

Supplementary Materials

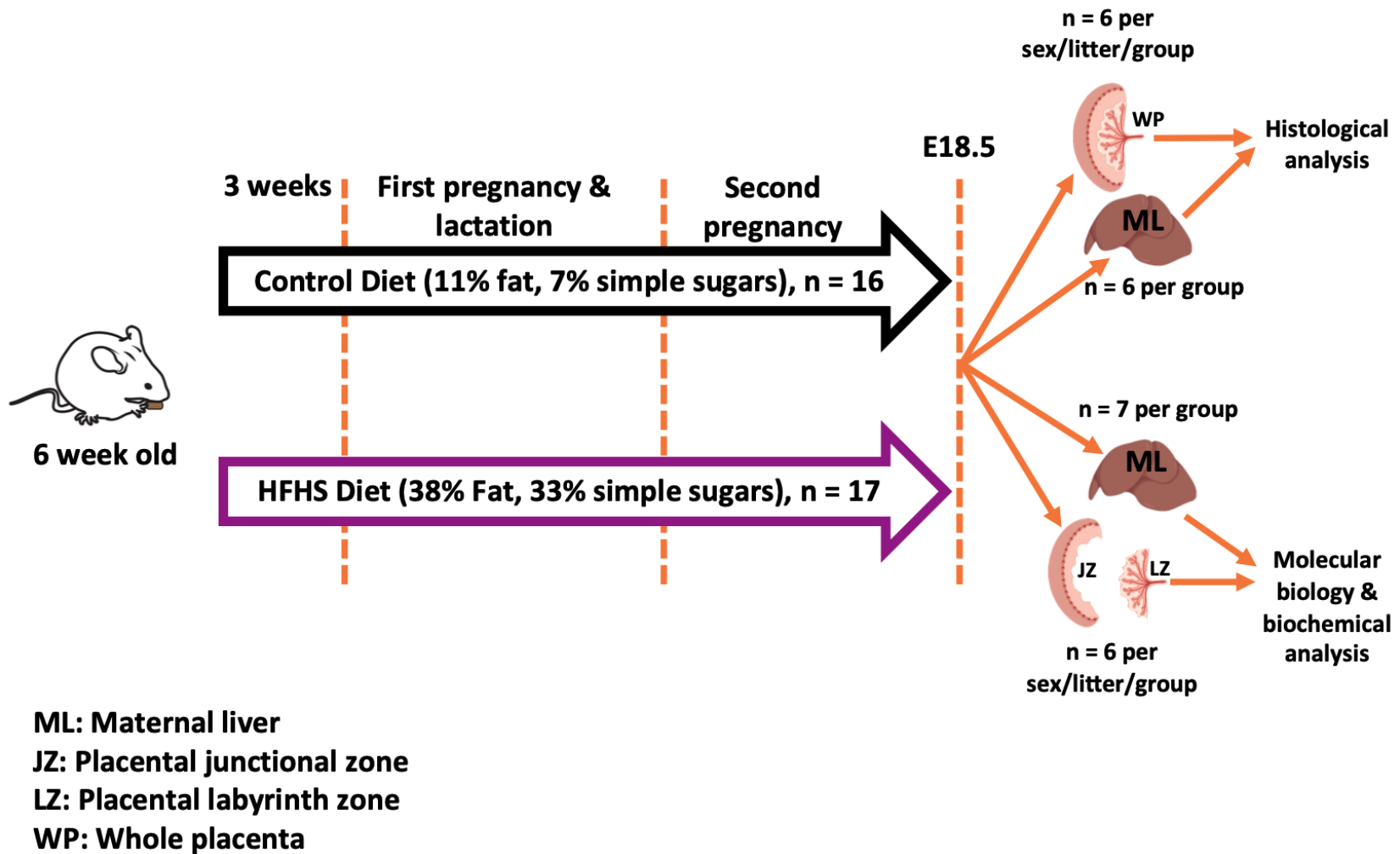


Figure S1. Study design.

