

Supplemental Table S1: Statistical data of SBP and BPM

Three-way ANOVA Sex effect SBP	F (DFn, DFd)	P value
Treatment	F (3, 123) = 4.692	P=0.0039
Genotype	F (1, 123) = 57.05	P<0.0001
Sex	F (1, 123) = 3.103	P=0.0807
Treatment x Genotype	F (3, 123) = 3.819	P=0.0117
Treatment x Sex	F (3, 123) = 0.6550	P=0.5813
Genotype x Sex	F (1, 123) = 0.9970	P=0.3200
Treatment x Genotype x Sex	F (3, 123) = 0.1893	P=0.9035

Three-way ANOVA sex effect BPM	F (DFn, DFd)	P value
Treatment	F (3, 125) = 5.543	P=0.0013
Genotype	F (1, 125) = 19.71	P<0.0001
Sex	F (1, 125) = 0.4535	P=0.5019
Treatment x Genotype	F (3, 125) = 1.623	P=0.1873
Treatment x Sex	F (3, 125) = 0,2480	P=0.8627
Genotype x Sex	F (1, 125) = 1.456	P=0.2299
Treatment x Genotype x Sex	F (3, 125) = 0.5289	P=0.6632

Two-way ANOVA SBP	F (DFn, DFd)	P value
Interaction	F (3, 131) = 4.032	P=0.0088
Treatment	F (3, 131) = 5.777	P=0.0010
Genotype	F (1, 131) = 62.25	P<0.0001

Tukey's multiple comparisons test	Adjusted P Value
VEHICLE:WT vs. VEHICLE:CD	P<0.0001
VEHICLE:WT vs. VER:WT	P>0.9999
VEHICLE:WT vs. VER:CD	P=0.0003
VEHICLE:WT vs. CUR:WT	P>0.9999
VEHICLE:WT vs. CUR:CD	P=0.0013
VEHICLE:WT vs. CURVER:WT	P>0.9997
VEHICLE:WT vs. CURVER:CD	P>0.9995
VEHICLE:CD vs. VER:WT	P<0.0001
VEHICLE:CD vs. VER:CD	P=0.9381
VEHICLE:CD vs. CUR:WT	P<0.0001
VEHICLE:CD vs. CUR:CD	P=0.6030

VEHICLE:CD vs. CURVER:WT

P<0.0001

VEHICLE:CD vs. CURVER:CD

P<0.0001

Two-way ANOVA BPM	F (DFn, DFd)	P value
Interaction	F (3, 133) = 1,692	P=0,1718
Treatment	F (3, 133) = 5,677	P=0,0011
Genotype	F (1, 133) = 21,49	P<0,0001

Supplemental Table S2: Statistical data of Ascending Aorta parameters

ANOVA wall thickness T. Media	F (DFn, DFd)	P value
Interaction	F (1, 30) = 11,60	P=0,0019
Treatment	F (1, 30) = 9,898	P=0,0037
Genotype	F (1, 30) = 27,99	P<0,0001
Tukey's multiple comparisons test	Adjusted P Value	
VEHICLE:WT vs. VEHICLE:CD	P<0,0001	
VEHICLE:WT vs. CURVER:CD	P=0,4408	
VEHICLE:CD vs. CURVER:CD	P=0,0004	

Two-way ANOVA diameter Lumen	F (DFn, DFd)	P value
Interaction	F (1, 30) = 1,262	P=0,2701
Treatment	F (1, 30) = 19,34	P=0,0001
Genotype	F (1, 30) = 42,17	P<0,0001

Two-way ANOVA ELN content	F (DFn, DFd)	P value
Interaction	F (1, 30) = 0,05941	P=0,8091
Treatment	F (1, 30) = 0,5833	P=0,4510
Genotype	F (1, 30) = 43,72	P<0,0001

Two-way ANOVA Density VSMC	F (DFn, DFd)	P value
Interaction	F (1, 20) = 0,1171	P=0,7358
Treatment	F (1, 20) = 9,485	P=0,0059
Genotype	F (1, 20) = 53,93	P<0,0001

Two-way ANOVA Total Collagen	F (DFn, DFd)	P value
Interaction	F (1, 45) = 20,81	P<0,0001
Treatment	F (1, 45) = 2,773	P=0,1028

Genotype	F (1, 45) = 4,878	P=0,0323
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Tukey's multiple comparisons test**Adjusted P Value**

