Electronic Supplementary Materials

Table S1. Antibodies for flow cytometry

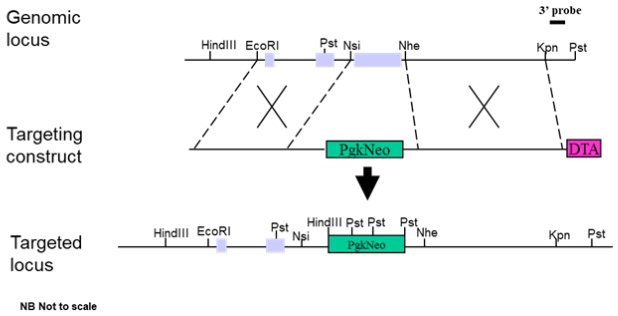
Antigen	Fluorophore	Clone	Company
Lineage Cocktail (CD3, Ly-6G/C, CD11b, CD45R, TER-119)	Pacific blue	17°2, RB6-8C5, Ra3-6B2, Ter-119, M1/70	BioLegend
Isotype control	Pacific blue	Rat IgG2a K	BioLegend
CD117 (c-kit)	FITC	2B8	eBioscience
Ly-6A/E (Sca-1)	PE	D7	eBioscience
F40-80	APC/Cy7	BM8	BioLegend
Ly-6G/C (Gr-1)	PE	RB6-8C5	eBioscience
CD3	FITC	145-2C11	eBioscience
CD11b	PerCP-eFluor710	M1/70	eBioscience
CD150	PE-Cy7	TC15-12F12.2	BioLegend
CD16/32	PerCP-eFluor710	93	Invitrogen
CD34	eFluor 660	RAM34	eBioscience

Table s2. Primers for qPCR

Gene	**Forward Primer**	**Reverse Primer**
Lifr	TCCAAGGACGGAACCAGTAG	AGGTCTGAGGTCCAGTTCCA
Osmr	AGTTGATTCATAGCTGGGGCG	GGAGGAAGGCTGGATGAAGG
Osm	AGCCCTATATCCGCCTCCAA	GTGTGTCCTCACTGGGGAAG
PPAR-α	TGCCCTGAACATCGAGTGTCGAAT	TCGTACACCAGCTTCAGCCGAATA
Nr1h2 (LXRβ)	CTTGGTGGTGTCTTCTTGA	TGTGGTAGGCTGAGGTGTA
Ldlr	TCAGACGAACAAGGCTGTCC	CCATCTAGGCAATCTCGGTCTC
CPt1-α	CTCCGCCTGAGCCATGAAG	CACCAGTGATGATGCCATTCT
Srebf1	GATGTGCGAACTGGACACAG	CATAGGGGGCGTCAAACAG
FASN	AGAGATCCCGAGACGCTTCT	GCTTGGTCCTTTGAAGTCGAAGA
ACC1/ACACA	ACATTCCGAGCAAGGGATAAG	GCTTGGTCCTTTGAAGTCGAAGA
Nr1h3 (LXRα)	AGGAGTGTCGACTTCGCAAA	CTCTTCTTGCCGCTTCAGTTT
IL1β	GACAGCCCAGGTCAAAGGTT	AGCTTCCTTGTGCAAGTGTCT
TNFα	GTGGAACTGGCAGAAGAG	CCATAGAACTGATGAGAGG
CCL2 (MCP-1)	GTGCTGAAGACCTTAGGGCA	AGCTGTAGTTTTTGTCACCAAGC
Il6	AGTCTCCTCTCCGGACTTGT	TCCTCTCTGCAAGAGACTTCC
CD36	TCATATTGTGCTTGCAAATCCAA	TGTAGATCGGCTTTACCAAAGATG
PCK1	ATGAAAGGCCGCACCATGTA	GCACAGATATGCCCATCCGA
PPAR-γ	CGTGCAGCTACTGCATGTGA	GGGTGGGACTTTCCTGCTAA
PGC1-α	GGAATGCACCGTAAATCTGC	TTCTCAAGAGCAGCGAAAGC
Mrc1	TTGCACTTTGAGGGAAGCGA	CCTTGCCTGATGCCAGGTTA
Ubc	GCCCAGTGTTACCACCAAGA	CCCATCACACCCAAGAACA

Mice and generation of *Osm*$^{-/-}$ mice

C57BL/6J wild-type (Wt) mice were purchased from The Jackson Laboratory and established as a colony since 2001. C57BL/6J *Osm*$^{-/-}$ mice were obtained from GlaxoSmithKline (Stevenage, U.K.), and a colony was established in 2015. *Osm*$^{-/-}$ mice were bred as a separate mouse line from Wt mice. *Osm*$^{-/-}$ mice were generated as follows.



