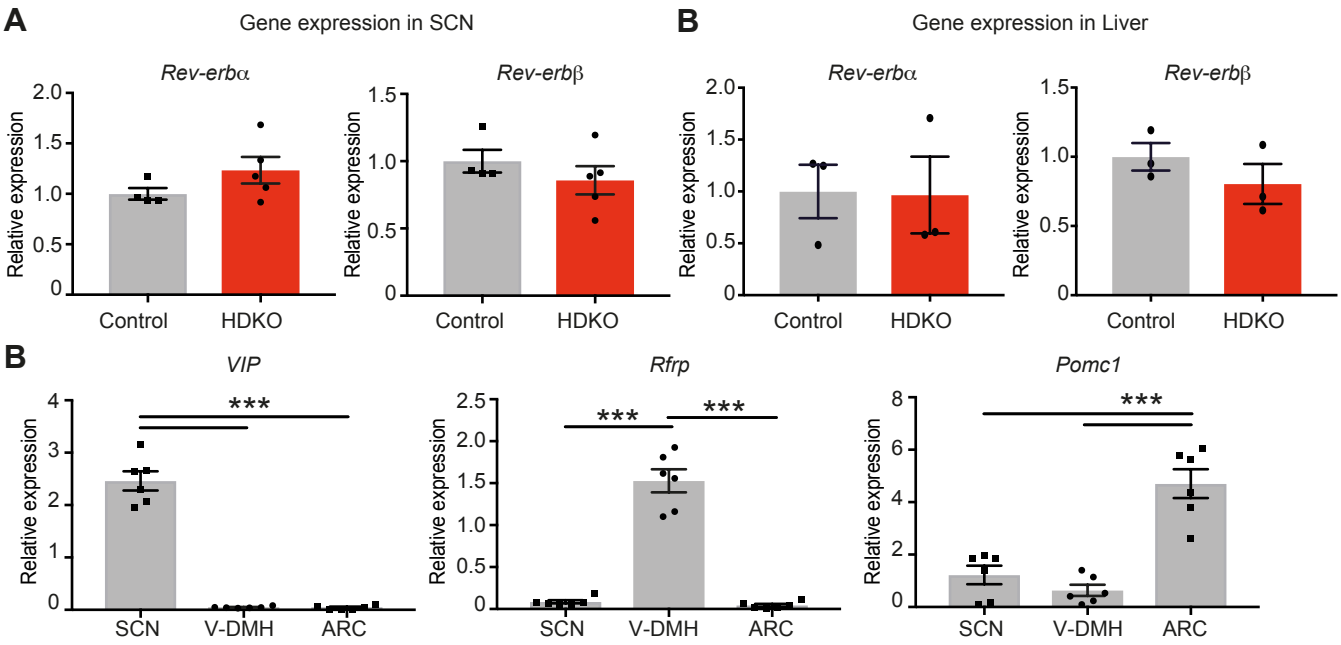
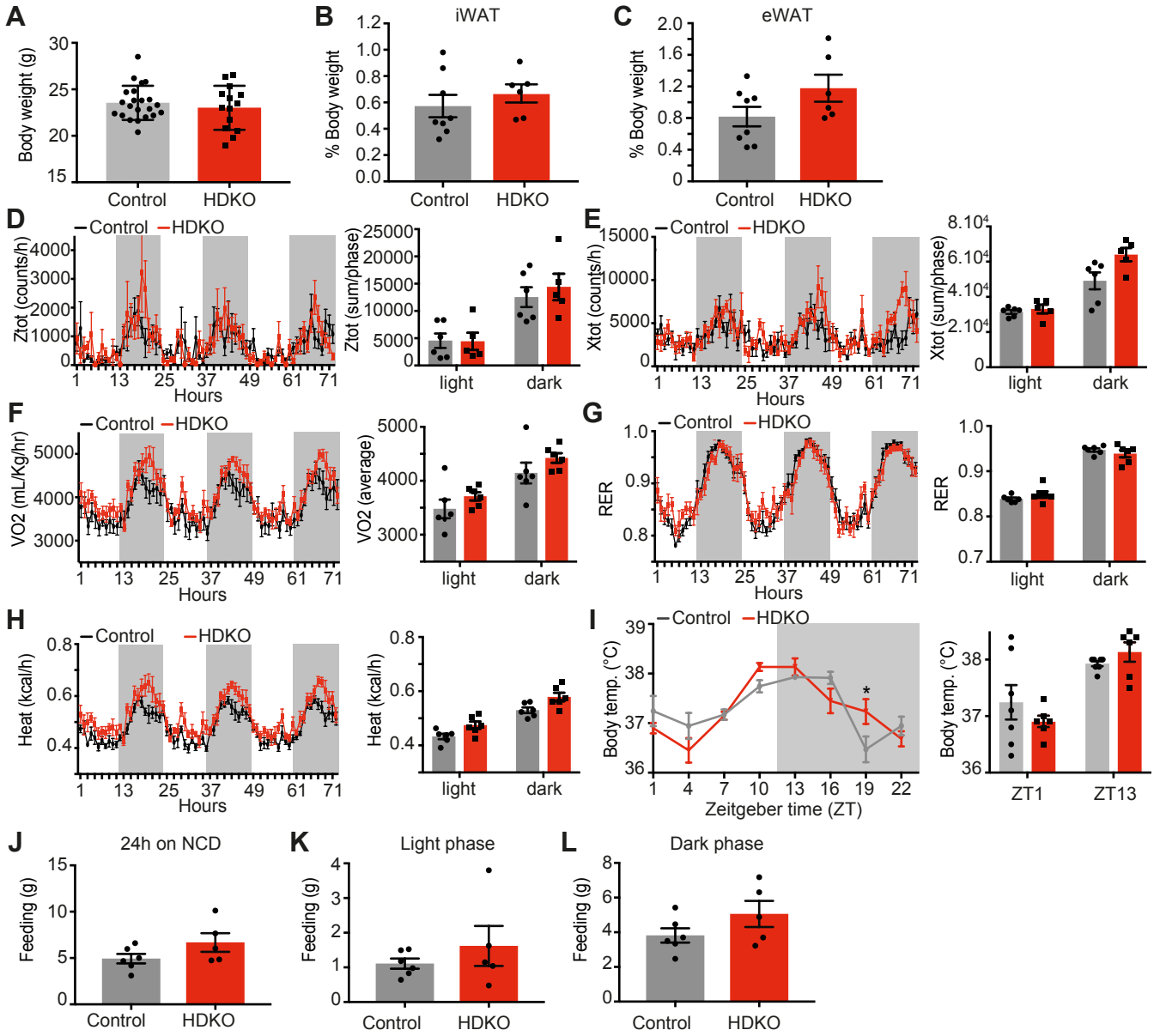
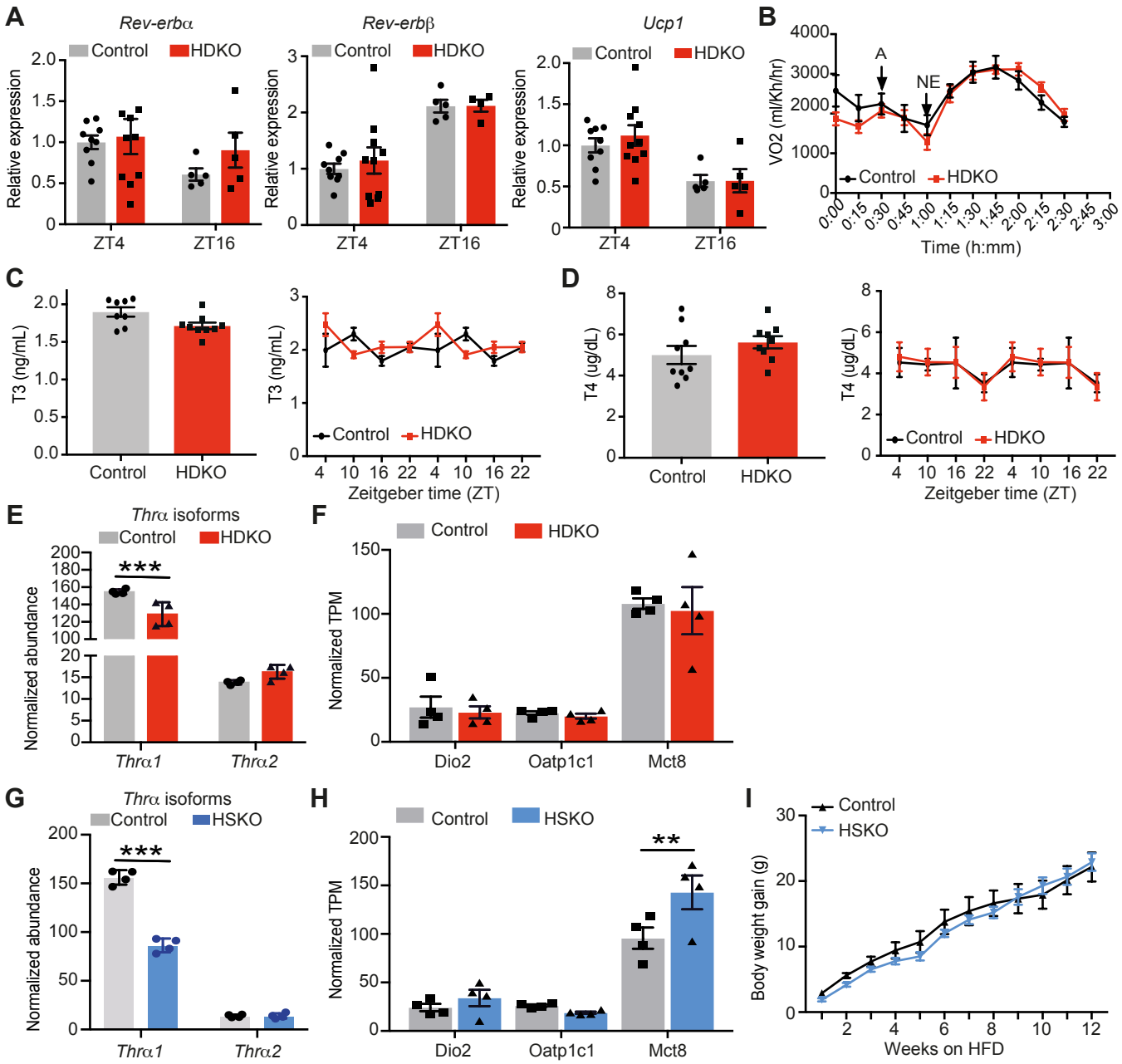


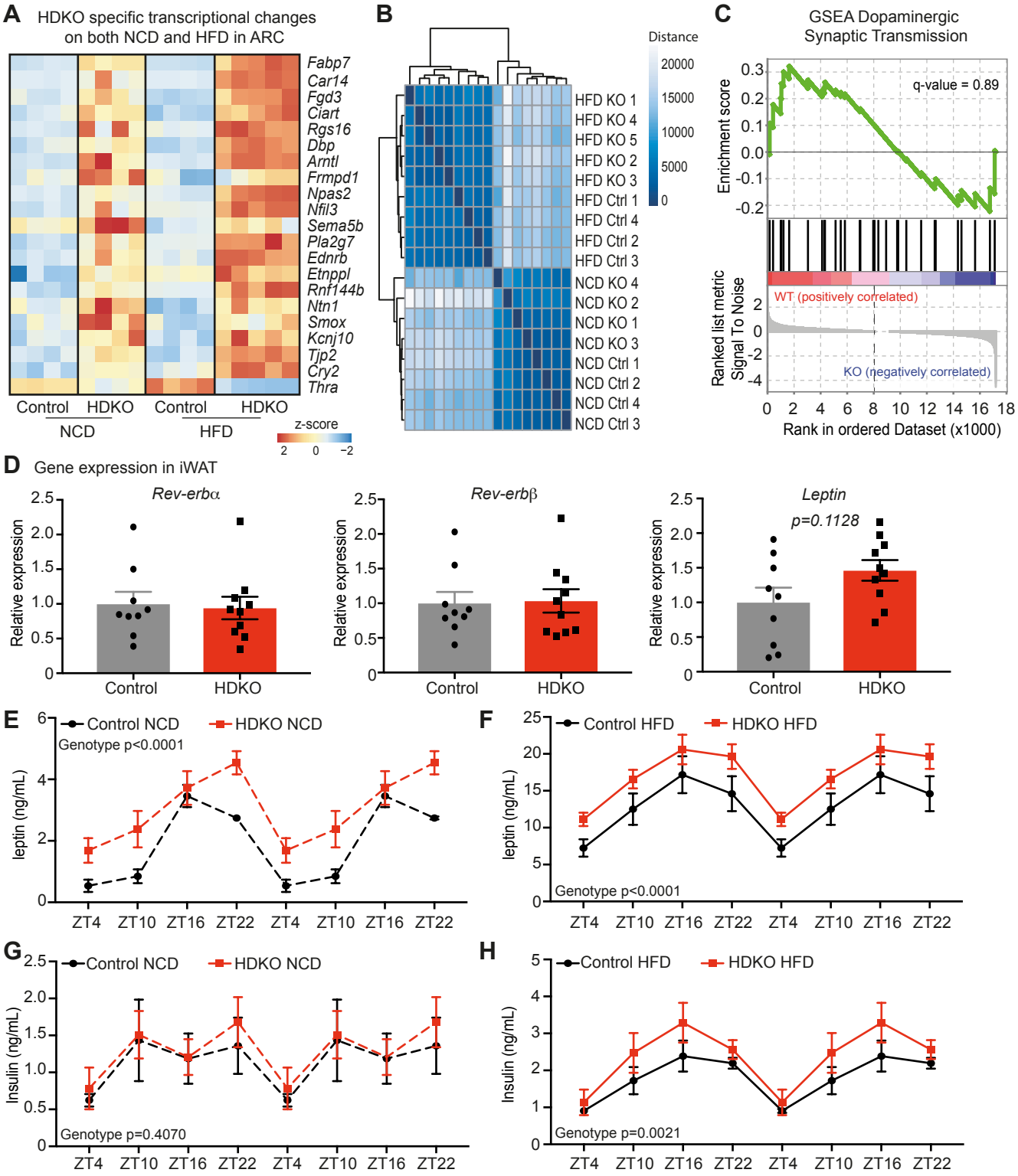
Supplemental Figure 1. REV-ERBs expression in SCN and liver are maintained in HDKO mice. A. *Reverbα* and *Reverbβ* gene expression in SCN from HDKO mice compared to their control littermates on NCD at ZT4 (n = 4-5, mean +/- SEM). Results were compared by Mann Whitney test. **B.** *Reverbα* and *Reverbβ* gene expression in liver from HDKO mice compared to their control littermates on NCD at ZT10 (n = 3, mean +/- SEM). Results were compared by Mann Whitney test. **C.** *Vip* (SCN-specific), *Rfrp* (VMH/DMH-specific) and *Pomc1* (ARC-specific) genes expression in SCN, VMH/DMH and ARC hypothalamic nucleus punch-out in control and HDKO mice on NCD at ZT4 (n = 6, mean +/- SEM). Results were compared by one-way ANOVA and Holm-Sidak's multiple comparisons test. ***P < 0.001.



