA results, whereas the additional *P* values shown below correspond to subsequent two-way ANOVA analyses performed when significant interactions were detected in the three-way ANOVA. Only significant partial interactions between factors were represented. The letters indicate Student's *t*-test comparisons. b denotes young vs. old comparisons within the same type of diet. **P* < 0.05.

SUPPLEMENTARY DATA



SUPPLEMENTARY DATA

Supplementary Figure 9. Sex stratified analysis of body weight loss and glucose homeostasis parameters. Percentage of body weight loss (%BWL) in females (**A**) and males (**B**). Circulating levels of glucose and insulin in females (**C**) and males (**D**) and calculated indices QUICKI in females (**E**) and males (**F**) and HOMA-IR in females (**G**) and males (**H**). Data are presented as the mean $\pm$ SEM. Exact sample sizes for each analysis are provided in Supplementary Table 3. Differences between groups were tested by three- or two-way ANOVA followed by Student's t-tests when necessary. *P* values displayed at the top of each graph correspond to three-way ANOVA results, whereas the additional *P* values shown below correspond to subsequent two-way ANOVA analyses performed when significant interactions were detected in the three-way ANOVA. Only significant partial interactions between factors were represented. The letters indicate Student's t-test comparisons. a denotes HFD vs. ND comparisons within the same age group; b denotes young vs. old comparisons within the same type of diet. **P* < 0.05, ***P* < 0.01, ****P* < 0.001.

Supplementary Table 1. Primer sequences for RT-qPCR analysis of mRNA expression.

Gene (GenBank accession n°)	Oligonucleotide sequence (5'-3')
<i>Acaca</i> (NM_133360)	
Forward	TCAGTATGCTAGCAACATCACATCAG
Reverse	GCTCAGATTTCCGGTTCAGTGTA
TaqMan® Probe	FAM-AGTTTCCCAGCCAGCAGATTGCCA-TAMRA
<i>Acta2</i> (NM_007392)	
Forward	GTATCCGATAGAACACGGCATCA
Reverse	GGCCACACGAAGCTCGTTATAG
TaqMan® Probe	FAM-CATGGAAAAGATCTGGCACC-TAMRA
<i>Adipoq</i> (NM_009605)	
Forward	AAGGAGATGCAGGTCTTCTTGGT
Reverse	CACTGAACGCTGAGCGATACAT
TaqMan® Probe	FAM-TGGAATGACAGGAGCTGAAGGGCCA-TAMRA
<i>Akt1</i> (NM_001331107)	
Forward	TGCCCACACGCTTACTGAGA
Reverse	GTCGTGGGTCTGGAATGAGTACTT
TaqMan® Probe	FAM-TCTAGGCATCCCTTCCTTACGGCCCT-TAMRA
<i>Angpt2</i> (NM_007426)	
Forward	GAGTCCAACACTACAGGATTCACCTTACA
Reverse	CATTGTCCGAATCCTTTGTGCTA
TaqMan® Probe	FAM-TAGCATCAGCCAACCAGGAAGTGATT-TAMRA
<i>Atgl</i> (NM_001428372)	
Forward	TGCAGAAAAAAGACCACAAGCA
Reverse	CGGTTGATGGCCCAAACT
TaqMan® Probe	FAM-TGGATGGGACTGCAGAATGACAGAT-TAMRA
<i>Atp5b</i> (NM_016774.3)	
Forward	TGGTGACTGGGATAAAGGTTGTG
Reverse	CGACATTGTTGATTAGCTCCATGA
TaqMan® Probe	FAM-CAAGGGTGGGAAAATCGGACTCTTTGG-TAMRA
<i>Cd36</i> (NM_007643)	
Forward	TTCCTCTGACATTTGCAGGTCTATC
Reverse	TGGCTGGAAGAACAAATCTGTACA
TaqMan® Probe	FAM-CGCTGTGTTCGGATCTGAAATCGACCT-TAMRA
<i>Cd68</i> (NM_009853)	
Forward	TACATGGCGGTGGAATACAATG
Reverse	GAACAGCTGGAGAAAGAACTATGCTT
TaqMan® Probe	FAM-AGGCAGCACAGTGGACATTCATGGC-TAMRA