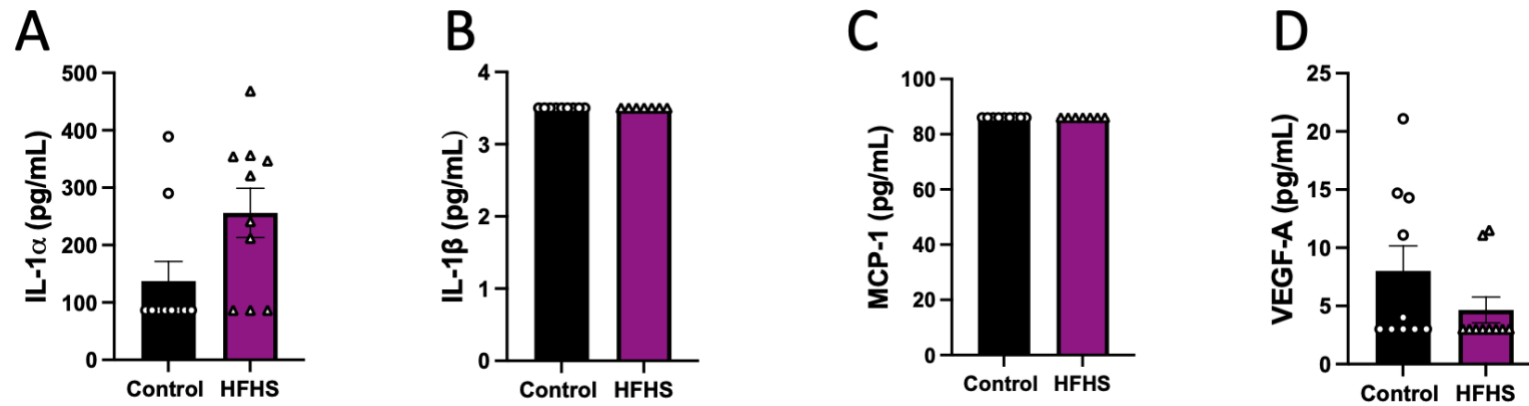


Figure S2. Maternal cytokines below detectable levels of the assay.

Plasma maternal levels of IL-1 α (A), IL-1 β (B), MCP-1 (C), and VEGF-A (D). Groups are controlled (Control, black bars, circles n=10) and high-fat high-sugar diet (HFHS, magenta bars, triangles, n=10). Statistical analysis was not performed due to the under-detection of most of the cytokines.

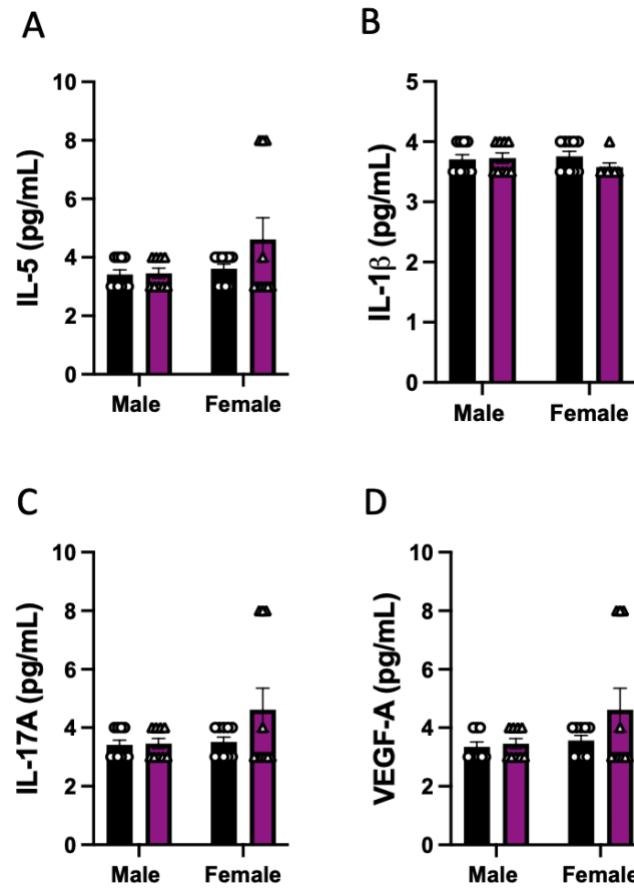


Figure S3. Fetal cytokines below detectable levels of the assay.