The strategy results in the deletion of exon 3 of the oncostatin M gene removing exonic sequences encoding the c-terminal 208 of a total of 265 amino acids and all of the 3' noncoding sequences. The deleted OSM region is replaced by a positive selection cassette containing the neomycin phophotransferase gene driven by the PGK promoter (PgkNeo). 5' and 3' homology arms (2.7kb and 4.2kb respectively) were cloned from a 129 SVj BAC library and placed either side of the PgkNeo positive selection cassette to generate the targeting construct. Homologous recombination in neomycin resistant ES cells was confirmed by Southern blot of PstI I digested genomic DNA using a 3' external probe (black bar) which detects ~7kb and 4.9 kb bands at the wild-type and targeted loci respectively. Gene targeting was performed in E14.1 ES cells. Three targeted clones were injected into C57Bl6/J-derived blastocysts. Male chimaeras were crossed with C57Bl6/J females to produce N1F0 offspring, which were subsequently bred on an additional generation into the C57Bl6/J background before being inter-crossed to generate [C57Bl6/J x 129Ola] N2F1 generation. The targeting strategy deletes the 3rd exon of the OSM gene. The remaining two 5' exons contain the coding regions for the first 56 amino acids of the OSM pre-protein.

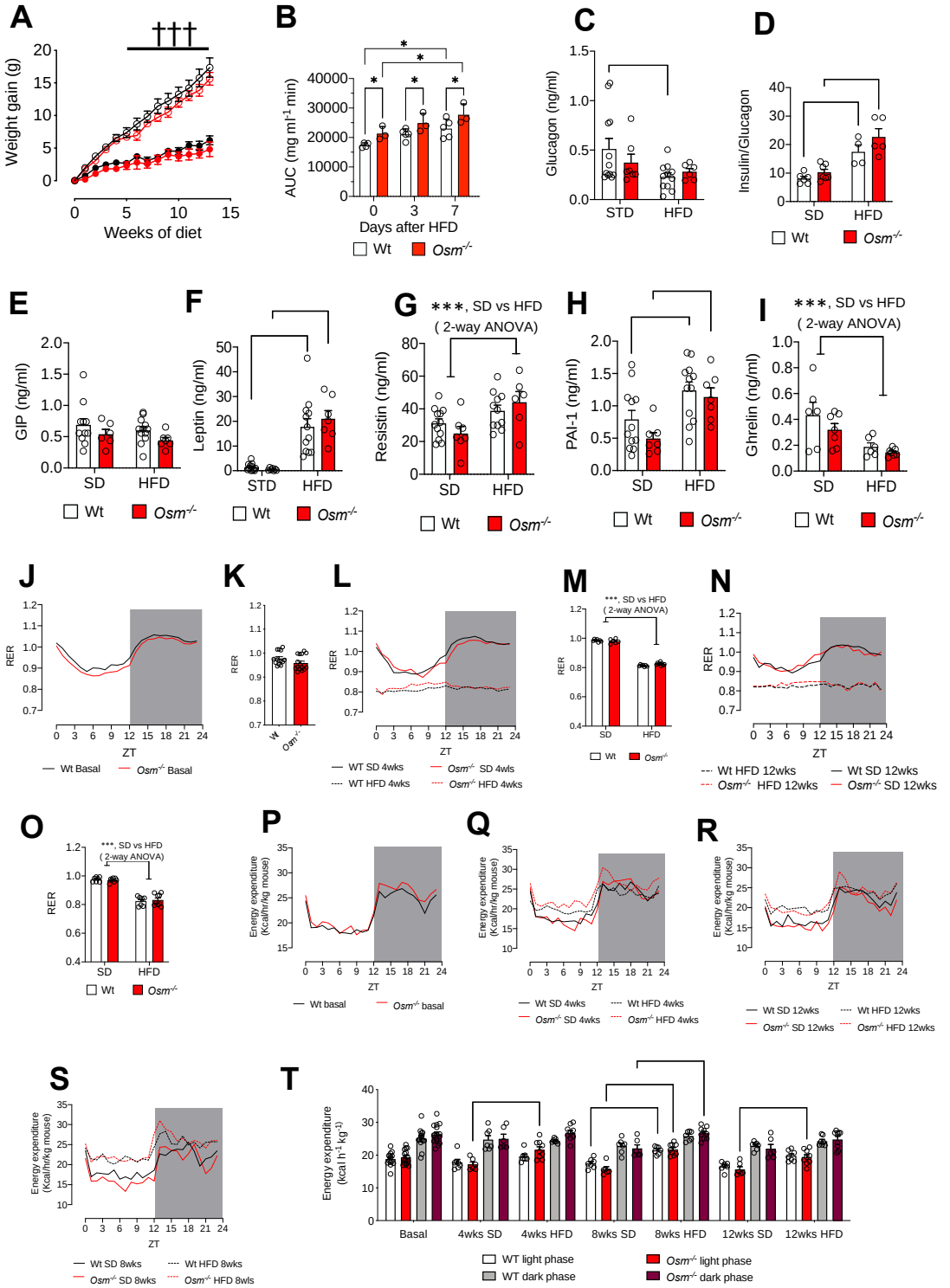
MQTRLLRTLLSLTLSLLILSMALANRGCSNSSSQLLSQLQNQANLTGNTESLLEPYIRLQNLNT
PDLRAACTQHSVAFPSEDTLRQLSKPHFLSTVYTTLDRVLYQLDALRQKFLKTPAFPKLDSAR
HNILGIRNNVFCMARLLNHSLEIPEPTQTDSGASRSTTTPDVFNTKIGSCGFLWGYHRFMGSV
GRVFREWDDGSTRSRRQSPLRARRKGTRRIRVRHKGTRRIRVRRKGTRRIWVRRKGSRKIRP
SRSTQSPTTRA