SUPPLEMENTARY DATA

<i>Cpt1b</i> (NM_009948)	
Forward	GCGGTAATATGCTTCATCATCCA
Reverse	TCCAAACGTCCTGCCTAAGCT
TaqMan® Probe	FAM-CCAGCCACAATTCACCGGTACTTGGA-TAMRA
<i>Fgf2</i> (NM_008006)	
Forward	CCAACCGGTACCTTGCTATGAA
Reverse	GGAGTATTTCCGTGACCGGTAAG
TaqMan® Probe	FAM-TGCTGGCTTCTAAGTGTGTTACAGAA-TAMRA
<i>Foxo1</i> (NM_019739)	
Forward	GCGGGCTGGAAGAATTCAAT
Reverse	TCCTTCATTCTGCACTCGAATAAAC
TaqMan® Probe	FAM-CGCCACAATCTGTCCCTTCACA-TAMRA
<i>Cidea</i> (NM_007702)	
Forward	CCTTAAGGGACAACACGCATTT
Reverse	GGCTATTCCCGATTTCTTTGGT
TaqMan® Probe	FAM-TTGGAAGGGACAGAAATGGACACCG-TAMRA
<i>Col6a3</i> (NM_001243008)	
Forward	TGATGGCACCTCTCAGGACTCT
Reverse	TTGTGCGAGCCATCCAAAAG
TaqMan® Probe	FAM-CCACGGAAGTTCACGTAA-TAMRA
<i>Cox4i1</i> (NM_009941.3)	
Forward	GCAGCCTTTCCAGGGATGA
Reverse	GCCATGCCCACTGTCTT
TaqMan® Probe	FAM-AAGTTCAGTTGTACCGCATCCAGTT-TAMRA
<i>Gdf15</i> (NM_001330687)	
Forward	GAGAGGACTCGAACTCAGAACCA
Reverse	CGTGGGACCCCAATCTCA
TaqMan® Probe	FAM-CCTGACCCAGCTGTCCGGATACTCAG-TAMRA
<i>Gfral</i> (NM_205844)	
Forward	TATGCAGGACACACTACCGAACA
Reverse	ATCTTCATGGCACTTCCAGTT
TaqMan® Probe	FAM-CCAGACAGAATGCTGGCCCCACA-TAMRA
<i>Glut4</i> (NM_009204)	
Forward	GTCCTGAGAGCCCCAGATACCT
Reverse	TCCAACTTCCGTTTCTCATCCTT
TaqMan® Probe	FAM-CCTGCCCCGAAAGAGTCTAAAGCGCC-TAMRA
<i>Il1a</i> (NM_010554)	
Forward	ACCCATGATCTGGAAGAGACCAT
Reverse	GACGAGCTTCATCAGTTTGTATC
TaqMan® Probe	FAM-CCCAGATCAGCACCTTACACCTACCAGAGTG-TAMRA
<i>Il1b</i> (NM_008361)	
Forward	TGACAGTGATGAGAATGACCTGTTC
Reverse	TGATGTGCTGCTGCGAGATT
TaqMan® Probe	FAM-ACCCCAAAGATGAAGGGCTGCTTCC-TAMRA
<i>Il1rn</i> (NM_001159562)	
Forward	CCAGCTGGAGGAAGTTAACATCA
Reverse	TCCTGGACAGGCAGCTGACT
TaqMan® Probe	FAM-TTCATCCGCTCTGAGAAAGGCCCC-TAMRA
<i>Il6</i> (NM_031168)	
Forward	CGGAGGCTTAATTACACATGTTCTC
Reverse	CAGTTTGGTAGCATCCATCATTCT
TaqMan® Probe	FAM-CGTGGAATGAGAAAAGAGTTGTGCAATGG-TAMRA
<i>Itgax</i> (NM_021334)	
Forward	CTGGACTTTGTTAAAGCTGTGATGAG
Reverse	GACGTGGAGATGAAGTTGTTGAAA
TaqMan® Probe	FAM-CCTAGCACACGGTTCTCCCTGATGCA-TAMRA