Plasma fetal levels of IL-5 (A), IL- β (B), IL-17A (C) and VEGF-A (D). Groups are controlled (Control, black bars, circles n=10) and high-fat high-sugar diet (HFHS, magenta bars, triangles, n=10). Statistical analysis was not performed due to the under-detection of most of the cytokines.

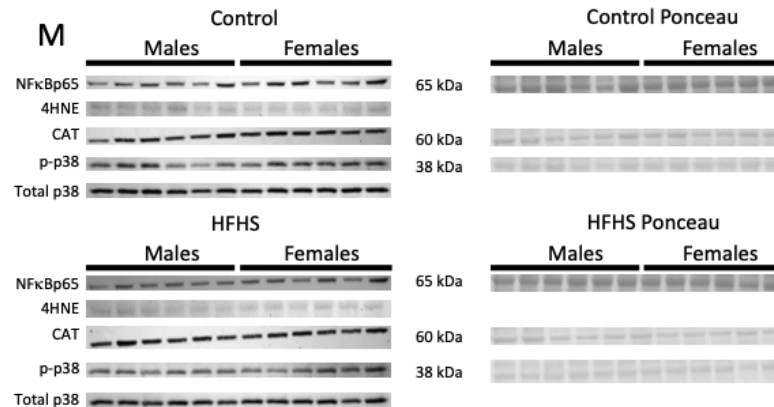
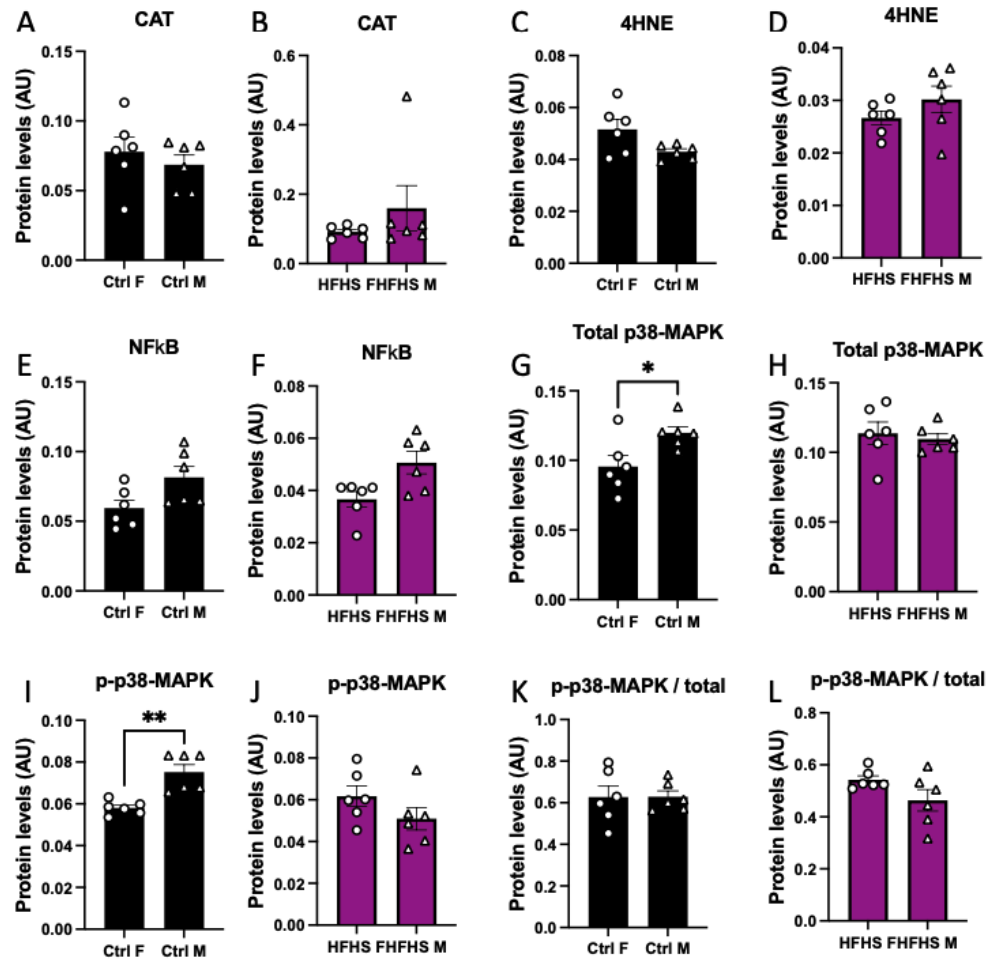


