



Supplementary Figure 1. Cadm2 expression in high fat diet fed tissues and food and body weight measurements after leptin injection. **A**, Western blot analysis of Cadm2 in total lysates from BAT and skeletal muscle of wild type mice on normal chow diet and littermate controls on high fat diet (HFD) feeding. **B**, Quantification of food intake and body weight in 11-week old Cadm2KO and littermate controls during leptin challenge (n=4) or PBS injected vehicle control (n=5-6). Daily food intake and body weight was measured for 5 days prior to leptin administration for base line. **C**, Quantification of food intake and body weight change in 11-week old *Lep^{ob/ob}* mice during leptin (n=4) or PBS injection (n=3). Results are presented as mean ± SEM. *P<0.05, ** P<0.01, *** P<0.001.

Supplementary Table 1. Summary of statistical analyses

Figure	Sample size (n)	Statistical Test	Values
1A	TT: n=71 TG: n=27 GG: n=2	Linear regression	t=3.24, P=0.0018
1B	TT: n=57 TG: n=23 GG: n=2	Linear regression	t=3.51, P=0.0009
1C	TT: n=74 TG: n=29 GG: n=0	Linear regression	t=2.92, P=0.0045
1D	TT: n=56 TG: n=24 GG: n=1	Linear regression	t=2.03, P=0.0467
2G	Wild-type (n=19) Cadm2KO (n=9)	Two-way repeated-measure ANOVA Post-hoc multiple comparisons test (Sidak's)	Interaction: F=2.707, P=0.0468 Time: F=1027, P<0.0001 Genotype: F=37.44, P<0.10001 Multiple comparison: *P<0.05
2H	Wild-type (n=4) Cadm2KO (n=4)	Two-way repeated-measure ANOVA Post-hoc multiple comparisons test (Sidak's)	<u>Food intake:</u> Interaction: F=2.22, P=0.0634 Time: F=24.94, P<0.0001 Genotype: F=2.624, P=0.1564 Multiple comparison: *P<0.05 <u>Body weight:</u> Interaction: F=3.343, P=0.0101 Time: F=42.26, P<0.0001 Genotype: F=5.769, P=0.0532 Multiple comparison: *P<0.05
3B	Wild-type (n=19) Lep ^{ob/ob} (n=13) Cadm2/ob (n=8)	Two-way repeated-measure ANOVA Post-hoc multiple comparisons test (Sidak's)	<u>Lep^{ob/ob} vs Cadm2/ob:</u> Interaction: F=2.195, P=0.0484 Time: F=1983, P<0.0001 Genotype: F=37.32, P=0.0025 Multiple comparison: 4 weeks, P<0.01; 6 weeks, P<0.001; 8 weeks, P<0.001; 12 weeks, P<0.001; 14 weeks, P<0.001; 16 weeks, P<0.001 <u>Cadm2/ob vs Wild-type:</u> Interaction: F=65.95, P<0.0001 Time: F=445.2, P<0.0001 Genotype: F=1072, P<0.0001 Multiple comparison: 4 weeks, P>0.05; 6 weeks, P<0.001; 8 weeks, P<0.001; 12 weeks, P<0.001; 14 weeks, P<0.001; 16 weeks, P<0.001 <u>Lep^{ob/ob} & Wild-type:</u> Interaction: F=104.9, P<0.0001 Time: F=624, P<0.0001 Genotype: F=2657, P<0.0001 Multiple comparison: 4 weeks, P<0.05; 6 weeks, P<0.001; 8 weeks, P<0.001; 12 weeks, P<0.001; 14 weeks, P<0.001; 16 weeks, P<0.001