SUPPLEMENTARY DATA

<i>Kdr</i> (NM_001403141)	
Forward	AGATGCAGGAAACTACACGGTCAT
Reverse	CATAGGCGAGATCAAGGCTTTCT
TaqMan® Probe	FAM-TCTCTGGTTGTGAATGTCCCACCCCA-TAMRA
<i>Lep</i> (NM_008493)	
Forward	CAAAACCCTCATCAAGACCAT
Reverse	CAGGAATGAAGTCCAAGCCAG
TaqMan® Probe	FAM-CAGGAATGAAGTCCAAGCCAG-TAMRA
<i>Lox</i> (NM_010728)	
Forward	AGCAGGAACCGACCTGGATAC
Reverse	GTACGTGGAAGCCTGGATGTAGTAG
TaqMan® Probe	FAM-TTACTTCCAGTACGGTCTC-TAMRA
<i>Mmp2</i> (NM_008610)	
Forward	TGCTCCACCACATACAACCTTTGA
Reverse	GAAGCGGAACGGGAACCTG
TaqMan® Probe	FAM-TCTGCCCCCATGAAGCCTTGTTTACC-TAMRA
<i>Mmp14</i> (NM_008608)	
Forward	CAGAGAACTTCGTGTTGCCTGAT
Reverse	CCGAGAGGTAGTTCTGGGTGTA
TaqMan® Probe	FAM-CTTTATGGAAGCAAGTCAGGGTCACC-TAMRA
<i>Ndufa6</i> (NM_025987.3)	
Forward	TTCATGAAGAATGCCCATGTCA
Reverse	TCCGCTGCTTCCATACTTTGAT
TaqMan® Probe	FAM-TGCTGGTCATTAAGGGAAAGATGGA-TAMRA
<i>Nr4l1a</i> (NM_001411254)	
Forward	TGCCTTCCTGGAACCTCTTCATC
Reverse	GTTGTCAATCCAATCACCAAAGC
TaqMan® Probe	FAM-CCTGGCATAACCGATCTAAACCCGGTG-TAMRA
<i>Ppara</i> (NM_011144)	
Forward	ACTACGGAGTTCACGCATGTGA
Reverse	CACCAGCTTCAGCCGAATAGTT
TaqMan® Probe	FAM-TGTAAGGGCTTCTTTTCGG-TAMRA
<i>Pparg</i> (NM_011146)	
Forward	GCTTCCACTATGGAGTTCATGCTT
Reverse	ATCCGGCAGTTAAGATCACACCTA
TaqMan® Probe	FAM-AGGATGCAAGGGTTTTTTCCGA-TAMRA
<i>Ppargc1a</i> (NM_001402990.1)	
Forward	ATGCTCAAGCCAAACCAACAAC
Reverse	GGTTCGCTCAATAGTCTTGTTCTCA
TaqMan® Probe	FAM-CACCAAATGACCCCAAGGGTTCC-TAMRA
<i>Prdm16</i> (NM_027504)	
Forward	GATGGGAGATGCTGACGGATAC
Reverse	CTCGCTACCCAAGTCTTCAGACAT
TaqMan® Probe	FAM-CATCCCAGGAGAGCTGCATCAAAAAGC-TAMRA
<i>Saa3</i> (NM_011315)	
Forward	AGTCATCAGCGATGCCAGAGA
Reverse	CCCCACTCATTGGCAAACCTG
TaqMan® Probe	FAM-CACGGGACATGGAGCAGAGGACTCA-TAMRA
<i>Sdhc</i> (NM_025321.3)	
Forward	TGTATCAGAAATGCTGCTCCTTTG
Reverse	GAGGACGGTTTGAACCTCGTGTT
TaqMan® Probe	FAM-AGCTAAGGAGGAGATGGAGCGGTTCTGG-TAMRA
<i>Serpinf1</i> (NM_011340)	
Forward	AGGACATGAAGCTACAGTCGTTGTT
Reverse	CTCGAAAGCAGCCCTGTGTT

SUPPLEMENTARY DATA

TaqMan® Probe	FAM-AGCAAGATTACTGGCAAACCCGTGAAGC TAMRA
<i>Spp1</i> (NM_009263)	
Forward	TTTGCTGTGTTGGCATTGC
Reverse	TGGGTGCAGGCTGTAAAGCT
TaqMan® Probe	FAM-TCCTCCCTCCCGGTGAAAGTGAAGT-TAMRA
<i>Thbs1</i> (NM_011580)	
Forward	CCATCAGGGCAAAGAACTTGTC
Reverse	CGAAAACAAAGCCAGCGTAGTC
TaqMan® Probe	FAM-CCCTGGACTTGCTGTAGGTTATGAT-TAMRA
<i>Tgfb1</i> (NM_011480)	
Forward	TCCCAAGAGCCCTGCACTT
Reverse	GTCCACAAAGAAACGGTGACCTA
TaqMan® Probe	FAM-TTGACACGTTTCTTCTGAGCAGCGC-TAMRA
<i>Timp2</i> (NM_011594)	
Forward	CCTTTGGCACTCTGGTCTACACTATTA
Reverse	CTGCTTGATCTCATACTGAATCCTCTT
TaqMan® Probe	FAM-AGTGAGCGAGAAGGAGGTGGATTCCG-TAMRA
<i>Timp3</i> (NM_011595)	
Forward	GGCCTCAAGCTAGAAGTCAACAAA
Reverse	CCACCTCTCCACAAAAGTTGCA
TaqMan® Probe	FAM-CTGCTGACAGGGCGCGTGTATGAAG-TAMRA
<i>Tnf</i> (NM_013693)	
Forward	CCAGACCCTCACACTCAGATCAT
Reverse	ACTCCAGCTGCTCCTCCACTT
TaqMan® Probe	FAM-CCTGTAGCCACGTCGTAGCAAACCA-TAMRA
<i>Ucp1</i> (NM_009463)	
Forward	CGATGTCCATGTACACCAAGGA
Reverse	ACCCGAGTCGCAGAAAAGAAG
TaqMan® Probe	FAM-ACCGACGGCCTTTTCAAAGGGTTTG-TAMRA
<i>Uqcrb</i> (NM_026219.2)	
Forward	CGATCTGCTGTTTCAGCATCAA
Reverse	ATCATCTCGCATTAAACCCAGTT
TaqMan® Probe	FAM-CAAGTGGCTGGATGGTTTTCGA-TAMRA
<i>Vegfa</i> (NM_001287056)	
Forward	TGCACCCACGACAGAAGA
Reverse	GTAGCTTCGCTGGTAGACATCCAT
TaqMan® Probe	FAM-TCCCATGAAGTGATCAAGTT-TAMRA