VEHICLE:WT vs. VEHICLE:CD	P<0,0001
VEHICLE:WT vs. CURVER:CD	P=0,9769
VEHICLE:CD vs. CURVER:CD	P=0,0005

Two-way ANOVA Green Collagen**F (DFn, DFd)****P value**

Interaction	F (1, 48) = 19,20	P<0,0001
Treatment	F (1, 48) = 2,121	P=0,1518
Genotype	F (1, 48) = 17,77	P=0,0001

Tukey's multiple comparisons test**Adjusted P Value**

VEHICLE:WT vs. VEHICLE:CD	P<0,0001
VEHICLE:WT vs. CURVER:CD	P=0,1822
VEHICLE:CD vs. CURVER:CD	P=0,0015

Two-way ANOVA Red Collagen**F (DFn, DFd)****P value**

Interaction	F (1, 46) = 8,411	P=0,0057
Treatment	F (1, 46) = 0,4011	P=0,5296
Genotype	F (1, 46) = 0,3175	P=0,5759

Tukey's multiple comparisons test**Adjusted P Value**

VEHICLE:WT vs. VEHICLE:CD	P=0,2564
VEHICLE:WT vs. CURVER:CD	P=0,8036
VEHICLE:CD vs. CURVER:CD	P=0,0853

Supplemental Table S3: Statistical data of Hearts

Three way ANOVA Sex effect	F (DFn, DFd)	P value
Treatment	F (1, 97) = 22,70	P<0,0001
Genotype	F (1, 97) = 15,48	P=0,0002
Sex	F (1, 97) = 0,1639	P=0,6865
Treatment x Genotype	F (1, 97) = 11,97	P=0,0008
Treatment x Sex	F (1, 97) = 6,940	P=0,0098
Genotype x Sex	F (1, 97) = 0,07919	P=0,7790
Treatment x Genotype x Sex	F (1, 97) = 6,555	P=0,0120
Šídák's multiple comparisons test	Adjusted P Value	

VEHICLE:WT-MALES vs. VEHICLE:WT-FEMALES	P=0,0777
VEHICLE:CD-MALES vs. VEHICLE:CD-FEMALES	P>0,9999
CURVER:WT-MALES vs. CURVER:WT-FEMALES	P=0,1547
CURVER:CD-MALES vs. CURVER:CD-FEMALES	P>0,9999

Two-way ANOVA Heart vs Body weight	F (DFn, DFd)	P value
Interaction	F (1, 101) = 20,76	P<0,0001
Treatment	F (1, 101) = 15,13	P=0,0002
Genotype	F (1, 101) = 16,37	P=0,0001

Tukey's multiple comparisons test	Adjusted P Value
VEHICLE:WT vs. VEHICLE:CD	P <0,0001
VEHICLE:WT vs. CURVER:WT	P =0,9640
VEHICLE:WT vs. CURVER:CD	P =0,9995
VEHICLE:CD vs. CURVER:CD	P <0,0001

Two-way ANOVA Thickness LV	F (DFn, DFd)	P value
Interaction	F (1, 25) = 7,988	P=0,0091
Treatment	F (1, 25) = 3,832	P=0,0615
Genotype	F (1, 25) = 14,30	P=0,0009

Tukey's multiple comparisons test	Adjusted P Value
VEHICLE:WT vs. VEHICLE:CD	P= 0,0009
VEHICLE:WT vs. CURVER:WT	P=0,9306
VEHICLE:WT vs. CURVER:CD	P= 0,5941
VEHICLE:CD vs. CURVER:CD	P= 0,0099

Supplemental Table S4: Statistical data of 3-NT and XOR

Two-way ANOVA 3-NT Aorta	F (DFn, DFd)	P value
Interaction	F (1, 28) = 12,12	P=0,0017
Treatment	F (1, 28) = 11,27	P=0,0023
Genotype	F (1, 28) = 7,793	P=0,0093

Tukey's multiple comparisons test	Adjusted P Value
VEHICLE:WT vs. VEHICLE:CD	P=0,0008
VEHICLE:WT vs. CURVER:WT	P=0,9997
VEHICLE:WT vs. CURVER:CD	P=0,9756
VEHICLE:CD vs. CURVER:CD	P =0.0007