3C	Wild-type (n=7) Lep ^{ob/ob} (n=3) Cadm2/ob (n=4)	Two-tailed unpaired Student's t-test	<u>random:</u> Lep ^{ob/ob} vs Cadm2/ob: t=4.289, P=0.0078 Cadm2/ob vs Wild-type: t=3.467, P=0.0071 Lep ^{ob/ob} vs Wild-type: t=7.161, P<0.0001
3C	Wild-type (n=6) Lep ^{ob/ob} (n=6) Cadm2/ob (n=7)	Two-tailed unpaired Student's t-test	<u>fasting:</u> Lep ^{ob/ob} vs Cadm2/ob: t=2.232, P=0.0473 Cadm2/ob vs Wild-type: t=3.578, P=0.0043 Lep ^{ob/ob} vs Wild-type: t=6.723, P<0.0001
3D	Wild-type (n=6) Lep ^{ob/ob} (n=3) Cadm2/ob (n=3)	Two-tailed unpaired Student's t-test	<u>random:</u> Lep ^{ob/ob} vs Cadm2/ob: t=2.448, P=0.0401 Cadm2/ob vs Wild-type: t=2.462, P=0.0490 Lep ^{ob/ob} vs Wild-type: t=5.114, P=0.0009
3D	Wild-type (n=4) Lep ^{ob/ob} (n=6)	Two-tailed unpaired Student's t-test	<u>fasting:</u> Lep ^{ob/ob} vs Cadm2/ob: t=5.059,

	Cadm2/ob (n=4)		P=0.0072 Cadm2/ob vs Wild-tyt: t=12.87, P<0.0001 Lep ^{ob/ob} vs Wild-type: t=18.81, P<0.0001
3E	Wild-type (n=6) Lep ^{ob/ob} (n=4) Cadm2/ob (n=4)	Two-way repeated-measure ANOVA Post-hoc multiple comparisons test (Sidak's)	Lep ^{ob/ob} vs Cadm2/ob: Interaction: F=6.795, P=0.0008 Time: F=51.96, P<0.0001 Genotype: F=88.04, P<0.0001 Multiple comparison: 0 min, P>0.05; 15 min, P<0.001; 30 min, P<0.001; 60 min, P<0.001; 120 min, P>0.05 <u>Cadm2/ob vs Wild-type:</u> Interaction: F=49.59, P<0.0001 Time: F=93.59, P<0.0001 Genotype: F=89.98, P<0.0001 Multiple comparison: 0 min, P>0.05; 15 min, P<0.001; 30 min, P<0.001; 60 min, P<0.001; 120 min, P<0.001 <u>Lep^{ob/ob} & Wild-type:</u> Interaction: F=40.72, P<0.0001 Time: F=42.08, P<0.0001 Genotype: F=945.8, P<0.0001 Multiple comparison: 0 min, P>0.05; 15 min, P<0.001; 30 min, P<0.001; 60 min, P<0.001; 120 min, P<0.001