Acaca, acetyl-CoA carboxylase alpha; *Acta2*, actin alpha 2; *Adipoq*, adiponectin; *Akt1*, AKT serine/threonine kinase 1; *Angpt2*, angiopoietin 2; *Atg5*, autophagy related 5; *Atp5b*, ATP synthase F1 subunit beta; *Cd36*, CD36 molecule; *Cd68*, CD68 molecule; *Cidea*, cell death inducing DFFA like effector A; *Col6a3*, collagen type VI alpha 3 chain; *Cox4i1*, cytochrome c oxidase subunit 4I1; *Cpt1b*, carnitine palmitoyltransferase 1B; *Fgf2*, fibroblast growth factor 2; *Foxo1*, forkhead box O1; *Gdf15*, growth differentiation factor 15; *Gfral*, GDNF family receptor alpha like; *Slc2a4*, solute carrier family 2 member 4; *Il1a*, interleukin 1 alpha; *Il1b*, interleukin 1 beta; *Il1rn*, interleukin 1 receptor antagonist; *Il6*, interleukin 6; *Itgax*, integrin subunit alpha X; *Kdr*, kinase insert domain receptor; *Lep*, leptin; *Lox*, lysyl oxidase; *Mmp2*, matrix metalloproteinase 2; *Mmp14*, matrix metalloproteinase 14; *Ndufa6*, NADH:ubiquinone oxidoreductase subunit A6; *Nr4a1*, nuclear receptor subfamily 4 group A member 1; *Ppara*, peroxisome proliferator activated receptor alpha; *Pparg*, peroxisome proliferator activated receptor gamma; *Ppargc1a*, PPARG coactivator 1 alpha; *Prdm16*, PR/SET domain 16; *Saa3*, serum amyloid A3; *Sdhc*, succinate dehydrogenase complex subunit C; *Serpinf1*, serpin family F member 1 (pigment epithelium derived factor, PEDF); *Spp1*, secreted phosphoprotein 1; *Thbs1*, thrombospondin 1; *Tgfb1*, transforming growth factor beta 1; *Timp2*, tissue inhibitor of metalloproteinases 2; *Timp3*, tissue inhibitor of metalloproteinases 3; *Tnf*, tumor necrosis factor; *Ucp1*, uncoupling protein 1; *Uqcrb*, ubiquinol-cytochrome c reductase binding protein; *Vegfa*, vascular endothelial growth factor A.

SUPPLEMENTARY DATA

Supplementary Table 2. Subset of genes with significant main effects of sex or sex-dependent interactions with GDF15 treatment identified by four-way ANOVA.

Tissue	Gene	P <i>Sex</i>	P <i>Sex*tto</i>	P <i>Sex*age</i>	P <i>Sex*diet</i>	P <i>Sex*diet*tto</i>	P <i>Sex*tto*age</i>	P <i>Sex*diet*tto*age</i>
eWAT	<i>Angpt2</i>	* ↑ males						
	<i>Cd68</i>	*** ↑ males						
	<i>Gdf15</i>	*** ↑ males						
	<i>Il1a</i>	*** ↑ males						
	<i>Il1b</i>	** ↑ males						
	<i>Il1ra</i>	*** ↑ males						
	<i>Il6</i>	** ↑ males						
	<i>Itgax</i>	*** ↑ males						*
	<i>Mmp2</i>	*** ↑ males						
	<i>Mmp14</i>	** ↑ males						*
	<i>Ppargc1a</i>	* ↑ males						*
	<i>Spp1</i>	*** ↑ males						
	<i>Tnfa</i>	*** ↑ males						
scWAT	<i>Adipoq</i>						*	
	<i>Atp5b</i>						*	
	<i>Cox4i1</i>		*				*	
	<i>Ppargc1a</i>						*	
	<i>Sdhc</i>							**
BAT	<i>Atp5b</i>	*** ↑ males						*
	<i>Cd68</i>	** ↑ males						
	<i>Col6a3</i>	* ↑ males						
	<i>Cox4i1</i>	*** ↑ males						*
	<i>Mmp14</i>	** ↑ males						
	<i>Saa3</i>	0.053 ↑ females					*	
	<i>Spp1</i>	** ↑ males						
Gastroc nemius	<i>Atp5b</i>	* ↑ males	*					
	<i>Cd36</i>							
	<i>Cox4i1</i>	* ↑ males						
	<i>Cpt1b</i>	** ↑ males	**					
	<i>Foxo1</i>	*						