ANOVA table XOR Aorta (Immunofluorescence)	F (DFn, DFd)	P value
Interaction	F (1, 19) = 5,952	P=0,0247
Treatment	F (1, 19) = 11,49	P=0,0031
Genotype	F (1, 19) = 2,167	P=0,1574

Tukey's multiple comparisons test	Adjusted P Value
VEHICLE:WT vs. VEHICLE:CD	P=0,0478
VEHICLE:WT vs. CURVER:WT	P=0,9002
VEHICLE:WT vs. CURVER:CD	P=0,5591
VEHICLE:CD vs. CURVER:CD	P=0,0037

One-way ANOVA XOR Aorta (Western)	F (DFn, DFd)	P value
Treatment	F (2, 21) = 34,02	P<0,0001

Tukey's multiple comparisons test	Adjusted P Value
VEHICLE:WT vs. VEHICLE:CD	P=0,0014
VEHICLE:WT vs. CURVER:CD	P=0,5770
VEHICLE:CD vs. CURVER:CD	P=0,0004

Two-way ANOVA 3-NT LV	F (DFn, DFd)	P value
Interaction	F (1, 36) = 39,09	P<0,0001
Treatment	F (1, 36) = 13,10	P=0,0009
Genotype	F (1, 36) = 29,96	P<0,0001

Tukey's multiple comparisons test	Adjusted P Value
VEHICLE:WT vs. VEHICLE:CD	P<0,0001
VEHICLE:WT vs. CURVER:WT	P=0,2959

VEHICLE:WT vs. CURVER:CD	P=0,5088
VEHICLE:CD vs. CURVER:CD	P <0,0001

Two-way ANOVA XOR LV (Immunofluorescence)

	F (DFn, DFd)	P value
Interaction	F (1, 16) = 2,697	P=0,1201
Treatment	F (1, 16) = 8,725	P=0,0093
Genotype	F (1, 16) = 8,653	P=0,0096

One-way ANOVA XOR LV (Western)

	F (DFn, DFd)	P value
Treatment	F (2, 21) = 34,02	P<0,0001

Tukey's multiple comparisons test

Adjusted P Value

VEHICLE:WT vs. VEHICLE:CD	P<0,0001
VEHICLE:WT vs. CURVER:CD	P=0,0145
VEHICLE:CD vs. CURVER:CD	P=0,0001

Supplemental Table S5: Statistical data of pNRF2

Two-way ANOVA Aorta

	F (DFn, DFd)	P value
Interaction	F (1, 34) = 19,30	P=0,0001
Treatment	F (1, 34) = 17,89	P=0,0002
Genotype	F (1, 34) = 36,27	P<0,0001

Tukey's multiple comparisons test

Adjusted P Value

VEHICLE:WT vs. VEHICLE:CD	P<0,0001
VEHICLE:WT vs. CURVER:WT	P=0,9995
VEHICLE:WT vs. CURVER:CD	P=0,5890
VEHICLE:CD vs. CURVER:CD	P <0,0001

One Way ANOVA Heart

	F (DFn, DFd)	P value
Treatment	F (2,28) = 8	P=0.0014

Tukey's multiple comparisons test

Adjusted P Value

VEHICLE WT vs. VEHICLE CD	P=0.0084
VEHICLE WT vs. CURVER CD	P=0.8771
VEHICLE CD vs. CURVER CD	P=0.002

Supplemental Table S6: Statistical data of treatment intake and body weight

Two-way RM ANOVA Intake-MALES		
	F (DFn, DFd)	P value
Treatment x Time	F (45, 240) = 0,7963	P=0,8189
Treatment	F (3, 16) = 0,2570	P=0,8552
Time	F (6,238, 99,80) = 0,6699	P=0,6799
Two-way RM ANOVA Intake-FEMALES		
	F (DFn, DFd)	P value
Treatment x Time	F (45, 240) = 0,7335	P=0,8936
Treatment	F (3, 16) = 1,846	P=0,1794
Time	F (6,061, 96,97) = 0,9496	P=0,4642
Two-way ANOVA Intake- WT vs CD		
	F (DFn, DFd)	P value
Interaction	F (3, 24) = 0,1347	P=0,9384
Treatment	F (3, 24) = 0,5263	P=0,6685
Genotype	F (1, 24) = 2,915	P=0,1007
Two-way ANOVA Body weight- MALES		
	F (DFn, DFd)	P value
Interaction	F (3, 102) = 0,9029	P=0,4425
Treatment	F (3, 102) = 1,219	P=0,3068
Genotype	F (1, 102) = 92,76	P<0,0001
Two-way ANOVA Body weight-FEMALES		
	F (DFn, DFd)	P value
Interaction	F (3, 62) = 1,681	P=0,1803
Treatment	F (3, 62) = 1,483	P=0,2279
Genotype	F (1, 62) = 38,57	P<0,0001