3F	Wild-type (n=6) Lep ^{ob/ob} (n=4) Cadm2/ob (n=4)	Two-way repeated-measure ANOVA Post-hoc multiple comparisons test (Sidak's)	Lep ^{ob/ob} vs Cadm2/ob: Interaction: F=4.295, P=0.0092 Time: F=103.1, P<0.0001 Genotype: F=9.811, P=0.0203 Multiple comparison: 0 min, P>0.05; 15 min, P>0.05; 30 min, P<0.001; 60 min, P>0.05; 120 min, P>0.05 <u>Cadm2/ob vs Wild-type:</u> Interaction: F=11.23, P<0.0001 Time: F=57.12, P<0.0001 Genotype: F=13.90, P=0.0058 Multiple comparison: 0 min, P>0.05; 15 min, P<0.001; 30 min, P<0.001; 60 min, P>0.05; 120 min, P>0.05 <u>Lep^{ob/ob} & Wild-type:</u> Interaction: F=51.11, P<0.0001 Time: F=140.6, P<0.0001 Genotype: F=42.02, P=0.0002 Multiple comparison: 0 min, P>0.05; 15 min, P<0.001; 30 min, P<0.001; 60 min, P<0.001; 120 min, P>0.05
3G	Wild-type (n=6) Lep ^{ob/ob} (n=4) Cadm2/ob (n=4)	Two-way repeated-measure ANOVA Post-hoc multiple comparisons test (Sidak's)	Lep ^{ob/ob} vs Cadm2/ob: Interaction: F=0.5025, P=0.7342 Time: F=32.44, P<0.0001 Genotype: F=4.328, P=0.0827 Multiple comparison: 0 min, P>0.05; 15 min, P>0.05; 30 min, P>0.05; 60 min, P>0.05; 120 min, P>0.05 <u>Cadm2/ob vs Wild-type:</u> Interaction: F=3.155, P=0.0270 Time: F=32.38, P<0.0001 Genotype: F=32.58, P=0.0005 Multiple comparison: 0 min, P>0.05; 15 min, P<0.001; 30 min, P<0.01; 60 min, P>0.05; 120 min, P<0.05 <u>Lep^{ob/ob} & Wild-type:</u> Interaction: F=6.764, P=0.0005 Time: F=42.83, P<0.0001 Genotype: F=46.20, P=0.0001 Multiple comparison: 0 min, P>0.05; 15 min, P<0.001; 30 min, P<0.001; 60 min, P<0.001; 120 min, P<0.01
3H	Lep ^{ob/ob} (n=8) Cadm2/ob (n=6)	Two-tailed unpaired Student's t-test	day: t=2.051, P=0.0628 night: t=2.432, P=0.0316
3I	Lep ^{ob/ob} (n=8) Cadm2/ob (n=6)	Two-tailed unpaired Student's t-test	day: t=2.296, P=0.0390 night: t=2.596, P=0.0222
3J	Lep ^{ob/ob} (n=8) Cadm2/ob (n=6)	Two-tailed unpaired Student's t-test	day: t=0.9194, P=0.3760 night: t=0.6186, P=0.5477
3K	Lep ^{ob/ob} (n=8) Cadm2/ob (n=6)	Two-tailed unpaired Student's t-test	day: t=1.437, P=0.1764 night: t=4.406, P=0.0009
3L	Lep ^{ob/ob} (n=9)	Two-tailed unpaired Student's t-test	Mass/BW (%):

	Cadm2/ob (n=6)		fat: t=1.818, P=0.0921 LBM: t=1.919, P=0.0772 Mass: BW: t=4.271, P=0.0009 fat: t=3.323, P=0.0055 LBM: t=0.1594, P=0.8758
3M	Lep ^{ob/ob} (n=8) Cad2m2/ob (n=6)	Linear regression	F=7.1391, P=0.02172
3N	Lep ^{ob/ob} (n=8) Cad2m2/ob (n=6)	Linear regression	F=0.387647, P=0.5462
3O	Lep ^{ob/ob} (n=8) Cad2m2/ob (n=6)	Two-tailed unpaired Student's t-test	t=1.778, P=0.1057