SUPPLEMENTARY DATA

		↑ males		
	<i>Gdf15</i>	*		
		↑ females		
	<i>Il6</i>		*	
	<i>Ndufa6</i>	**	*	
		↑ males		
	<i>Timp2</i>			**
Liver	<i>Acaca</i>	**		
		↑ females		
	<i>Cd36</i>	**		
		↑ males		
	<i>Cd68</i>	**		
		↑ males		
	<i>Cox4i1</i>			*
	<i>Gdf15</i>	*		
		↑ males		
	<i>Il6</i>	**		
		↑ males		
	<i>Itgax</i>	***		
		↑ females		
	<i>Ndufa6</i>			*
	<i>Ppara</i>	**	**	
		↑ males		
	<i>Ppargc1a</i>	*		0.053
		↑ females		
	<i>Saa3</i>		*	
	<i>Sdhc</i>			*
	<i>Spp1</i>	***		
		↑ males		
	<i>Tgfb1</i>	*		
		↑ females		
	<i>Tnf</i>	***		
		↑ males		
	<i>Uqcrb</i>		*	**

Acaca, acetyl-CoA carboxylase alpha; *Adipoq*, adiponectin; *Angpt2*, angiopoietin 2; *Atp5b*, ATP synthase F1 subunit beta; *Cd36*, CD36 molecule; *Cd68*, CD68 molecule; *Col6a3*, collagen type VI alpha 3 chain; *Cox4i1*, cytochrome c oxidase subunit 4I1; *Cpt1b*, carnitine palmitoyltransferase 1B; *Foxo1*, forkhead box O1; *Gdf15*, growth differentiation factor 15; *Glut4* (Slc2a4), solute carrier family 2 member 4; *Il1a*, interleukin 1 alpha; *Il1b*, interleukin 1 beta; *Il1rn*, interleukin 1 receptor antagonist; *Il6*, interleukin 6; *Itgax*, integrin subunit alpha X; *Mmp2*, matrix metalloproteinase 2; *Mmp14*, matrix metalloproteinase 14; *Ndufa6*, NADH:ubiquinone oxidoreductase subunit A6; *Ppara*, peroxisome proliferator activated receptor alpha; *Ppargc1a*, PPARG coactivator 1 alpha; *Saa3*, serum amyloid A3; *Sdhc*, succinate dehydrogenase complex subunit C; *Spp1*, secreted phosphoprotein 1 (osteopontin); *Timp2*, tissue inhibitor of metalloproteinases 2; *Tnf*, tumor necrosis factor.

SUPPLEMENTARY DATA

Supplementary Table 3. Sample sizes for each experimental group and analysis.