Supplemental Figure

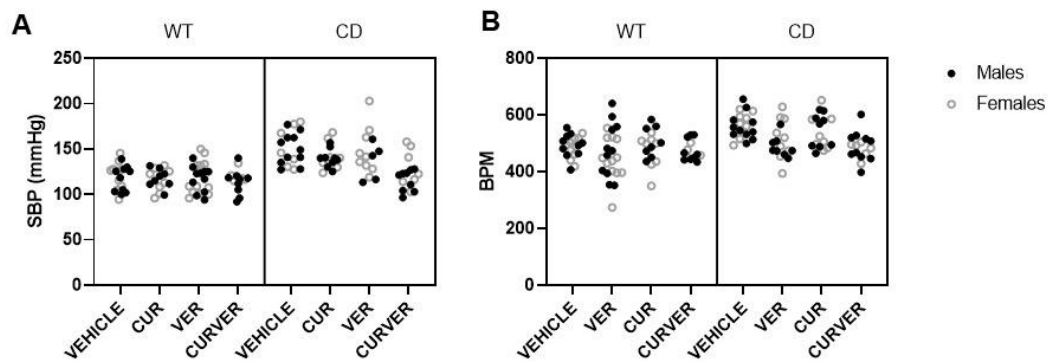


Figure S1: No effect of sex on SBP and BPM

(A) SBP and (B) BPM measurements in the conscious state using the indirect tail-cuff method in WT (n=14-23) and CD (n=14-18) mice treated with single (CUR, VER) or combined (CURVER) treatments. No significant differences were observed due to sex. Data are represented as mean \pm SEM. Three-way ANOVA. Statistical data in Tables S1