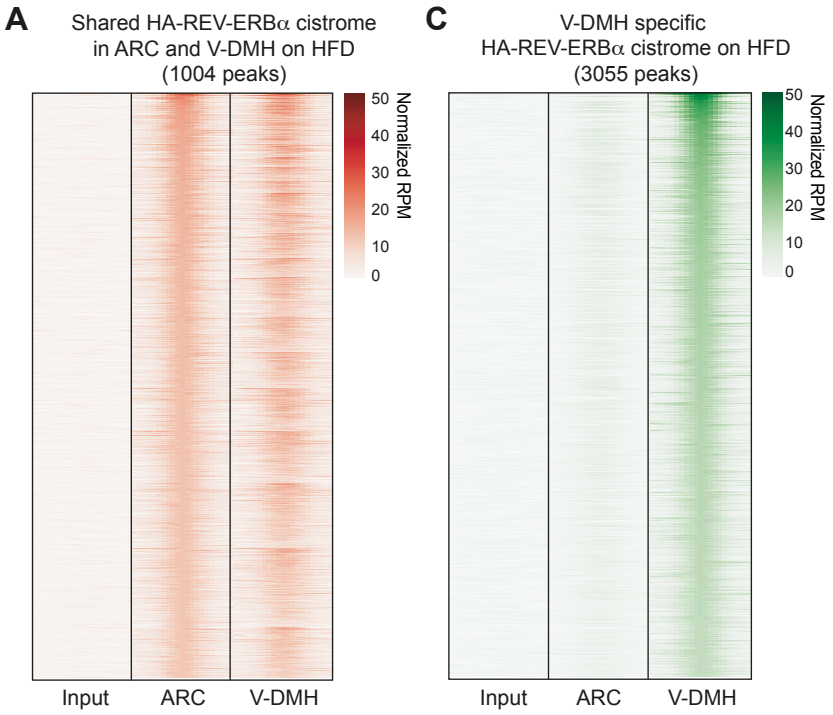
Supplemental Figure 2. REV-ERBs deletion in non-SCN hypothalamic nuclei does not induce metabolic syndrome on NCD. A. Body weight of HDKO mice and their control littermates on NCD in 14-16 week old mice (n = 14-22, mean +/- SEM). Results were compared by Mann Whitney test. **B.** Inguinal (iWAT) and **C**. epididymal (eWAT) white adipose tissues weights from HDKO mice and their control littermates on NCD in 14-16 week-old mice (n = 6-8, mean +/- SEM). Results were compared by Mann Whitney test. **D-E**. Circadian activity **F.** oxygen consumption (VO2), **G.** respiratory Exchange Ratio (RER) and **H.