		Young- ND- Veh	Young- ND- GDF15	Young- HFD- Veh	Young- HFD- GDF15	Aged- ND- Veh	Aged- ND- GDF15	Aged- HFD- Veh	Aged- HFD- GDF15
Fig. 1B	%BWG before tto	16		29		16		31	
Fig. 1C	%BWL after tto	8	8	8	8	10	10	12	10
Fig. 1D	Cumulative food intake	8	8	11	10	8	8	12	10
Fig. 1E	Cumulative food intake	8	8	11	10				
Fig. 1F	Cumulative food intake					8	8	12	10
Fig. 2A	Glucose	8	8	8	8	11	10	12	10
Fig. 2B	AUC IPGTT	8	8	8	8	10	10	10	10
Fig. 2C	Insulin	8	7	8	8	10	10	12	10
Fig. 2D	QUICKI	8	7	8	8	11	10	12	10
Fig. 2E	HOMA-IR	8	7	8	8	11	10	12	10
Fig. 2F	TG	8	7	8	8	11	10	12	10
Fig. 2G	Cholesterol	8	8	8	8	11	9	12	8
Fig. 2H	Adiponectin	8	7	8	8	11	10	12	10
Fig. 2I	Leptin	7	6	8	8	11	8	11	10
Fig. 2J	Adipoq/Lep ratio	7	6	7	7	10	8	11	10
Fig. 3A	Liver <i>Gdf15</i>	8	8	6	8	10	10	12	9
Fig. 3B	eWAT <i>Gdf15</i>	7	7	8	7	10	9	11	9
Fig. 3C	scWAT <i>Gdf15</i>	7	7	7	8	10	9	12	9
Fig. 3D	BAT <i>Gdf15</i>	7	8	7	8	12	10	11	8
Fig. 3E	Gastrocnemius <i>Gdf15</i>	7	7	7	8	11	10	11	10
Fig. 4B	CSA	6	6	6	6	6	6	6	6
Fig. 4C	<i>Tnf</i>	8	7	7	8	10	10	11	9
Fig. 4C	<i>Il6</i>	8	7	8	7	11	9	11	9
Fig. 4C	<i>Saa3</i>	7	8	7	8	10	10	11	9
Fig. 4D	<i>Cd68</i>	7	7	7	8	10	9	11	10
Fig. 4D	<i>Itgax</i>	7	7	8	7	10	9	11	10
Fig. 4D	<i>Spp1</i>	7	7	8	7	10	9	11	9
Fig. 4E	<i>Akt1</i>	7	8	7	7	7	9	8	8
Fig. 4F	<i>Ppargc1a</i>	7	6	8	7	10	10	11	10
Fig. 5B	Lipid droplet area	6	6	6	6	6	6	6	6
Fig. 5C	<i>Ucp1</i>	8	7	8	8	10	10	12	9
Fig. 5D	<i>Ppargc1a</i>	8	7	7	7	11	9	12	9
Fig. 5E	<i>Prdm16</i>	8	7	7	8	10	9	11	8
Fig. 5E	<i>Cidea</i>	8	8	7	8	10	10	12	8
Fig. 5E	<i>Cpt1b</i>	8	7	7	7	10	9	11	8
Fig. 5F	<i>Saa3</i>	8	8	8	8	10	10	11	9
Fig. 5G	<i>Cd68</i>	7	8	8	8	11	9	12	9
Fig. 5G	<i>Spp1</i>	8	8	8	8	10	9	11	8
Fig. 6A	<i>Ppargc1a</i>	8	8	8	8	11	10	12	10
Fig. 6B	<i>Cpt1b</i>	7	8	7	8	11	10	11	10
Fig. 6C	<i>Ppara</i>	7	7	8	7	11	10	12	9
Fig. 6C	<i>Cd68</i>	8	8	8	8	10	10	11	10
Fig. 6D	<i>Tnf</i>	7	6	8	7	11	10	11	10
Fig. 6D	<i>Il6</i>	8	8	8	8	10	9	11	10
Fig. 6E	<i>Cd68</i>	8	7	8	7	10	9	11	10

SUPPLEMENTARY DATA

Fig. 6E	<i>Spp1</i>	8	8	7	7	10	9	11	10
Fig. 6F	<i>Col6a3</i>	8	8	7	8	10	10	12	10
Fig. 6G	<i>Mmp2</i>	7	8	8	8	10	10	11	10
Fig. 6G	<i>Mmp14</i>	8	7	8	8	10	10	11	9
Fig. 6H	<i>Timp2</i>	8	7	7	7	10	9	11	8
Fig. 6H	<i>Timp3</i>	8	7	8	7	11	10	11	10
Fig. 7B	Liver TG	8	8	7	8	11	10	11	10
Fig. 7C	<i>Cd38</i>	8	8	6	8	10	10	10	10
Fig. 7C	<i>Acaca</i>	8	7	6	8	9	10	11	10
Fig. 7C	<i>Ppara</i>	7	8	7	8	11	9	11	9
Fig. 7D	<i>Tnf</i>	7	8	7	7	10	10	12	9
Fig. 7D	<i>Il6</i>	7	8	6	8	10	9	11	10
Fig. 7D	<i>Saa3</i>	7	8	7	8	10	9	10	9
Fig. 7E	<i>Cd68</i>	7	7	7	7	10	9	10	9
Fig. 7E	<i>Itgax</i>	7	8	6	8	9	9	10	8
Fig. 7E	<i>Spp1</i>	7	8	7	8	11	10	11	9
Fig. 7F	<i>Ppargc1a</i>	8	8	7	8	11	10	10	10
Fig. 7G	<i>Ndufa6</i>	8	7	7	8	11	9	12	10
Fig. 7G	<i>Sdhc</i>	8	8	7	8	10	10	11	10
Fig. 7G	<i>Uqcrb</i>	8	8	7	7	10	9	10	10
Fig. 7G	<i>Cox4i1</i>	8	8	7	7	11	9	11	10
Fig. 7G	<i>Atp5b</i>	8	7	7	7	11	9	10	10
Fig. 8B	Liver fibrosis area	6	6	6	6	6	6	6	6
Fig. 8C	<i>Col6a1</i>	7	7	5	6	10	9	9	10
Fig. 8D	<i>Tgfb1</i>	8	7	6	7	11	10	10	10
Fig. 8D	<i>Acta2</i>	7	8	7	8	10	9	11	10
Fig. 8E	<i>Vegfa</i>	7	6	7	8	7	8	11	8
Fig. 8E	<i>Fgf2</i>	7	7	6	8	9	9	12	8
Fig. 8F	<i>Thbs1</i>	8	7	7	7	10	10	12	9
Fig. 8F	<i>Serpinf1</i>	8	8	7	7	10	9	11	10
Fig. 8G	<i>Mmp14</i>	8	7	7	7	11	9	10	9
Fig. 8G	<i>Lox</i>	7	6	6	8	8	8	10	7
Sup Fig. 1A	eWAT weight	8	8	8	8	11	10	12	10
Sup Fig. 1A	scWAT weight	8	8	8	8	11	10	12	10
Sup Fig. 1B	prWAT weight	8	8	8	8	11	9	12	10
Sup Fig. 1C	Total AT weight	8	8	8	8	11	9	12	10
Sup Fig. 1D	BAT weight	8	8	8	8	11	10	12	10
Sup Fig. 1E	Kidney weight	8	8	8	8	11	10	12	10
Sup Fig. 1E	Heart weight	8	8	8	8	11	10	12	10
Sup Fig. 1E	Spleen weight	8	8	8	8	10	10	12	9
Sup Fig. 1F	Liver weight	8	8	8	8	11	10	11	9
Sup Fig. 1G	Gastrocnemius weight	8	8	8	8	11	10	10	10
Sup Fig. 1H	Soleus weight	8	8	7	8	11	10	12	10
Sup Fig. 2A	Glucose IPGTT	8	8	8	8				
Sup Fig. 2B	Glucose IPGTT					10	10	10	10