3Q	Wild-type (n=9) Cad2m2KO (n=6)	Two-way repeated-measure ANOVA Post-hoc multiple comparisons test (Sidak's)	Interaction: F=4.419, P=0.0091 Time: F=975.5, P<0.0001 Genotype: F=15.23, P=0.0018 Multiple comparison: **P<0.01
3R	Wild-type (n=9) Cad2m2KO (n=6)	Two-way repeated-measure ANOVA Post-hoc multiple comparisons test (Sidak's)	Interaction: F=3.242, P=0.0190 Time: F=36.31, P<0.0001 Genotype: F=2.571, P=0.1329 Multiple comparison: *P<0.05
3S	Wild-type (n=9) Cad2m2KO (n=6)	Two-way repeated-measure ANOVA Post-hoc multiple comparisons test (Sidak's)	Interaction: F=3.043, P=0.0250 Time: F=72.41, P<0.0001 Genotype: F=6.717, P=0.0224 Multiple comparison: *P<0.05, **P<0.01
4A	Wild-type (n=16) Lep ^{ob/ob} (n=5) Cad2m2/ob (n=4)	Two-tailed unpaired Student's t-test	Lep ^{ob/ob} vs Cad2m2/ob: t=3.561, P=0.0092 Cad2m2/ob vs Wild-type: t=4.815, P<0.0001 Lep ^{ob/ob} vs Wild-type: t=8.130, P<0.0001
4B	Wild-type (n=4) Lep ^{ob/ob} (n=5) Cad2m2/ob (n=3)	Two-tailed unpaired Student's t-test	<u>ingWAT mass:</u> Lep ^{ob/ob} vs Cad2m2/ob: t=3.308, P=0.0162 Cad2m2/ob vs Wild-type: t=18.15, P<0.0001 Lep ^{ob/ob} vs Wild-type: t=18.03, P<0.0001 <u>Liver mass:</u> Lep ^{ob/ob} vs Cad2m2/ob: t=2.554, P=0.0433 Cad2m2/ob vs Wild-ty: t=14.78, P=0.0043 Lep ^{ob/ob} vs Wild-type: t=11.43, P<0.0001
4D	Wild-type (n=5) Lep ^{ob/ob} (n=6) Cad2m2/ob (n=5)	Two-tailed unpaired Student's t-test	<u>Ucp1:</u> Lep ^{ob/ob} vs Cad2m2/ob: t=2.417, P=0.0388 Cad2m2/ob vs Wild-ty: t=2.461, P=0.0392 Lep ^{ob/ob} vs Wild-type: t=6.834, P<0.0001 <u>Acadl:</u> Lep ^{ob/ob} vs Cad2m2/ob: t=2.687, P=0.0249 Cad2m2/ob vs Wild-ty: t=2.654, P=0.0291 Lep ^{ob/ob} vs Wild-type: t=7.048, P<0.0001 <u>Prdm16:</u> Lep ^{ob/ob} vs Cad2m2/ob: t=2.379, P=0.0446 Cad2m2/ob vs Wild-ty: t=3.580, P=0.0090 Lep ^{ob/ob} vs Wild-type: t=5.403, P=0.0004 <u>Pgc1α:</u> Lep ^{ob/ob} vs Cad2m2/ob: t=2.581, P=0.0417 Cad2m2/ob vs Wild-ty: t=3.965, P=0.0054 Lep ^{ob/ob} vs Wild-type: t=5.251, P=0.0012 <u>Cidea:</u> Lep ^{ob/ob} vs Cad2m2/ob: t=3.399, P=0.0094 Cad2m2/ob vs Wild-ty: t=2.927,