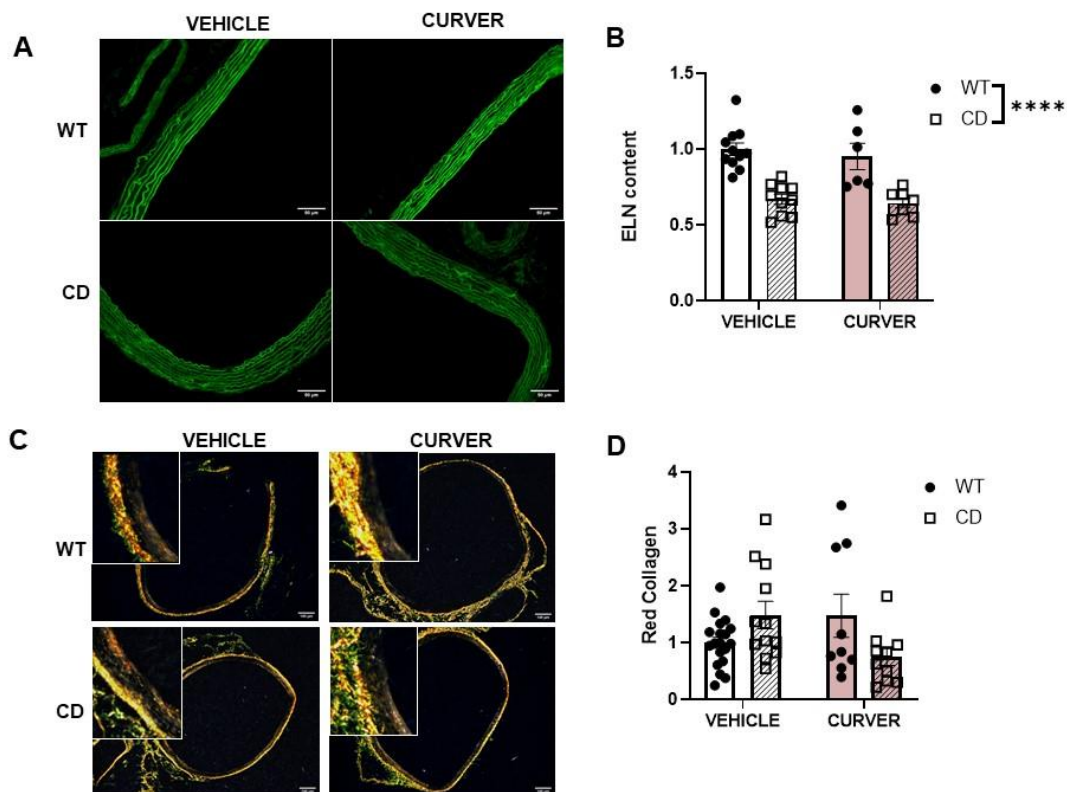


Figure S2: Analysis of ascending aortas

(A) Representative images of green autofluorescence ELN of ascending aortas (B) No significant differences were observed in ELN content due to treatment. (C) Representative images of ascending aortas under polarised light. A representative magnification is presented in the upper left box. (D) No significant differences were

observed in mature (red) collagen content. Data are represented as mean \pm SEM. Two-way ANOVA. Statistical data in Tables S2

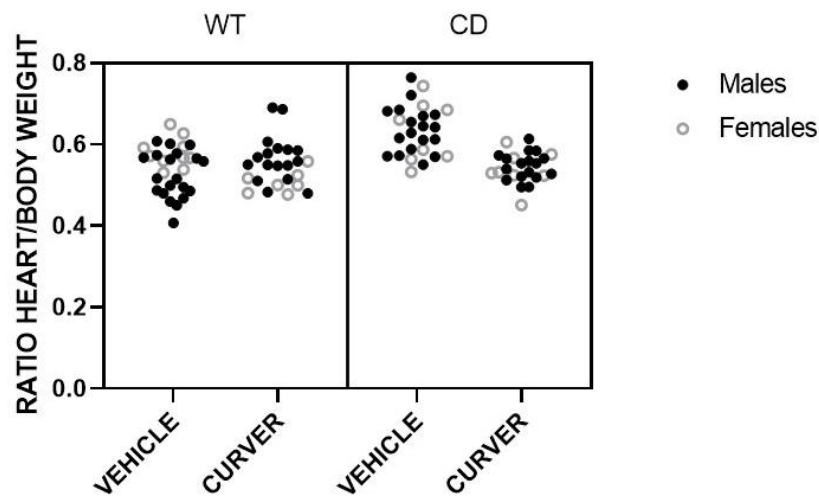


Figure S3: No effect of sex on the heart vs body weight ratio

Data are represented as mean \pm SEM. Three-way ANOVA. Statistical data in Table S3

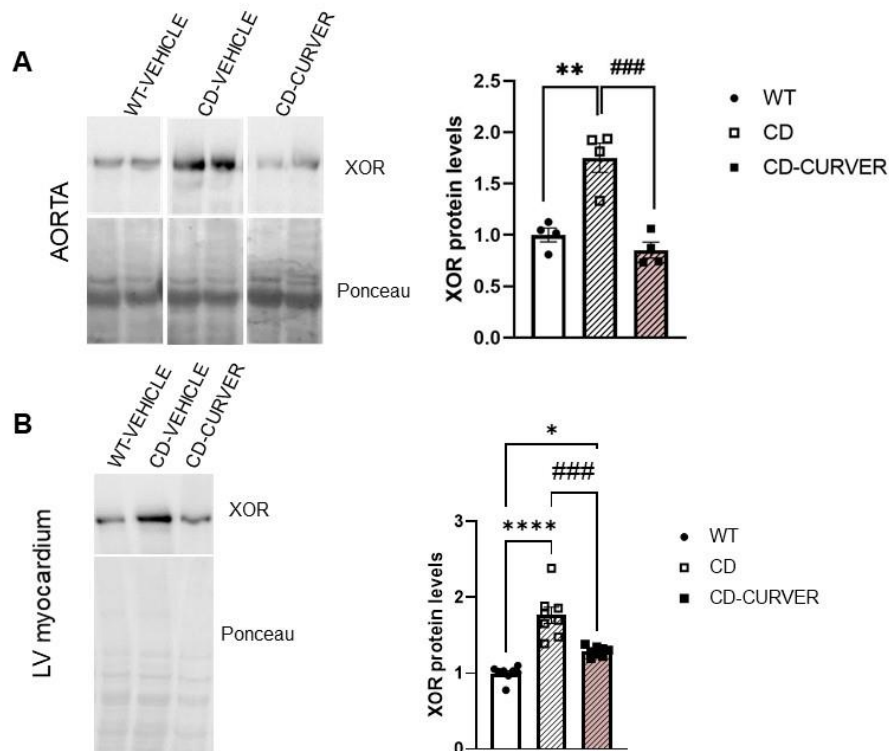


Figure S4: Western blot analysis of XOR levels in ascending aortas and LV-myocardium