SUPPLEMENTARY DATA

Sup Fig. 2C	Osteopontin	8	7	8	8	11	9	12	10
Sup Fig. 2D	SAA	7	7	8	7	11	10	12	10
Sup Fig. 2E	TNF- α	7	7	8	8	11	9	12	9
Sup Fig. 2F	GDF15	8	7	8	8	11	9	11	10
Sup Fig. 3A	Liver <i>Gfral</i>	6	8	6	7	10	8	11	9
Sup Fig. 3B	Gastrocnemius <i>Gfral</i>	7	8	7	8	11	9	10	9
Sup Fig. 4A	<i>Il1a</i>	8	8	8	8	10	9	11	10
Sup Fig. 4A	<i>Il1b</i>	8	8	8	8	10	9	11	9
Sup Fig. 4A	<i>Il1ra</i>	7	7	8	7	10	9	11	8
Sup Fig. 4B	<i>Adipoq</i>	8	7	7	8	10	9	11	10
Sup Fig. 4B	<i>Lep</i>	7	8	7	8	10	9	10	10
Sup Fig. 4C	<i>Atgl</i>	7	6	6	7	10	8	11	7
Sup Fig. 4C	<i>Acaca</i>	8	8	8	7	10	10	11	10
Sup Fig. 4D	<i>Ppara</i>	7	7	7	8	11	10	12	9
Sup Fig. 4D	<i>Pparg</i>	8	7	7	8	10	10	8	9
Sup Fig. 4E	<i>Ndufa6</i>	7	7	8	8	10	10	10	9
Sup Fig. 4E	<i>Sdhc</i>	8	5	8	8	10	9	10	9
Sup Fig. 4E	<i>Uqcrb</i>	8	5	8	7	10	9	11	9
Sup Fig. 4E	<i>Cox4i1</i>	8	8	8	8	10	9	10	9
Sup Fig. 4E	<i>Atp5b</i>	8	7	8	8	10	9	10	10
Sup Fig. 5A	<i>Adipoq</i>	7	7	6	7	10	8	11	8
Sup Fig. 5A	<i>Lep</i>	7	8	6	7	10	8	11	9
Sup Fig. 5B	<i>Ppargc1a</i>	7	8	6	7	10	9	11	8
Sup Fig. 5C	<i>Ndufa6</i>	8	8	7	8	10	10	12	8
Sup Fig. 5C	<i>Sdhc</i>	8	8	7	8	11	10	11	8
Sup Fig. 5C	<i>Uqcrb</i>	8	8	7	8	10	10	10	9
Sup Fig. 5C	<i>Cox4i1</i>	8	7	7	7	11	10	11	9
Sup Fig. 5C	<i>Atp5b</i>	8	7	7	7	9	9	11	9
Sup Fig. 6A	<i>Col6a3</i>	8	8	7	8	10	9	12	9
Sup Fig. 6A	<i>Tgb1</i>	8	8	8	8	10	9	11	9