Figure S4. Placental labyrinth zone protein levels – Comparison by sex.

Protein levels of catalase (CAT, A-B), 4-Hydroxynonenal (4-HNE, C-D), total levels of p65-NF κ B (E-F), total p38 (G-H), phosphorylated p38 (I-J), phosphorylated to total p38 (K-L) and representative image of western blots (M) from placental labyrinth zone of control (Ctrl F, Ctrl M,) and HFHS (HFHS M, HFHS M) are shown. Groups are control (Control, black bars, circles, n=6) and high-fat high-sugar diet (HFHS, magenta bars, triangles, n=6). Each dot represents one individual. Mean \pm SEM is shown. Rout test was applied to identify outliers and Shapiro-Wilk to determine the normality of data. Data was submitted to the t-Student test or Mann-Whitney according to data distribution. *p \leq 0.05 vs. female; **p \leq 0.005 vs. female.

Table S1. Gene Identification

Gene ID	Gene Symbol				
ENSMUSG00000026051	1500015O10Rik	ENSMUSG00000040828	Catsperd	ENSMUSG00000093507	Gm20627
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ENSMUSG00000024245	Tmem178	ENSMUSG00000031362	Xlr4c		

Table S2. Biological process of interest for genes upregulated by a maternal HFHS diet (overall, female-specific and male-specific comparisons). Biological processes determined by the DAVID analysis tool and the comparison when altered are shown for upregulated genes related to immune response, lipid or fatty acid metabolic process, response to hypoxia & ROS, iron transport, nutrients transport, and angiogenesis. Data are n = 12 per dietary group for overall and n = 6 per group for sex-specific comparisons.

	Biological process related to:						Altered when comparing Ctrl vs HFHS:		
Upregulated DEGs	Immune response	Lipid or fatty acid metabolic process	Response to hypoxia & ROS	Ion transport	Nutrients transport	Angiogenesis	Overall	Females	Males
Chil3	x						Yes	Yes	Yes
Pla2g4a	x	x					Yes	Yes	Yes
Slc9b2				x			Yes	Yes	Yes
Bdh2		x					Yes	Yes	No
Slc26a7				x			Yes	Yes	No
Slc6a14				x			Yes	Yes	No
Cd28	x						Yes	No	No
Rasgrp1	x						Yes	No	Yes
Tgtp1	x						Yes	No	No
Hamp	x			x			Yes	No	Yes
Il1a	x						Yes	No	Yes
Snhg1	x						Yes	No	Yes
Apold1		x	x		x	x	Yes	No	Yes
Cyb5r2		x					Yes	No	Yes

