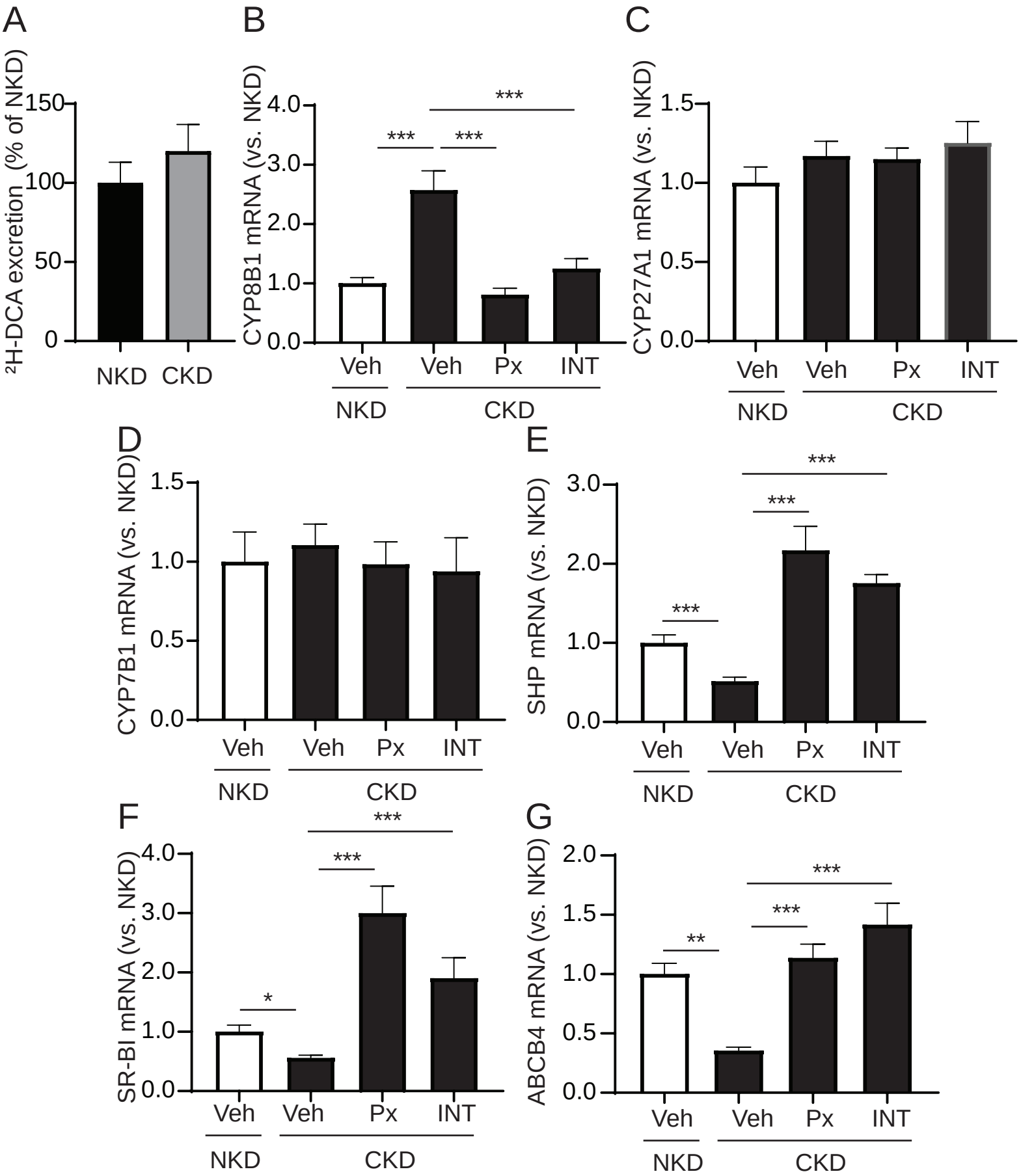
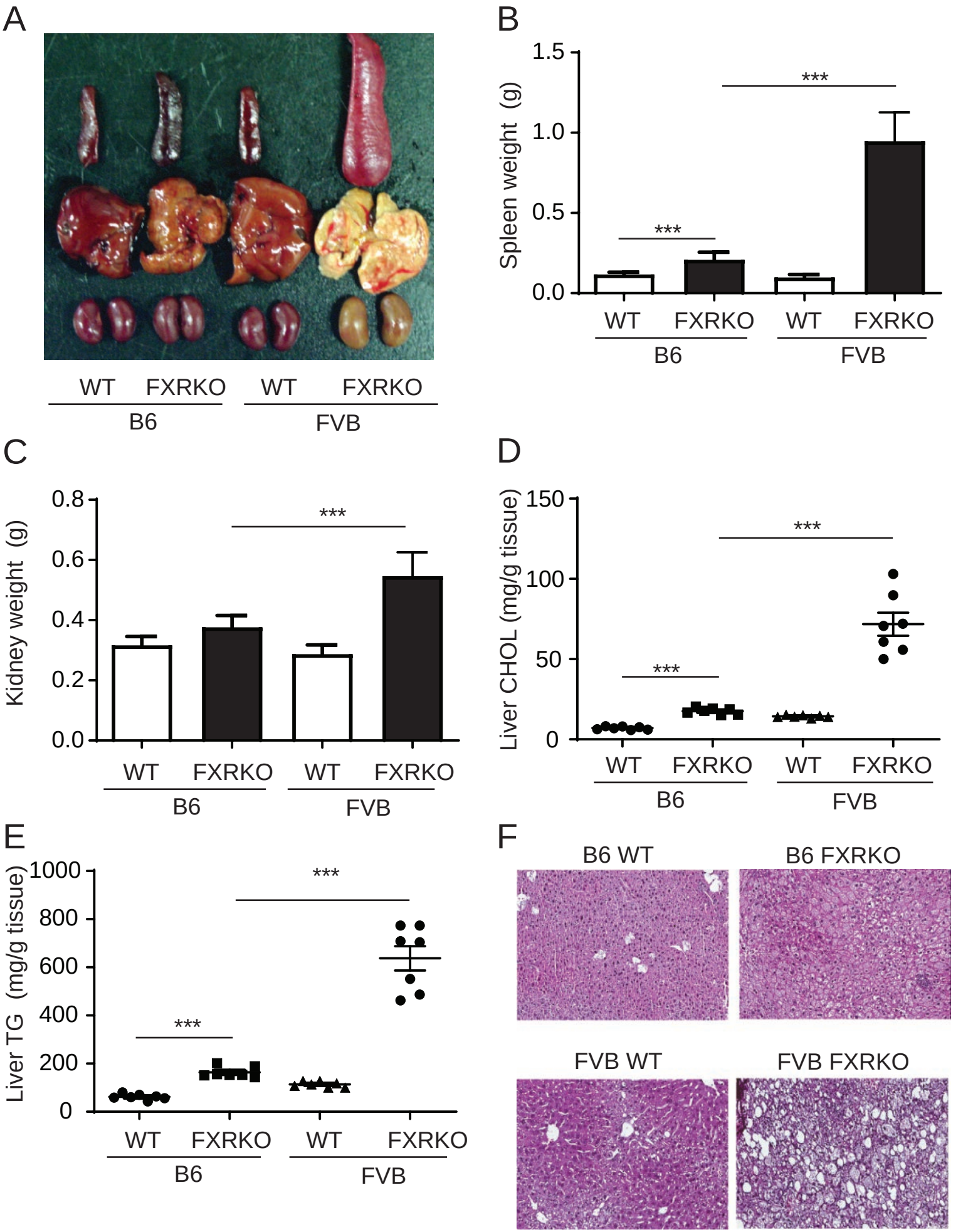
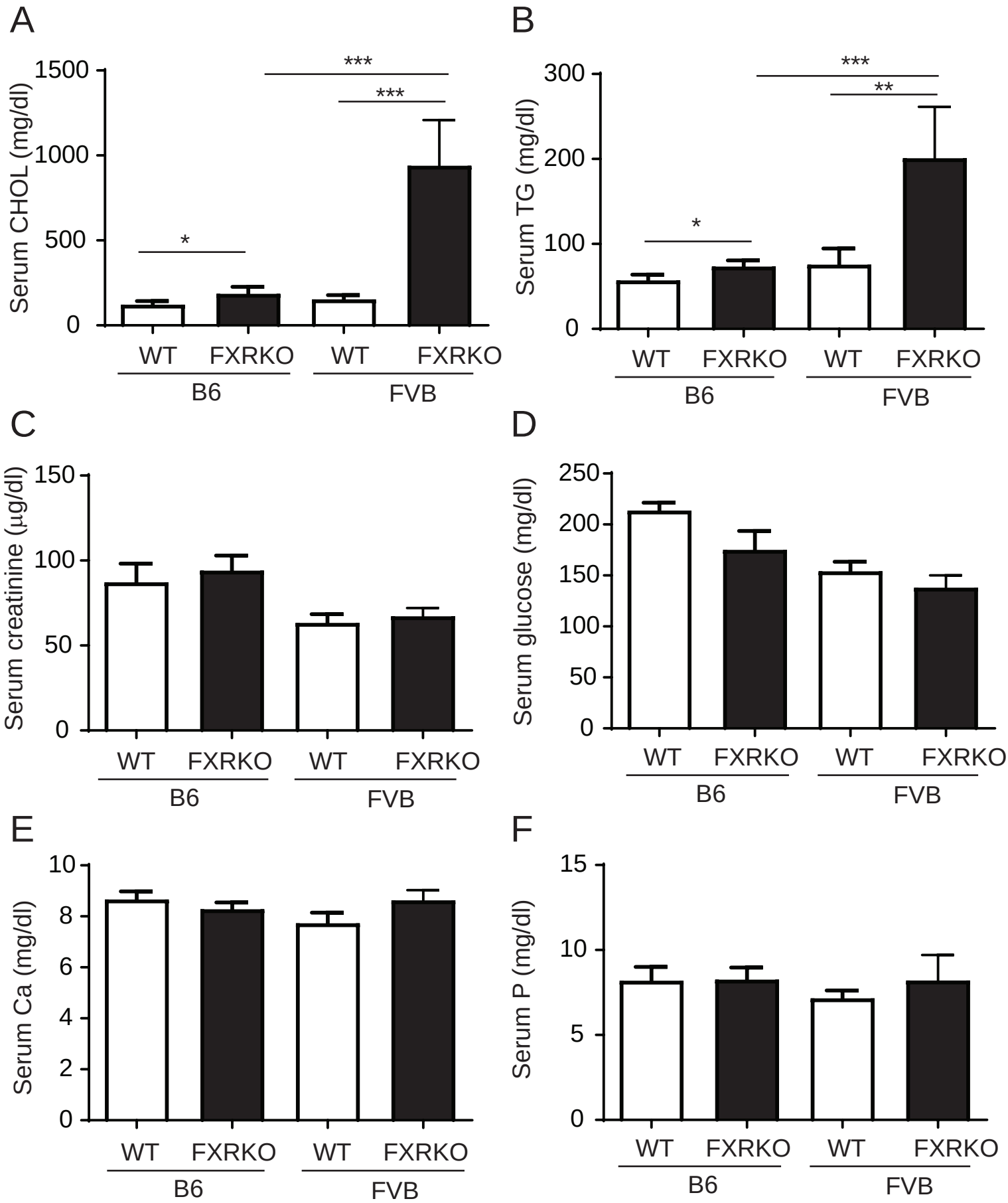


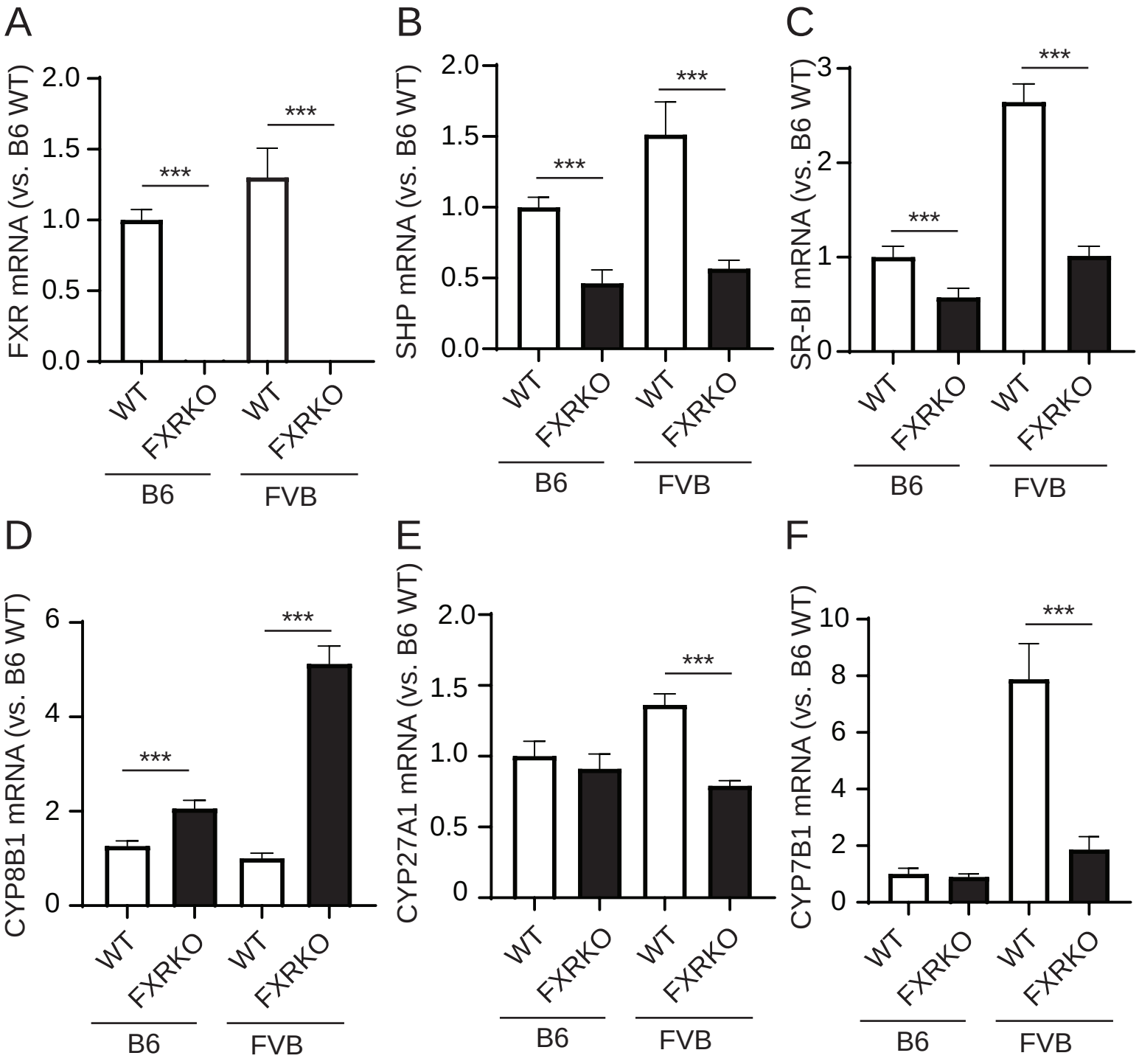
Supplemental Figure 1. Fecal DCA excretion in CKD mice and expression of bile acid synthesis enzymes in the livers of CKD mice treated with FXR agonists. D) Fecal DCA excretion. Twenty-week old CKD DBA/2J mice were intraperitoneally injected with ²H-DCA (30mg/kg body weight). Urine and feces samples were collected