Signal peptide

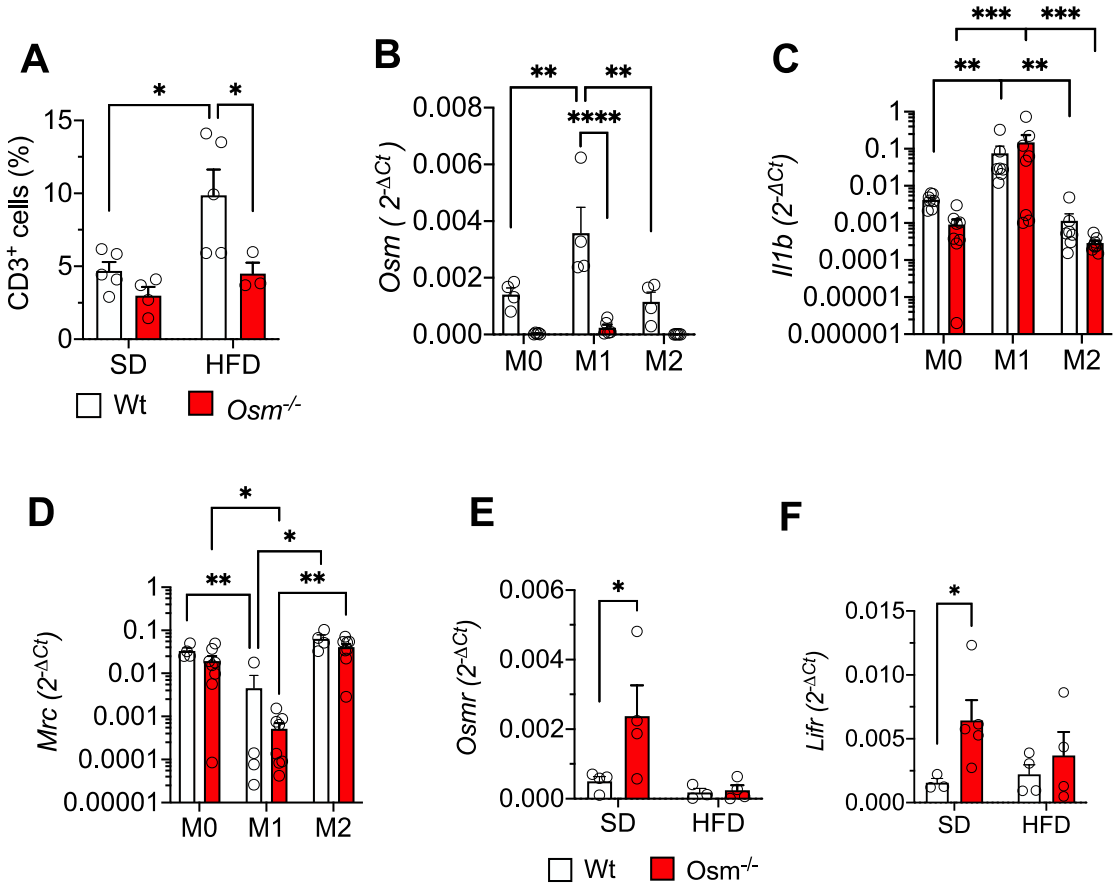
Potentially translated in OSM KO

Deleted in OSM KO

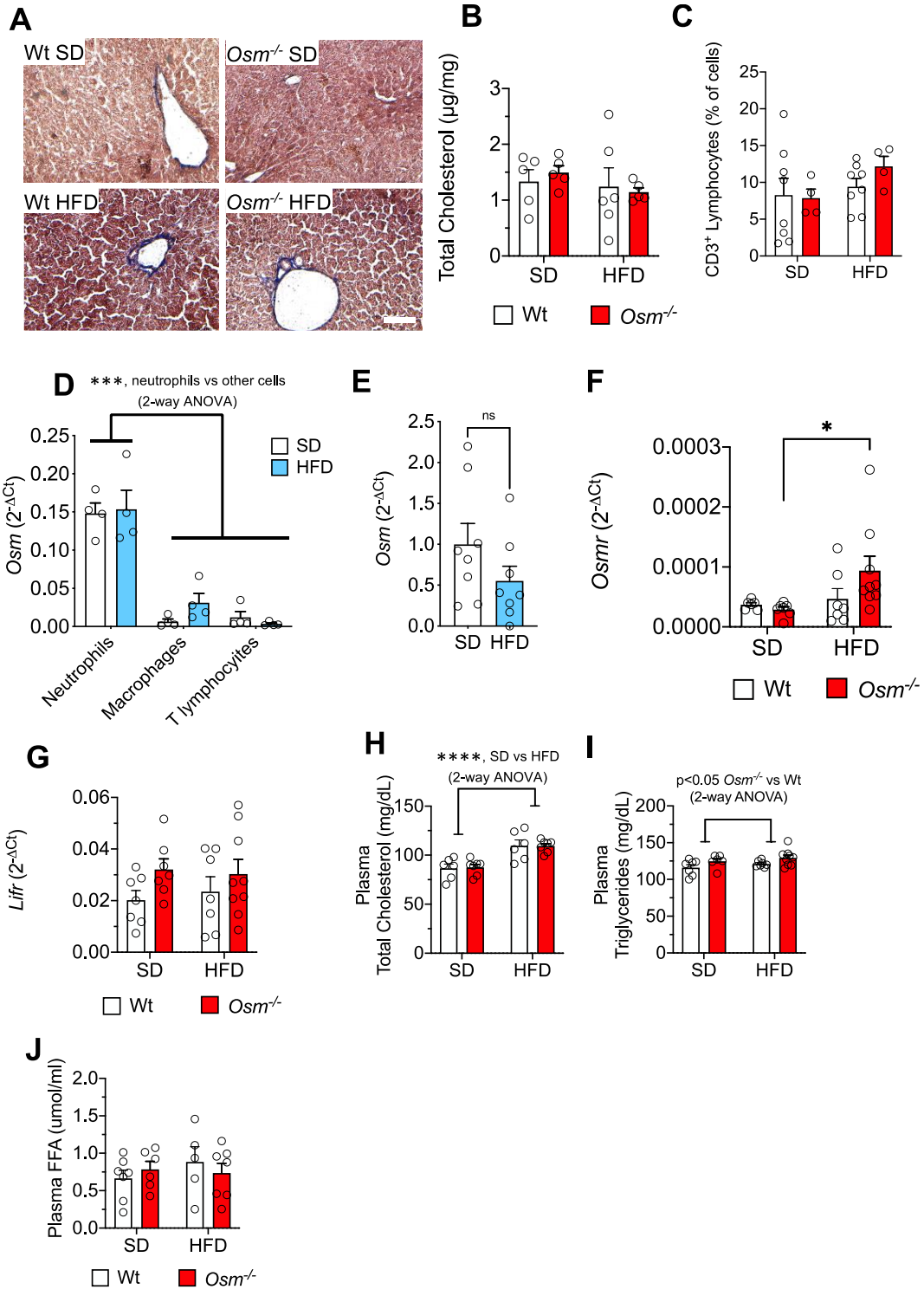
Supplementary Figure 1. (**A**) Weight gain of Wt and *Osm*$^{-/-}$ mice on SD and HFD; n≥10/group. (**B**) Glucose tolerance measured before and at day 3 and 7 of HFD (**C**) Plasma concentration of glucagon. (**D**) Insulin/Glucagon ratio. Plasma concentration of GIP (**E**), Leptin (**F**), Resistin (**G**), PAI-1 (**H**), Ghrelin (**I**). (**J**) 24 hours RER measurement of 8 weeks-old Wt and *Osm*$^{-/-}$ mice and all-day RER average (**K**); n=14/group. (**L**) 24 hours RER measurement of Wt and *Osm*$^{-/-}$ mice after 4 weeks of HFD and all-day RER average (**M**); n≥7/group. (**N**) 24 hours RER measurement of Wt and *Osm*$^{-/-}$ mice after 12 weeks of HFD and all-day RER average (**O**); n≥7/group. (**P-S**) Circadian measurement of energy expenditure at baseline and after 4 weeks, 8 weeks and 12 weeks of HFD. (**T**) Light phase and dark phase average of energy expenditure. *, p<0.05; **, p<0.01; ***, p<0.001; ****, p<0.0001. ††† p<0.001 for SD vs HFD