Representative images of western blot analysis and the corresponding histogram quantification. Significant difference among groups are shown after one-way ANOVA

followed by Tukey's multiple comparisons test for ascending aorta ($F_{(2,9)} = 22$, $p = 0.0003$) **(A)** and LV-myocardium ($F_{(2,21)} = 34.02$, $p < 0.0001$) **(B)**.

Data are represented as mean \pm SEM. * Effect of genotype; #, effect of treatment. ***,#### $p < 0.001$; ****,##### $p < 0.0001$. Statistical data in Table S4

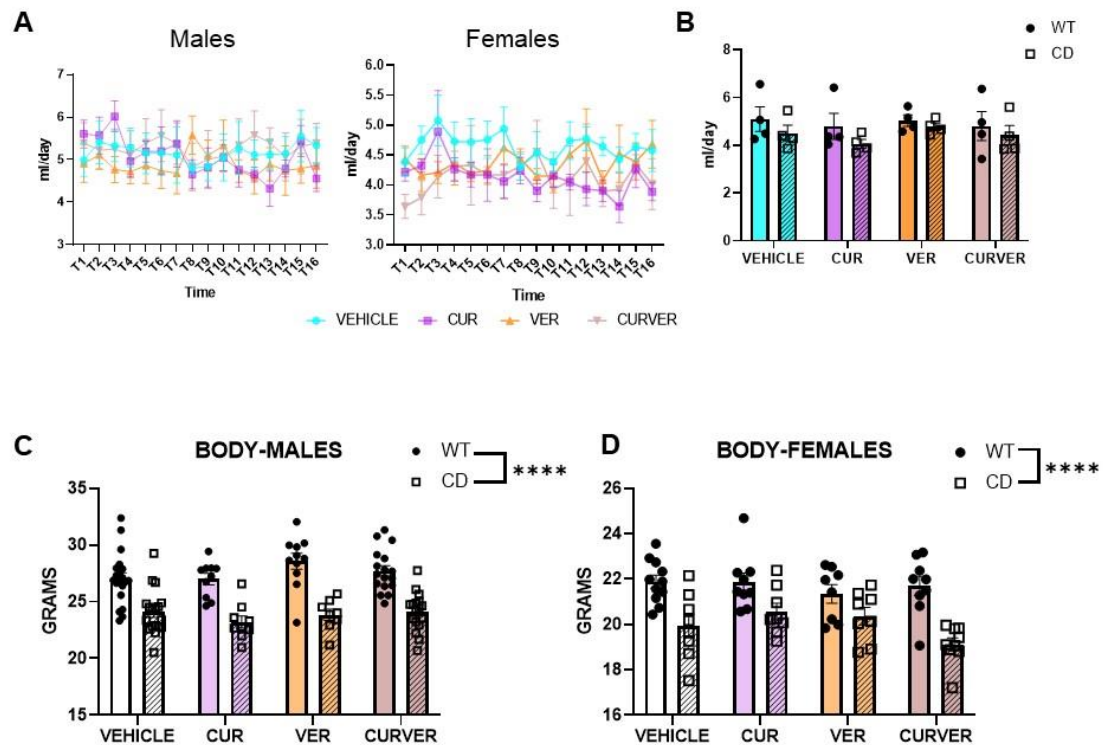


Figure S5: Treatment intake and body weight

(A) The amount of drunk per cage was quantified and normalised to the number of animals per cage (2 to 4) and to the time between each change (48 to 60 hours). Consumption was not significantly different between groups ($F_{45,240} = 0.7963$, $p = 0.8189$ in males; $F_{45,240} = 0.7335$, $p = 0.8936$ in females). **(B)** Daily intake was not significantly different among WT mice and the other groups ($F_{3,24} = 0.134$, $p = 0.9384$). **(C, D)**. None of the treatments altered the reduced body weight presented by CD compared with WT mice (effect of genotype $F_{1,102} = 92.76$, $p < 0.0001$ in males; $F_{1,62} = 38.57$, $p < 0.0001$ in females).