Gdpd3		x					Yes	No	No
Hpgds		x					Yes	No	Yes
Acsbg1		x					Yes	No	Yes
Acsm3		x					Yes	No	No
Nox4			x				Yes	No	No
Gucy1a2			x				Yes	No	No
Ptprn			x				Yes	No	No
Rgs4				x			Yes	No	Yes
Slc10a6				x			Yes	No	No
Fgf9						x	Yes	No	No
Slc30a4				x			No	Yes	No
Slc9b1				x			No	Yes	No
Oas1b	x						No	No	Yes
Clec2d	x						No	No	Yes
Gdap10	x						No	No	Yes
Il18bp	x						No	No	Yes
Lgals4	x						No	No	Yes
Pisd-ps1	x						No	No	Yes
Snhg20	x						No	No	Yes
Alms1		x					No	No	Yes
Echdc2		x					No	No	Yes
Phka2		x					No	No	Yes
Gabre				x			No	No	Yes
Gabrr2				x			No	No	Yes
Atg9b					x		No	No	Yes
Spx					x		No	No	Yes

Table S3. Biological process of interest for genes downregulated by a maternal HFHS diet (overall, female-specific and male-specific comparisons). Biological processes determined by the DAVID analysis tool and the comparison when altered are shown for downregulated genes related to immune response, lipid or fatty acid metabolic process, response to hypoxia & ROS, iron transport, nutrients transport, and angiogenesis. Data are n = 12 per dietary group for overall and n = 6 per group for sex-specific comparisons.

	Biological process related to:						Altered when comparing Ctrl vs HFHS:		
Upregulated DEGs	Immune response	Lipid or fatty acid metabolic process	Response to hypoxia & ROS	Iron transport	Nutrients transport	Angiogenesis	Overall	Females	Males
Chil3	x						Yes	Yes	Yes
Pla2g4a	x	x					Yes	Yes	Yes
Slc9b2				x			Yes	Yes	Yes
Bdh2		x					Yes	Yes	No
Slc26a7				x			Yes	Yes	No
Slc6a14				x			Yes	Yes	No
Cd28	x						Yes	No	No
Rasgrp1	x						Yes	No	Yes
Tgtp1	x						Yes	No	No
Hamp	x			x			Yes	No	Yes
Il1a	x						Yes	No	Yes
Snhg1	x						Yes	No	Yes
Apold1		x	x		x	x	Yes	No	Yes
Cyb5r2		x					Yes	No	Yes
Gdpd3		x					Yes	No	No

Hpgds		x					Yes	No	Yes
Acsbg1		x					Yes	No	Yes
Acsm3		x					Yes	No	No
Nox4			x				Yes	No	No
Gucy1a2			x				Yes	No	No
Ptpn			x				Yes	No	No
Rgs4				x			Yes	No	Yes
Slc10a6				x			Yes	No	No
Fgf9						x	Yes	No	No
Slc30a4				x			No	Yes	No
Slc9b1				x			No	Yes	No
Oas1b	x						No	No	Yes
Clec2d	x						No	No	Yes
Gdap10	x						No	No	Yes
Il18bp	x						No	No	Yes
Lgals4	x						No	No	Yes
Pisd-ps1	x						No	No	Yes
Snhg20	x						No	No	Yes
Alms1		x					No	No	Yes
Echdc2		x					No	No	Yes
Phka2		x					No	No	Yes
Gabre				x			No	No	Yes
Gabbr2				x			No	No	Yes
Atg9b					x		No	No	Yes
Spx					x		No	No	Yes

Table S4. Genes differentially expressed by a HFHS diet for overall, female-specific and male-specific comparisons that are located on the X chromosome.