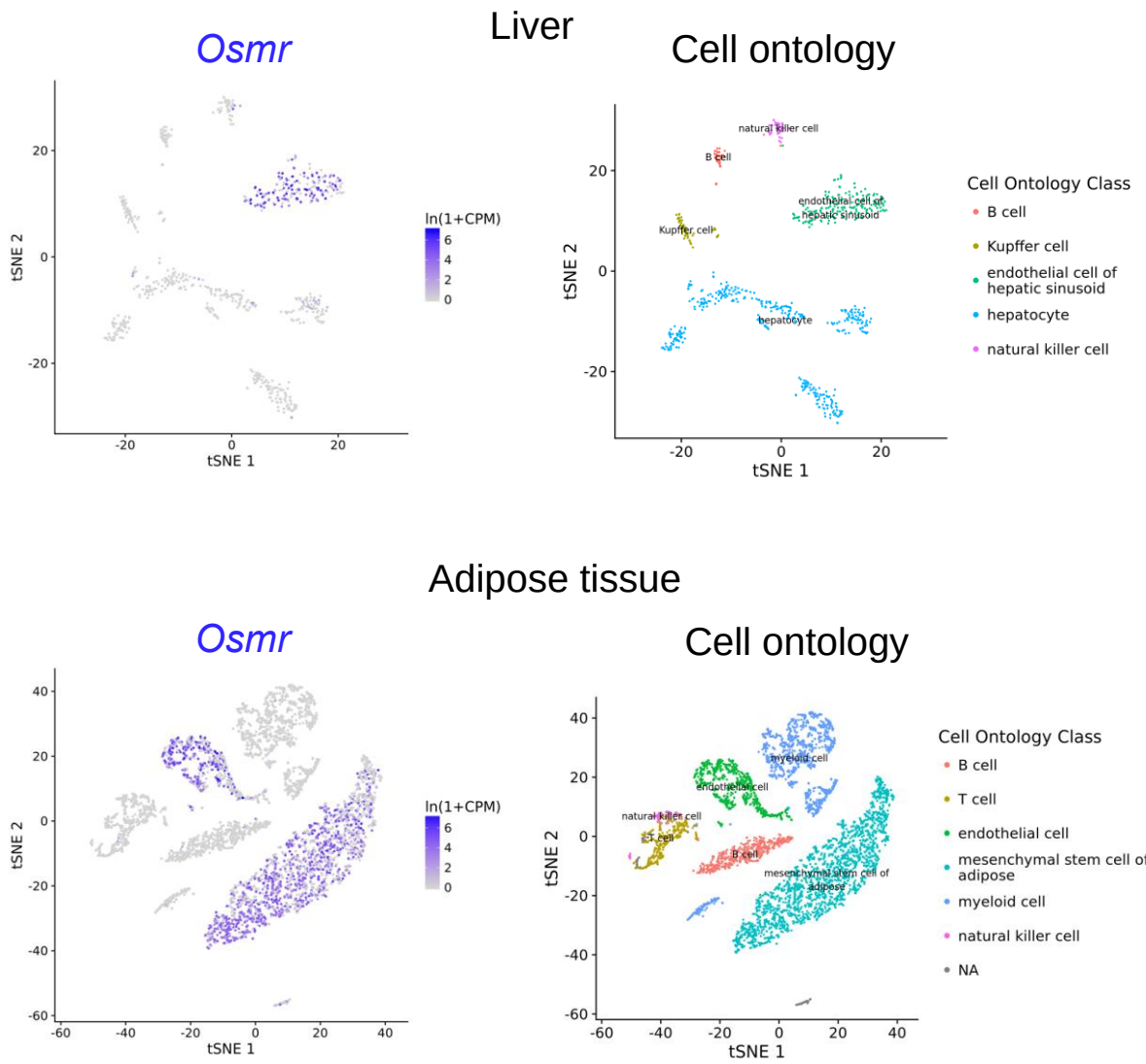
Supplementary Figure 2. (**A**) Quantification of $CD3^+$ cells with flow cytometry in the adipose tissue, n≥3/group. (**B-D**) Gene expression of bone marrow macrophages from SD Wt and *Osm*$^{-/-}$ mice polarized *in vitro*; n>3 biological replicates/group. (**E, F**) Adipose tissue *Osmr* and *Lifr* gene expression, n≥4/group. *, p<0.05; **, p<0.01; ***, p<0.001; ****, p<0.0001.



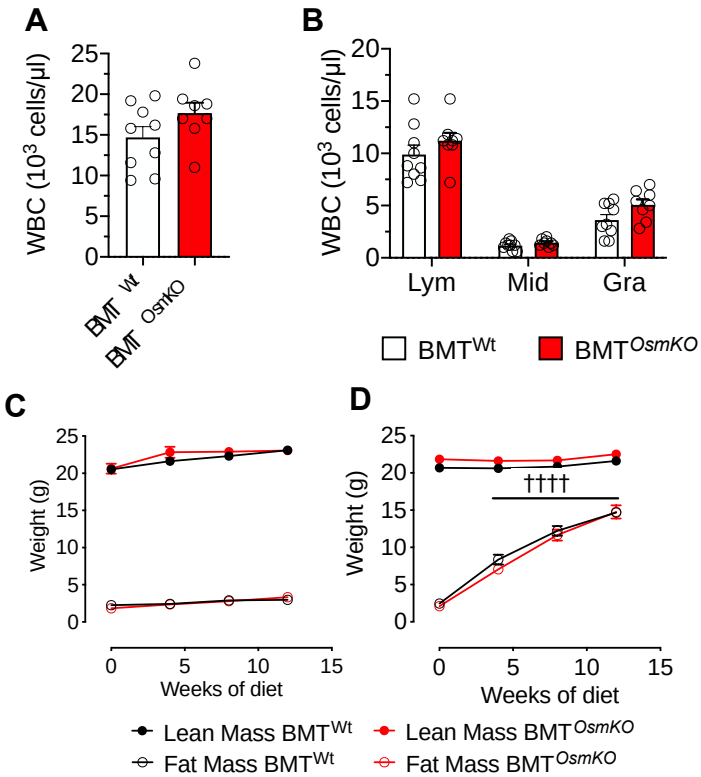
Supplementary Figure 3. (**A**) Masson trichrome staining of liver from Wt and *Osm*$^{-/-}$ mice on SD or HFD. Scale bar=120 µm. (**B**) Total cholesterol quantification in liver lysates. (C) Quantification of CD3^{+} cells with flow cytometry, n≥3/group (D) *Osm* gene expression of sorted populations after HFD, n≥3/group. (**E**) *Osm* gene expression of unfractioned liver, n>7 group. (**F, G**) *Osmr* and *Lifr* gene expression in the liver of Wt and *Osm*$^{-/-}$ mice on SD or HFD, n≥6/group. Blood chemistry of the 4 experimental groups measuring total cholesterol (**H**), triglycerides (**I**) and free fatty acids (FFA, **J**). *, p<0.05; **, p<0.01; ***, p<0.001; ****, p<0.0001.