** heat production in HDKO mice and their control littermates on NCD in 14-16 week-old mice. D-H: Circadian recording for 3 days is displayed (left panel), as well as corresponding quantification during the light and dark phases (right panel). Results were compared by RM two-way ANOVA and Sidak's multiple comparisons test (n = 6, mean +/- SEM). **I.** Body temperature in HDKO mice and their control littermates on NCD in 14-16 week old mice (n = 7, mean +/- SEM). Circadian recording is displayed, as well as peak (ZT1) and trough (ZT13) (right panel). Results were compared by RM two-way ANOVA and Sidak's multiple comparisons test. **J-L.** Food consumption in HDKO mice and their control littermates on NCD in 14-16 week-old mice. 24h (J), light phase (K) and dark phase (L) food consumption was calculated from 3 days of recording (n = 5-6, mean +/- SEM). Results were compared by Mann Whitney test.



Supplemental Figure 3. Thermogenic capacity and thyroid signaling are preserved in HDKO mice on HFD. A. *Reverbα*, *Reverbβ* and *Ucp1* gene expression in BAT from HDKO mice compared to their control littermates on HFD at ZT4 and ZT16 (n = 5-10, mean +/- SEM). Results were compared by two-way ANOVA and Sidak's multiple comparisons test. **B.** Oxygen consumption in response to norepinephrine (NE) at ZT1 in Control and HDKO mice on HFD. A: Anesthesia. The results were compared by two-way ANOVA (n=4/group, mean +/- SEM). **C-D.** T3 (E) and T4 (F) circulating level in control and HDKO mice on HFD. Measurements at ZT4 are presented in the left panels (n=8-9, mean +/- SEM), and compared by Mann-Whitney test. Circadian measurements are presented in the right panels (n=3, mean +/- SEM, double-plotted), and compared by two-way ANOVA. **E.** *Thrα* isoforms normalized abundance measured by RNA-seq in ARC from control and HDKO mice at ZT4 on NCD. The results were compared by two-way ANOVA (n=4/group). **F.** *Dio2, Mct8* and *Oatp1c1* expression measured by RNA-seq in ARC from control and HDKO mice at ZT4 on NCD. TPM: Transcripts Per Million. The results were compared by two-way ANOVA (n=4/group). **G.** *Thrα* isoforms normalized abundance measured by RNA-seq in ARC from control and HSKO mice at ZT4 on NCD. The results were compared by two-way ANOVA (n=4/group). **H.** *Dio2, Mct8* and *Oatp1c1* expression measured by RNA-seq in ARC from control and HSKO mice at ZT4 on NCD. TPM: Transcripts Per Million. The results were compared by two-way ANOVA (n=4/group). **I.** Body weight gain of HSKO male mice and their control littermates on HFD (n = 6-8, mean +/- SEM). Results were compared by RM two-way ANOVA and Sidak's multiple comparisons test. **P < 0.01, ***P < 0.001.