Gene ID	Gene Symbol	Chromosome	Direction of Change	Comparison
ENSMUSG000000031380	Vegfd	X:164373378-164402650	downregulated	Overall
ENSMUSG000000051228	Nyx	X:13466110-13489313	downregulated	Overall
ENSMUSG000000059327	Eda	X:99975606-100400762	downregulated	Overall
ENSMUSG000000087149	Itih5l-ps	X:150826972-150857053	downregulated	Overall
ENSMUSG000000031089	Slc6a14	X:21714896-21742355	upregulated	Overall
ENSMUSG000000031163	Glod5	X:8004200-8018492	upregulated	Overall
ENSMUSG000000073062	Zxdb	X:94724569-94730187	upregulated	Overall
ENSMUSG000000051228	Nyx	X:13466110-13489313	downregulated	Females
ENSMUSG000000059327	Eda	X:99975606-100400762	downregulated	Females
ENSMUSG000000031089	Slc6a14	X:21714896-21742355	upregulated	Females
ENSMUSG000000079584	Gm364	X:57409154-57488767	upregulated	Females
ENSMUSG000000031200	Mtcp1	X:75410444-75416588	upregulated	Males
ENSMUSG000000031295	Phka2	X:160502166-160598878	upregulated	Males
ENSMUSG000000031303	Map3k15	X:159988433-160123351	upregulated	Males
ENSMUSG000000031340	Gabre	X:72255999-72274803	upregulated	Males
ENSMUSG000000031362	Xlr4c	X:73233688-73243130	upregulated	Males
ENSMUSG000000031380	Vegfd	X:164373378-164402650	downregulated	Males
ENSMUSG000000034160	Ogt	X:101640060-101684351	upregulated	Males
ENSMUSG000000055653	Gpc3	X:52272426-52613950	downregulated	Males
ENSMUSG000000059327	Eda	X:99975606-100400762	downregulated	Males
ENSMUSG000000067768	Xlr4b	X:73214333-73222453	upregulated	Males
ENSMUSG000000073125	Xlr3b	X:73192207-73202930	upregulated	Males
ENSMUSG000000085396	Firre	X:50555744-50635321	upregulated	Males
ENSMUSG000000101603	Gm28730	X:53051194-53053159	upregulated	Males

Table S5. Genes differentially expressed by a HFHS diet compared to an intrauterine inflammation model.

Overlapped DEGs from Lien et al. 2020, and their direction of change. Genes differentially expressed in the placenta by a maternal HFHS diet (overall, female and male-specific comparisons) overlapped with the list of genes differentially expressed in response to intrauterine inflammation (50).

Comparison	Gene	Lien et al. 2020		Candia et al. 2023	
		LogFC	Direction of change	LogFC	Direction of change
Overall	Apoa2	0.4676	Upregulated	-1.664	Downregulated
	Derl3	-0.2909	Downregulated	-0.8214	Downregulated
	Hnf4a	0.2383	Upregulated	-0.6725	Downregulated
	Igfbp1	0.1945	Upregulated	-0.8751	Downregulated
	Endou	-0.2226	Downregulated	-0.6593	Downregulated
	Igfbp6	-0.4652	Downregulated	-0.9445	Downregulated
	Scd2	0.3195	Upregulated	-0.8336	Downregulated
	Ccdc184	1.249	Upregulated	-0.5979	Downregulated
	Elovl4	-0.2856	Downregulated	-0.8061	Downregulated
	Abtb2	0.6324	Upregulated	-0.5853	Downregulated
	Spata2l	-0.7153	Downregulated	-0.6037	Downregulated
	Cdhr2	0.4082	Upregulated	-1.981	Downregulated
	Thrsp	-0.5856	Downregulated	-0.749	Downregulated
	Cysrt1	-0.308	Downregulated	-0.677	Downregulated
	Asb10	0.3591	Upregulated	-0.6987	Downregulated
	Pcp4l1	-0.3033	Downregulated	-0.7501	Downregulated
	Unc5cl	0.395	Upregulated	-0.9061	Downregulated