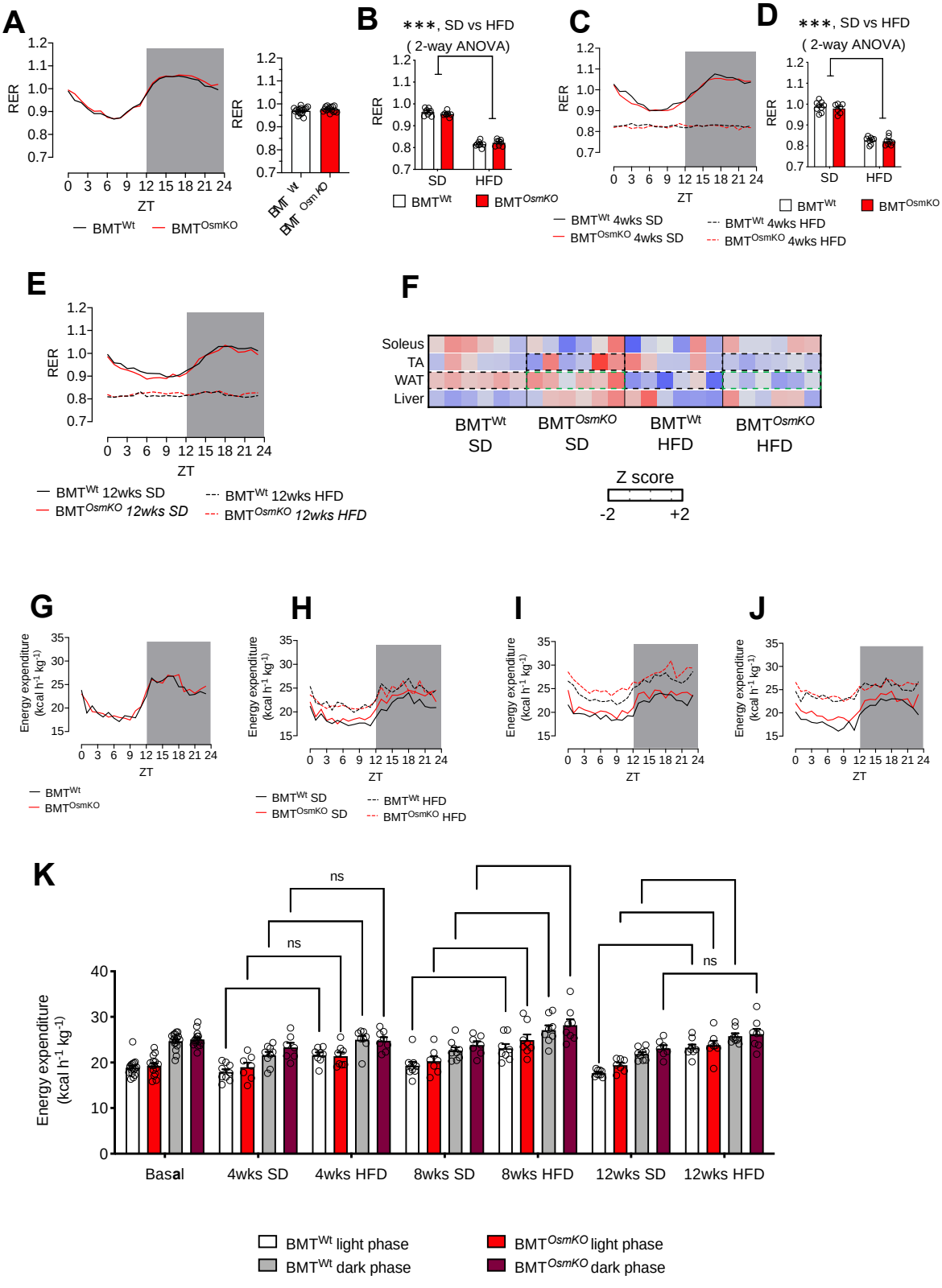
Supplementary Figure 4. Expression of *Osmrb* in the liver (top panels) and in the adipose tissue (bottom panels). tSNE plots show cell ontology (left) to identify the different populations as defined from scRNaseq from the Tabula Muris Consortium.