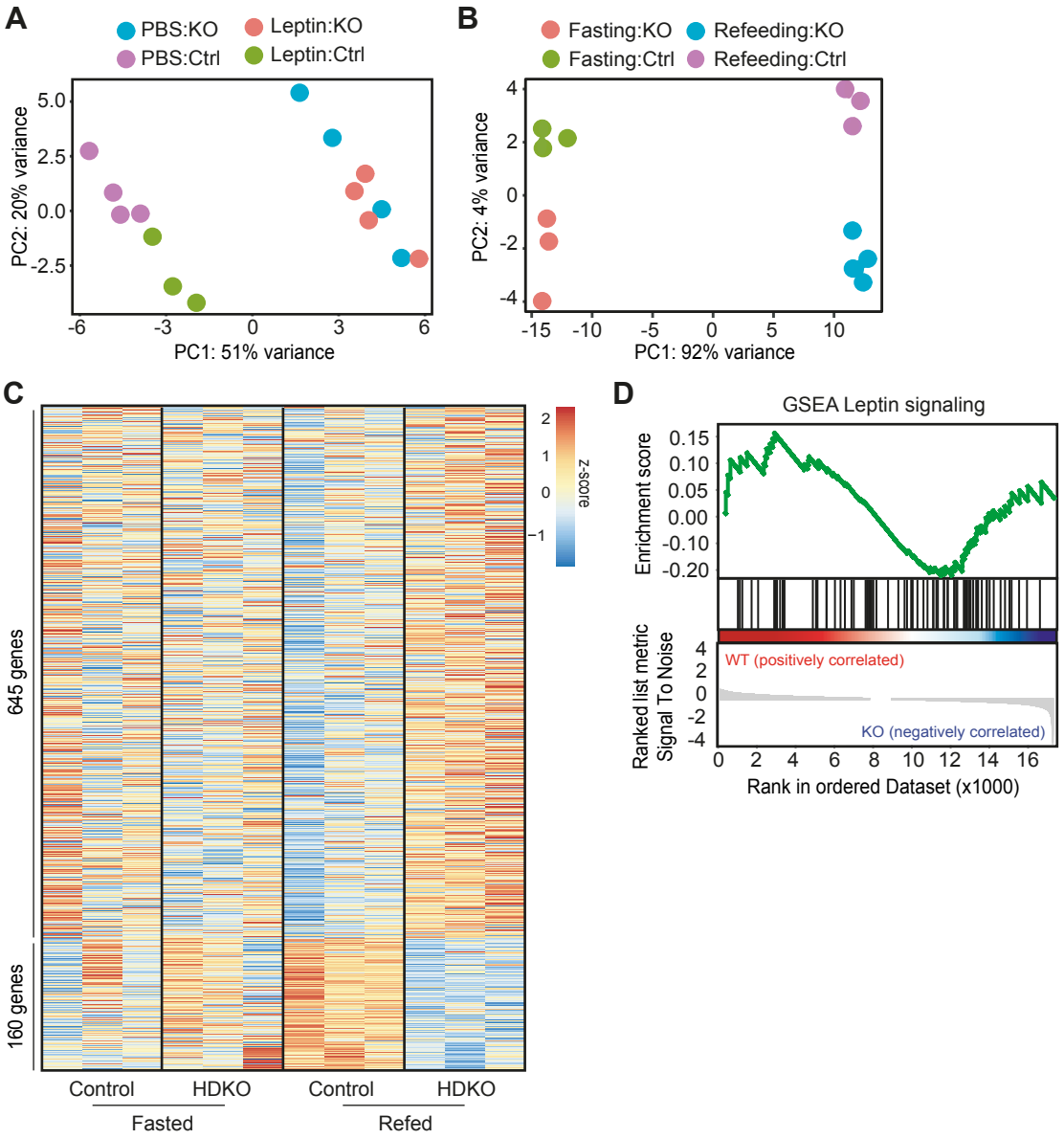
Supplemental Figure 4. Transcriptional regulation by REV-ERBs in the ARC is highly dependent on diet. A. Heatmap of genes differentially expressed in HDKO mice on both NCD and HFD in ARC. Gene expression analysis at ZT4 from HDKO mice and their control littermates on NCD and HFD in ARC (TPM > 0.1, FDR < 0.05). 2-4 independent hypothalamic nuclei punches were pooled together per biological replicate (n=4-5). **B.** Correlation heatmap of genome-wide gene expression in ARC from HDKO mice and their control littermates on NCD and HFD. **C.** GSEA analysis of dopamine signaling in DIO-HDKO specific transcriptome identified in ARC at ZT4. **D.** *Reverbα*, *Reverbβ* and *Leptin* gene expression in inguinal WAT (iWAT) from HDKO mice compared to their Control littermates on HFD at ZT4 (n = 9-10, mean +/- SEM). Results were compared by Mann-Whitney test. **E-F.** Leptin circulating level in control and HDKO mice on NCD (D, n=3) and HFD (E, n=8-10). **G-H.** Insulin circulating level in control and HDKO mice on NCD (F, n=3) and HFD (G, n=5-7). E-H : Results were compared by two-way ANOVA and Sidak's multiple comparisons test (mean +/- SEM.).