			<p>P=0.0221 Lep^{ob/ob} vs Wild-type: t=7.894, P<0.0001</p> <p><u>Acadm:</u> Lep^{ob/ob} vs Cadm2/ob: t=3.384, P=0.0096 Cadm2/ob vs Wild-ty: t=2.450, P=0.0441 Lep^{ob/ob} vs Wild-type: t=5.958, P=0.0002</p> <p><u>Cox8b:</u> Lep^{ob/ob} vs Cadm2/ob: t=3.105, P=0.0126 Cadm2/ob vs Wild-ty: t=2.541, P=0.0347 Lep^{ob/ob} vs Wild-type: t=8.083, P<0.0001</p> <p><u>Cox6a1:</u> Lep^{ob/ob} vs Cadm2/ob: t=3.663, P=0.0064 Cadm2/ob vs Wild-ty: t=2.395, P=0.0478 Lep^{ob/ob} vs Wild-type: t=7.489, P<0.0001</p> <p><u>Cox17:</u> Lep^{ob/ob} vs Cadm2/ob: t=2.474, P=0.0426 Cadm2/ob vs Wild-ty: t=2.657, P=0.0326 Lep^{ob/ob} vs Wild-type: t=8.412, P<0.0001</p>
4E	Wild-type (n=5) Lep ^{ob/ob} (n=3-6) Cadm2/ob (n=5)	Two-tailed unpaired Student's t-test	<p><u>Ucp1:</u> Lep^{ob/ob} vs Cadm2/ob: t=4.474, P=0.0015 Cadm2/ob vs Wild-ty: t=3.949, P=0.0055 Lep^{ob/ob} vs Wild-type: t=8.287, P<0.0001</p> <p><u>Acadl:</u> Lep^{ob/ob} vs Cadm2/ob: t=0.1030, P=0.9213 Cadm2/ob vs Wild-ty: t=4.495, P=0.0028 Lep^{ob/ob} vs Wild-type: t=4.484, P<0.0029</p> <p><u>Prdm16:</u> Lep^{ob/ob} vs Cadm2/ob: t=1.771, P=0.1270 Cadm2/ob vs Wild-ty: t=2.482, P=0.0421 Lep^{ob/ob} vs Wild-type: t=4.211, P=0.0040</p> <p><u>Pgc1α:</u> Lep^{ob/ob} vs Cadm2/ob: t=0.3523, P=0.7337 Cadm2/ob vs Wild-ty: t=6.993, P<0.0001 Lep^{ob/ob} vs Wild-type: t=12.65, P<0.0001</p> <p><u>Cidea:</u> Lep^{ob/ob} vs Cadm2/ob: t=0.7771, P=0.4625 Cadm2/ob vs Wild-ty: t=4.860, P=0.0013 Lep^{ob/ob} vs Wild-type: t=4.009, P=0.0051</p> <p><u>Acadm:</u> Lep^{ob/ob} vs Cadm2/ob: t=0.2704, P=0.7946 Cadm2/ob vs Wild-ty: t=5.140, P=0.0013 Lep^{ob/ob} vs Wild-type: t=6.126, P=0.0003</p> <p><u>Cox8b:</u> Lep^{ob/ob} vs Cadm2/ob: t=1.587, P=0.1513 Cadm2/ob vs Wild-ty: t=3.176,</p>

			<p>P=0.0131 Lep^{ob/ob} vs Wild-type: t=4.800, P=0.0014 <u>Cox6a1:</u> Lep^{ob/ob} vs Cadm2/ob: t=0.7166, P=0.4918 Cadm2/ob vs Wild-ty: t=3.690, P=0.0078 Lep^{ob/ob} vs Wild-type: t=3.852, P=0.0049 <u>Cox17:</u> Lep^{ob/ob} vs Cadm2/ob: t=0.2850, P=0.7828 Cadm2/ob vs Wild-ty: t=14.86, P<0.0001 Lep^{ob/ob} vs Wild-type: t=15.00, P<0.0001 <u>Tmem26:</u> Lep^{ob/ob} vs Cadm2/ob: t=0.9594, P=0.3693 Cadm2/ob vs Wild-ty: t=4.783, P=0.0014 Lep^{ob/ob} vs Wild-type: t=6.185, P=0.0005 <u>Cd137:</u> Lep^{ob/ob} vs Cadm2/ob: t=1.976, P=0.0836 Cadm2/ob vs Wild-ty: t=2.414, P=0.0423 Lep^{ob/ob} vs Wild-type: t=3.623, P=0.0068</p>