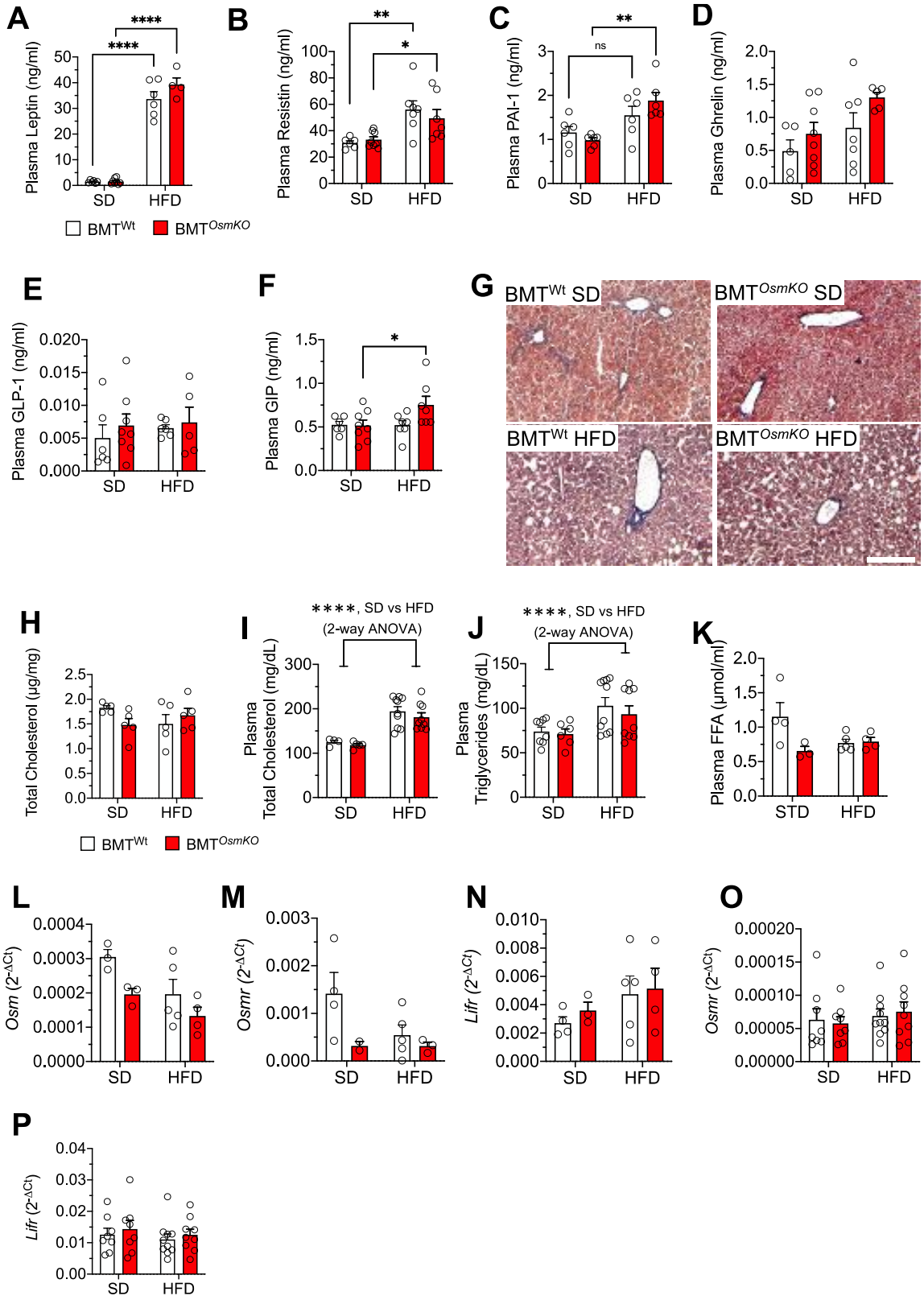
Supplementary Figure 5. (**A**) Total leukocytes count and differential count (**B**) 4 weeks after transplantation with Wt or *Osm*$^{-/-}$ bone marrow. Lym: lymphocytes; Mid: monocytes and basophils; Gra: granulocytes. Body composition of BMT^{Wt} and BMT^{OsmKO} mice on SD **(C)** and HFD **(D)**; n≥8/group. ††† p<0.001 for SD vs HFD *, p<0.05; **, p<0.01; ***, p<0.001; ****, p<0.0001.