B Motif of shared ARC/V-DMH enhancers

De novo motif	p-value	Name
	1e-247	REV-ERB
	1e-211	CEBP
	1e-148	EBF
	1e-140	NFIA
	1e-102	ETV1

Supplemental Figure 5. HA-REV-ERBα cistrome in hypothalamic nuclei. A. Shared HA-REV-ERBα cistrome in ARC and VMH/DMH (V-DMH) on HFD. ChIP-seq analysis of HA immunoprecipitation in V-DMH from HA-REV-ERBα mice on HFD at ZT 4 (RPM > 1, > 4-fold enrichment over input, FDR < 0.0001). 10 independent hypothalamic nuclei punches were pooled together (n=1). **B.** Motif analysis of shared ARC/V-DMH cistrome of HA-REV-ERBα on HFD with default HOMER parameters. **C.** V-DMH-specific HA-REV-ERBα cistrome on HFD. ChIP-seq analysis of HA immunoprecipitation in V-DMH from HA-REV-ERBα mice on HFD at ZT 4 (RPM > 1, > 4-fold enrichment over input, FDR < 0.0001). 10 independent hypothalamic nuclei punches were pooled together (n=1).



Supplemental Figure 6. Hypothalamic REV-ERBs regulate leptin signaling in ARC during refeeding and in response to leptin.

A. PCA analysis of the ARC transcriptome at ZT4 from HDKO mice and their control littermates during refeeding on HFD after injection with PBS or leptin (applied on variance stabilizing transformation values of genome-wide normalized read counts). 2 independent hypothalamic nuclei punches were pooled together per biological replicate (n=3-4). **B.** PCA analysis genome-wide of the ARC transcriptome at ZT4 from HDKO mice and their control littermates during fasting and refeeding on HFD (applied on variance stabilizing transformation values of genome-wide normalized read counts). **C.** Heatmap of the genes differentially expressed in HDKO mice in ARC after refeeding with HFD. Gene expression analysis at ZT4 from HDKO mice and their control littermates on HFD in ARC during fasting and refeeding (TPM > 0.1, FDR < 0.05). 2-4 independent hypothalamic nuclei punches were pooled together per biological replicate (n=3). **D.** GSEA analysis of leptin signaling in response to refeeding.

Supplementary Table I – Oligonucleotides sequences

Gene name	Forward	Reverse
Tbp	5'-ACCTTATGCTCAGGGCTTGG-3'	5'-TGCCGTAAGGCATCATTGGA-3'
Vip	5'-GAACTTCAGCACCCTAGACAG-3'	5'-GAAGAGTATCAGGAATGCCAGG- 3'
Rfrp	5'-CTGATTTGCCACAGAAACCC-3'	5'-CATCTGTTTCCACAAACGCTC-3'
Pomc1	5'- GAGGTTAAGAGCAGTGACTAAGAG-3'	5'-AGAATCTCGGCATCTTCCAC-3'
Rev-erbα	5'-GTCTCTCCGTTGGCATGTCT-3'	5'-CCAAGTTCATGGCGCTCT-3'
Rev-erbβ	5'-TCATGAGGATGAACAGGAACC-3'	5'-GAATTCGGCCAAATCGAAC-3'
Bmal1	5'-TAGGATGTGACCGAGGGAAG-3'	5'-TCAAACAAGCTCTGGCCAAT-3'
Npas2	5'-ATGTTCGAGTGGAAAGGAGAC-3'	5'-CAAGTGCATTAAAGGGCTGTG-3'
36B4	5'-TCATCCAGCAGGTGTTTGACA-3'	5'-GGCACCGAGGCAACAGTT-3'
Ucp1	5'-TCAGGATTGGCCTCTACGAC-3'	5'-TGCCACACCTCCAGTCATTA-3'