4F	Wild-type (n=5) Lep ^{ob/ob} (n=4) Cadm2/ob (n=4)	Two-tailed unpaired Student's t-test	<u>G6pc:</u> Lep ^{ob/ob} vs Cadm2/ob: t=4.307, P=0.0006 Cadm2/ob vs Wild-ty: t=2.483, P=0.0288 Lep ^{ob/ob} vs Wild-type: t=6.453, P<0.0001 <u>Pck:</u> Lep ^{ob/ob} vs Cadm2/ob: t=5.083, P=0.0003 Cadm2/ob vs Wild-ty: t=2.791, P=0.0210 Lep ^{ob/ob} vs Wild-type: t=7.292, P<0.0001 <u>Gck:</u> Lep ^{ob/ob} vs Cadm2/ob: t=3.225, P=0.0180 Cadm2/ob vs Wild-ty: t=4.817, P=0.0019 Lep ^{ob/ob} vs Wild-type: t=6.555, P=0.0003 <u>Slc2a2:</u> Lep ^{ob/ob} vs Cadm2/ob: t=4.176, P=0.0058 Cadm2/ob vs Wild-ty: t=5.460, P=0.0016 Lep ^{ob/ob} vs Wild-type: t=6.433, P=0.0007 <u>Fas:</u> Lep ^{ob/ob} vs Cadm2/ob: t=6.770, P=0.0005 Cadm2/ob vs Wild-ty: t=6.417, P=0.0004 Lep ^{ob/ob} vs Wild-type: t=10.27, P<0.0001 <u>Acc1:</u> Lep ^{ob/ob} vs Cadm2/ob: t=4.624, P=0.0036 Cadm2/ob vs Wild-ty: t=3.595, P=0.0088 Lep ^{ob/ob} vs Wild-type: t=8.598, P<0.0001 <u>Scd1:</u> Lep ^{ob/ob} vs Cadm2/ob: t=4.226, P=0.0055 Cadm2/ob vs Wild-ty: t=4.856,

			<p>P=0.0018 Lep^{ob/ob} vs Wild-type: t=14.78, P<0.0001 <u>Fgf21:</u> Lep^{ob/ob} vs Cadm2/ob: t=11.07, P<0.0001 Cadm2/ob vs Wild-typ: t=9.178, P<0.0001 Lep^{ob/ob} vs Wild-type: t=35.01, P<0.0001 <u>Hmgcs2:</u> Lep^{ob/ob} vs Cadm2/ob: t=4.451, P=0.0043 Cadm2/ob vs Wild-typ: t=4.457, P=0.0029 Lep^{ob/ob} vs Wild-type: t=7.427, P<0.0001</p>
Suppl. 1B	Wild-type (n=4) Cadm2KO (n=4)	Two-way repeated-measure ANOVA Post-hoc multiple comparisons test (Sidak's)	<p><u>Food intake (Leptin):</u> Interaction: F=1.853, P=0.1023 Time: F=23.23, P<0.0001 Genotype: F=0.0763, P=0.7916 <u>Body weight (Leptin):</u> Interaction: F=3.343, P=0.0101 Time: F=42.26, P<0.0001 Genotype: F=0.3072, P=0.5994 Multiple comparison: *P<0.05, **P<0.01</p>
Suppl. 1B	Wild-type (n=5) Cadm2KO (n=6)	Two-way repeated-measure ANOVA Post-hoc multiple comparisons test (Sidak's)	<p><u>Food intake (PBS):</u> Interaction: F=0.9279, P=0.4825 Time: F=6.305, P<0.0001 Genotype: F=0.001062, P=0.9747 <u>Body weight (PBS):</u> Interaction: F=1.28, P=0.2822 Time: F=3.761, P=0.0034 Genotype: F=1.661, P=0.2295</p>
Suppl. 1C	Lep ^{ob/ob} + PBS (n=4), Lep ^{ob/ob} + leptin (n=3)	Two-way repeated-measure ANOVA Post-hoc multiple comparisons test (Sidak's)	<p><u>Food intake:</u> Interaction: F=7.157, P=0.0006 Time: F=5.13, P<0.0001 Genotype: F=25.5, P=0.0072 Multiple comparison: *P<0.05, **P<0.01 <u>Body weight:</u> Interaction: F=24.41, P <0.0001 Time: F=10.58, P<0.0001 Genotype: F=27.08, P=0.0065 Multiple comparison: *P<0.05, **P<0.01</p>