SUPPLEMENTARY DATA

Sup Fig. 6A	<i>Mmp14</i>	8	8	8	8	11	10	12	10
Sup Fig. 6A	<i>Lox</i>	7	6	7	7	10	9	8	9
Sup Fig. 6B	<i>Thbs1</i>	7	8	7	8	11	8	9	8
Sup Fig. 6C	<i>Kdr</i>	8	8	6	7	10	10	9	8
Sup Fig. 6C	<i>Fgf2</i>	7	7	7	8	10	8	9	8
Sup Fig. 6C	<i>Angpt2</i>	7	7	6	8	10	10	9	9
Sup Fig. 7A	<i>Ndufa6</i>	8	8	7	8	11	10	11	9
Sup Fig. 7A	<i>Sdhc</i>	8	8	7	8	10	10	11	9
Sup Fig. 7A	<i>Uqcrb</i>	8	8	7	8	10	10	11	9
Sup Fig. 7A	<i>Cox4i1</i>	8	7	8	8	10	10	12	9
Sup Fig. 7A	<i>Atp5b</i>	8	8	8	8	11	9	12	9
Sup Fig. 7B	<i>Mmp14</i>	7	8	7	8	11	9	12	9
Sup Fig. 7C	<i>Col6a3</i>	7	8	8	8	11	10	12	8
Sup Fig. 8A	<i>Ndufa6</i>	7	6	6	8	9	8	10	9
Sup Fig. 8A	<i>Sdhc</i>	8	7	7	7	10	10	12	10
Sup Fig. 8A	<i>Uqcrb</i>	8	8	7	7	10	10	12	10
Sup Fig. 8A	<i>Cox4i1</i>	7	6	7	8	9	9	10	9
Sup Fig. 8A	<i>Atp5b</i>	7	7	6	7	9	9	10	9
Sup Fig. 8B	<i>Slc2a4</i>	7	8	8	8	9	8	12	8
Sup Fig. 8C	<i>Foxo1</i>	7	7	7	7	10	10	11	9
Sup Fig. 8C	<i>Nr4a1</i>	8	8	7	7	10	9	12	10
Sup Fig. 9A	♀%BWL after tto	4	4	4	4	6	6	6	6
Sup Fig. 9A	♂%BWL after tto	4	4	4	4	4	4	6	4
Sup Fig. 9C	♀Glucose	4	4	4	4	6	6	6	6
Sup Fig. 9C	♀Insulin	4	3	4	4	6	6	6	6
Sup Fig. 9D	♂Glucose	4	4	4	4	6	6	6	6
Sup Fig. 9D	♂Insulin	4	3	4	4	6	6	6	6
Sup Fig. 9E	♀QUICKI	4	3	4	4	6	6	6	6
Sup Fig. 9F	♂QUICKI	4	4	4	4	5	4	6	4
Sup Fig. 9G	♀HOMA-IR	4	3	4	4	6	6	6	6

SUPPLEMENTARY DATA

Sup Fig. 9H	♂HOMA-IR	4	4	4	4	5	4	6	4
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Acaca, acetyl-CoA carboxylase alpha; *Adipoq*, adiponectin; *Angpt2*, angiopoietin 2; *Atp5b*, ATP synthase F1 subunit beta; *Cd36*, CD36 molecule; *Cd68*, CD68 molecule; *Col6a3*, collagen type VI alpha 3 chain; *Cox4i1*, cytochrome c oxidase subunit 4I1; *Cpt1b*, carnitine palmitoyltransferase 1B; *Foxo1*, forkhead box O1; *Gdf15*, growth differentiation factor 15; *Glut4* (Slc2a4), solute carrier family 2 member 4; *Il1a*, interleukin 1 alpha; *Il1b*, interleukin 1 beta; *Il1rn*, interleukin 1 receptor antagonist; *Il6*, interleukin 6; *Itgax*, integrin subunit alpha X; *Mmp2*, matrix metalloproteinase 2; *Mmp14*, matrix metalloproteinase 14; *Ndufa6*, NADH:ubiquinone oxidoreductase subunit A6; *Ppara*, peroxisome proliferator activated receptor alpha; *Ppargc1a*, PPARG coactivator 1 alpha; *Saa3*, serum amyloid A3; *Sdhc*, succinate dehydrogenase complex subunit C; *Spp1*, secreted phosphoprotein 1 (osteopontin); *Timp2*, tissue inhibitor of metalloproteinases 2; *Tnf*, tumor necrosis factor; BWG, body weight gain; BWL, body weight loss; AUC, area under the curve; IPGTT, intraperitoneal glucose tolerance test; QUICKI, quantitative insulin sensitivity check index; HOMA-IR, homeostatic model assessment; TG, triglycerides; CSA, cross-sectional area; WAT, white adipose tissue; BAT, brown adipose tissue; SAA, serum amyloid A; TNF- α , tumor necrosis factor alpha; GDF15, growth differentiation factor 15; ♀, female; ♂, male.