Leptin	5'-AGCCTCACTCTACTCCACAG-3'	5'-CCTCTACATGATTCTTGGGAGC-3'

Supplementary Table II – Sequencing reads information

	Read length	Mapped reads
NC_ARC_Ctrl1	100	9135855
NC_ARC_Ctrl2	100	11210432
NC_ARC_Ctrl3	100	9036833
NC_ARC_Ctrl4	100	9634800
NC_VMH_Ctrl1	100	15863139
NC_VMH_Ctrl2	100	15246011
NC_VMH_Ctrl3	100	11991329
NC_VMH_Ctrl4	100	13774683
NC_ARC_DDKO1	100	9455004
NC_ARC_DDKO2	100	9029331
NC_ARC_DDKO3	100	10753991
NC_ARC_DDKO4	100	9574660
NC_VMH_DDKO1	100	11799100
NC_VMH_DDKO2	100	18499521
NC_VMH_DDKO3	100	16492694
NC_VMH_DDKO4	100	13538561
HFD_ARC_ZT4_Ctrl_1	50	9826998
HFD_ARC_ZT4_Ctrl_2	50	10344900
HFD_ARC_ZT4_Ctrl_3	50	11245339
HFD_ARC_ZT4_Ctrl_4	50	10571233
HFD_ARC_ZT4_DDKO_1	50	8121775
HFD_ARC_ZT4_DDKO_2	50	11271913
HFD_ARC_ZT4_DDKO_3	50	10630831
HFD_ARC_ZT4_DDKO_4	50	9998234
HFD_ARC_ZT4_DDKO_5	50	8410302
HFD_VMH_ZT4_Ctrl_1	50	11386678
HFD_VMH_ZT4_Ctrl_2	50	12344407
HFD_VMH_ZT4_Ctrl_3	50	9206788
HFD_VMH_ZT4_Ctrl_4	50	7506687
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HFD_VMH_ZT4_DDKO_2	50	9888727
HFD_VMH_ZT4_DDKO_3	50	9205327
HFD_VMH_ZT4_DDKO_4	50	7297991
HFD_VMH_ZT4_DDKO_5	50	7146082

ARC_fasting_Ctrl_1	50	6991621
ARC_fasting_Ctrl_2	50	10985656
ARC_fasting_Ctrl_3	50	7814786
ARC_fasting_DKO_1	50	7537999
ARC_fasting_DKO_2	50	11167577
ARC_fasting_DKO_3	50	7736454
ARC_refeed_Ctrl_1	50	17028993
ARC_refeed_Ctrl_2	50	9111388
ARC_refeed_Ctrl_3	50	7665491
ARC_refeed_Ctrl_4	50	8674734
ARC_refeed_DKO_1	50	10997463
ARC_refeed_DKO_2	50	8362823
ARC_refeed_DKO_3	50	7480773
ARC_refeed_DKO_4	50	10299727
ARC_leptin_Ctrl_1	50	10322423
ARC_leptin_Ctrl_2	50	13656786
ARC_leptin_Ctrl_3	50	8242173
ARC_leptin_DKO_1	50	7659337
ARC_leptin_DKO_2	50	8206748
ARC_leptin_DKO_3	50	25153090
ARC_leptin_DKO_4	50	11606218
VMH_fasting_Ctrl_1	50	10499227
VMH_fasting_Ctrl_2	50	10365806
VMH_fasting_Ctrl_3	50	9969764
VMH_fasting_DKO_1	50	11929427
VMH_fasting_DKO_2	50	12998719
VMH_fasting_DKO_3	50	15088753
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VMH_leptin_Ctrl_2	50	9013574
VMH_leptin_Ctrl_3	50	9238865
VMH_leptin_DKO_1	50	12494869
VMH_leptin_DKO_2	50	7327223
VMH_leptin_DKO_3	50	11292334
VMH_leptin_DKO_4	50	12716704
VMH_refeed_Ctrl_1	50	16877139
VMH_refeed_Ctrl_2	50	11088114
VMH_refeed_Ctrl_3	50	13628697
VMH_refeed_Ctrl_4	50	10596149
VMH_refeed_DKO_1	50	949418
VMH_refeed_DKO_2	50	7559780
VMH_refeed_DKO_3	50	10229574
VMH_refeed_DKO_4	50	6405892
ChIP Input_ARC	100	28033939
ChIP Input_VMH	100	28846413
ChIP_ARC_HA	50	22639166
ChIP_VMH_HA	50	32564386
ARC_ctrl 1	100	8581767
ARC_ctrl 2	100	10844235
ARC_ctrl 3	100	8814016
ARC_ctrl 4	100	8227836
ARC_SKO1	100	7656578
ARC_SKO2	100	10319803
ARC_SKO3	100	8903912
ARC_SKO4	100	9783570