	Rarres1	-0.2644	Downregulated	-0.6824	Downregulated
	Spink2	0.0994	Upregulated	-0.7265	Downregulated
	Chst8	0.3231	Upregulated	-0.5981	Downregulated
	Itih5l-ps	-0.3358	Downregulated	-0.7817	Downregulated
	Gm6967	-0.4597	Downregulated	-0.8069	Downregulated
	Adora2b	1.2272	Upregulated	0.5969	Upregulated
	4930412O13Rik	0.3467	Upregulated	0.8344	Upregulated
	Il1a	1.6012	Upregulated	0.9643	Upregulated
	Slc10a6	0.6251	Upregulated	0.7399	Upregulated
	Ing4	-0.2686	Downregulated	0.7233	Upregulated
	Gdpd3	1.0079	Upregulated	2.972	Upregulated
	Slc6a14	0.3296	Upregulated	0.5905	Upregulated
	Rgs4	0.6455	Upregulated	0.6297	Upregulated
	Chil3	-0.5241	Downregulated	1.416	Upregulated
	Samd9l	1.2516	Upregulated	0.6415	Upregulated
	Hamp	1.1941	Upregulated	1.18	Upregulated
	Tgtp1	1.321	Upregulated	0.9841	Upregulated
	Gm15972	-0.4264	Downregulated	0.6378	Upregulated
	Apold1	0.9598	Upregulated	0.8594	Upregulated
	Gm20627	-0.373	Downregulated	0.7379	Upregulated
	D5Erttd605e	-0.3257	Downregulated	0.6978	Upregulated
Females	Scd2	0.3195	Upregulated	-0.635	Downregulated
	Thrsp	-0.5856	Downregulated	-0.9754	Downregulated
	Pnoc	-0.2869	Downregulated	-2.585	Downregulated
	Slc6a14	0.3296	Upregulated	0.7507	Upregulated
	Chil3	-0.5241	Downregulated	1.268	Upregulated
Males	Ltbp1	0.3008	Upregulated	-0.6296	Downregulated
	Htra1	0.3239	Upregulated	-0.6936	Downregulated
	Slc5a1	0.3765	Upregulated	-1.662	Downregulated

	Slc9a5	0.3937	Upregulated	0.6846	Upregulated
	Wnt7b	-0.2844	Downregulated	-0.6233	Downregulated
	Endou	-0.2226	Downregulated	-0.6909	Downregulated
	Igfbp6	-0.4652	Downregulated	-0.9746	Downregulated
	Pgc	-0.092	Downregulated	-0.6118	Downregulated
	Zfp397	-0.3159	Downregulated	0.6907	Upregulated
	Cpn1	0.3036	Upregulated	-1.923	Downregulated
	Scd2	0.3195	Upregulated	-0.9842	Downregulated
	4930412O13Rik	0.3467	Upregulated	1.449	Upregulated
	Il1a	1.6012	Upregulated	1.345	Upregulated
	Echdc2	0.4017	Upregulated	0.6956	Upregulated
	Oas1b	0.7805	Upregulated	0.7144	Upregulated
	1600015I10Rik	-0.5099	Downregulated	0.8993	Upregulated
	Trpv6	-0.2448	Downregulated	-0.7122	Downregulated
	Clec2d	0.3596	Upregulated	0.6639	Upregulated
	Ing4	-0.2686	Downregulated	1.082	Upregulated
	Syt8	0.2537	Upregulated	0.7586	Upregulated
	Elovl4	-0.2856	Downregulated	-0.895	Downregulated
	Uba7	0.9647	Upregulated	0.951	Upregulated
	Ppip5k1	0.2791	Upregulated	0.7134	Upregulated
	Fam208b	0.2572	Upregulated	0.5851	Upregulated
	Ptgdr2	-0.5465	Downregulated	-0.603	Downregulated
	Cdhr2	0.4082	Upregulated	-2.572	Downregulated
	Creb3l3	0.3708	Upregulated	-1.15	Downregulated
	Cysrt1	-0.308	Downregulated	-0.6707	Downregulated
	Asb10	0.3591	Upregulated	-0.8802	Downregulated
	Rgs4	0.6455	Upregulated	0.7965	Upregulated
	A230050P20Rik	0.6014	Upregulated	0.6085	Upregulated
	Bace2	0.2868	Upregulated	-0.7172	Downregulated