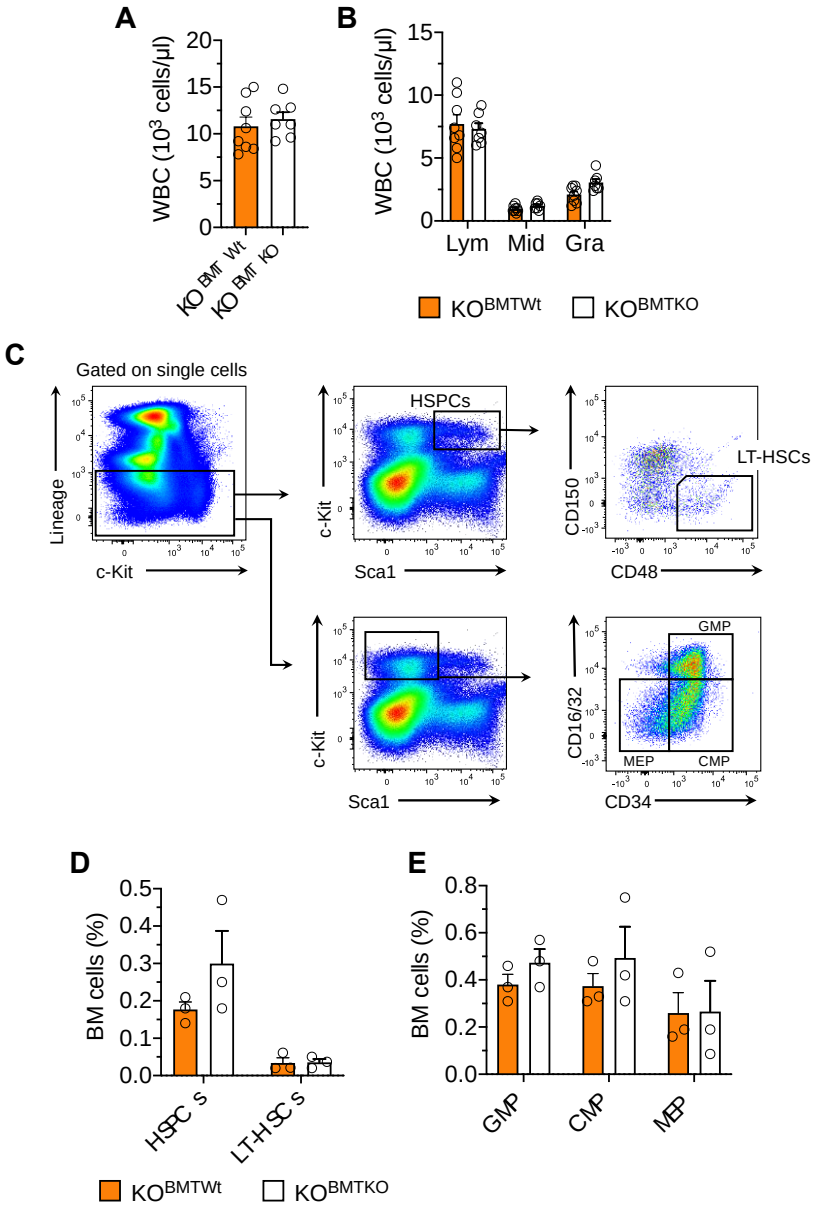
Supplementary Figure 6. (**A**) 24 hours RER measurement of baseline BMT^{Wt} and BMT^{OsmKO} mice and all-day RER average (**B**); n=8/group. (**C**) 24 hours RER measurement of BMT^{Wt} and BMT^{OsmKO} mice after 4 weeks of HFD and all-day RER average (**D**); n≥7/group. (**E**) 24 hours RER measurement of BMT^{Wt} and BMT^{OsmKO} mice after 12 weeks of HFD n≥7/group. (**F**) 2DG uptake ratio of individual SD vs HFD BMT^{Wt} and BMT^{OsmKO} mice. For each tissue, statistical significance is highlighted with color-coded dashed rectangles (p<0.05 SD vs HFD). n≥7/group. Circadian measurement of energy expenditure at baseline (**G**) and after 4 weeks (**H**), 8 weeks (**I**) and 12 weeks of HFD (**J**). (**K**) Light phase and dark phase average of energy expenditure. Unless specified, statistical significance is expressed as **** p<0.0001, *** p<0.001, ** p<0.01, * p<0.05.



Supplementary Figure 7. Plasma concentration of Leptin (**A**), Resistin (**B**), PAI-1 (**C**), Ghrelin (**D**), GLP-1 (**E**) and GIP (**F**). (**G**) Masson trichrome staining of liver from BMT^{Wt} and BMT^{OsmKO} mice on SD and HFD. (**H**) Total cholesterol quantification in liver lysates. Blood chemistry measuring plasma total cholesterol (**I**), triglycerides (**J**) and free fatty acids (FFA, **K**). (**L**) *Osm* gene expression of unfractioned liver of BMT animals, n>7 group. *Osmr* and *Lifr* gene expression in the adipose tissue (**M, N**) and in the liver (**O, P**) of BMT^{Wt} and BMT^{OsmKO} mice on SD or HFD n≥3/group. *, p<0.05; **, p<0.01; ***, p<0.001; ****, p<0.0001.



Supplementary Figure 8. (A) Total leukocytes count and differential count (**B**) 4 weeks after transplantation with Wt or *Osm*$^{-/-}$ bone marrow. (**C**) Gating strategy to assess BM reconstitution 4 weeks after transplantation with flow cytometry. (**D, E**) Quantification of hematopoietic progenitors in BMT^{Wt} and BMT^{OsmKO} mice after BM reconstitution. LT-HSCs: long term-hematopoietic stem cells; HSPCs: hematopoietic stem and multipotential progenitor cells; CMP: common myeloid progenitors; (GMP) granulocyte macrophage progenitors; MEP: megakaryocyte–erythroid progenitor. *, p<0.05; **, p<0.01; ***, p<0.001; ****, p<0.0001.



Supplementary Figure 9. (**A, B**) Whole-body quantification of fat mass and lean mass in BMT^{Wt} and BMT^{OsmKO} mice after HFD. (**C, D**) Assessment of myelopoiesis in BMT^{Wt} and BMT^{OsmKO} mice after HFD through quantification of hematopoietic progenitors in the BM.
* $p<0.05$.