	Chil3	-0.5241	Downregulated	1.599	Upregulated
	2010003K11Rik	0.1909	Upregulated	-2.457	Downregulated
	Lgals2	0.2674	Upregulated	-1.132	Downregulated
	Pnoc	-0.2869	Downregulated	-1.972	Downregulated
	Samd9l	1.2516	Upregulated	0.8596	Upregulated
	Rarres1	-0.2644	Downregulated	-0.7834	Downregulated
	Hamp	1.1941	Upregulated	1.234	Upregulated
	Cx3cr1	-0.2885	Downregulated	-0.7852	Downregulated
	Spink2	0.0994	Upregulated	-0.8786	Downregulated
	2010109I03Rik	0.5219	Upregulated	0.7922	Upregulated
	Hsp25-ps1	0.8689	Upregulated	-0.6478	Downregulated
	Pisd-ps1	-0.5627	Downregulated	0.6441	Upregulated
	Apold1	0.9598	Upregulated	0.947	Upregulated
	Gm20627	-0.373	Downregulated	0.9368	Upregulated
	Gdap10	0.318	Upregulated	1.103	Upregulated
	Gm4673	-0.3378	Downregulated	0.6196	Upregulated

Table S6. Genes differentially expressed by a HFHS diet related to biological processes of interest compared to an intrauterine inflammation model.

Overlapped DEGs from Lian et al. 2020 and Candia et al. 2023, and their direction of change related to biological process of interest.

Comparison	Gene	Lien 2020		Candia 2023	
		LogFC	Direction of change	LogFC	Direction of change
Overall	Il1a	1.6012	Upregulated	0.9643	Upregulated
	Slc10a6	0.6251	Upregulated	0.7399	Upregulated
	Gdpd3	1.0079	Upregulated	2.972	Upregulated
	Slc6a14	0.3296	Upregulated	0.5905	Upregulated
	Rgs4	0.6455	Upregulated	0.6297	Upregulated
	Chil3	-0.5241	Downregulated	1.416	Upregulated
	Hamp	1.1941	Upregulated	1.18	Upregulated
	Tgtp1	1.321	Upregulated	0.9841	Upregulated
	Apold1	0.9598	Upregulated	0.8594	Upregulated
	Elovl4	-0.2856	Downregulated	-0.8061	Downregulated
	Thrsp	-0.5856	Downregulated	-0.749	Downregulated
	Unc5cl	0.395	Upregulated	-0.9061	Downregulated
	Scd2	0.3195	Upregulated	-0.8336	Downregulated
Females	Slc6a14	0.3296	Upregulated	0.7507	Upregulated
	Chil3	-0.5241	Downregulated	1.268	Upregulated
	Scd2	0.3195	Upregulated	-0.635	Downregulated
	Thrsp	-0.5856	Downregulated	-0.9754	Downregulated
Males	Il1a	1.6012	Upregulated	1.345	Upregulated
	Echdc2	0.4017	Upregulated	0.6956	Upregulated
	Oas1b	0.7805	Upregulated	0.7144	Upregulated
	Clec2d	0.3596	Upregulated	0.6639	Upregulated

Rgs4	0.6455	Upregulated	0.7965	Upregulated
Chil3	-0.5241	Downregulated	1.599	Upregulated
Hamp	1.1941	Upregulated	1.234	Upregulated
Pisd-ps1	-0.5627	Downregulated	0.6441	Upregulated
Apold1	0.9598	Upregulated	0.947	Upregulated
Gdap10	0.318	Upregulated	1.103	Upregulated
Wnt7b	-0.2844	Downregulated	-0.6233	Downregulated
Scd2	0.3195	Upregulated	-0.9842	Downregulated
Trpv6	-0.2448	Downregulated	-0.7122	Downregulated
Elovl4	-0.2856	Downregulated	-0.895	Downregulated
Lgals2	0.2674	Upregulated	-1.132	Downregulated
Cx3cr1	-0.2885	Downregulated	-0.7852	Downregulated