after 24 hours in metabolic cages. Urinary 2H-DCA was analyzed with LC-MS/MS. mRNA levels of hepatic B) CYP8B1, C) CYP27A1, D) CYP7B1, E) SHP, F) SR-BI and G) ABCB4 in CKD DBA/2J mice. Eight-week-old male DBA/2J mice were subjected to sham operation or 5/6 nephrectomy. CKD mice were maintained on a Western diet containing Px20606 (5mg/kg body weight) for 16 weeks. *p<0.05, **p<0.01 & ***p<0.001


A
WT
FXRKO
WT
FXRKO
B6
FVB
B
Spleen weight (g)
1.5
1.0
0.5
0.0
***
***
WT
FXRKO
WT
FXRKO
B6
FVB
C
Kidney weight (g)
0.8
0.6
0.4
0.2
0.0
***
WT
FXRKO
WT
FXRKO
B6
FVB
D
Liver CHOL (mg/g tissue)
150
100
50
0
***
***
WT
FXRKO
WT
FXRKO
B6
FVB
E
Liver TG (mg/g tissue)
1000
800
600
400
200
0
***
***
WT
FXRKO
WT
FXRKO
B6
FVB
F
B6 WT
B6 FXRKO
FVB WT
FVB FXRKO

Supplemental Figure 2. FVB FXR KO deficiency elicits severe tissue enlargement and liver steatosis. A) Representative tissue pictures of B) spleen weight and C) kidney weight of FXR KO mice. D) Levels of liver cholesterol (CHOL). E) Levels of liver triacylglycerol (TG) and F) hematoxylin & eosin stain of livers of FXRKO mice on C57BL/6 or FVB backgrounds. Eight-week-old wild-type and FXR KO female mice were maintained on a Western diet for 16 weeks. *p<0.05, **p<0.01 & ***p<0.001



Supplemental Figure 3. **FVB FXR KO mice develop hyperlipidemia**. Levels of serum A) cholesterol (CHOL), B) triacylglycerol (TG), C) creatinine, D) glucose, E) calcium (Ca), and F) phosphorus of FXR KO mice on C57BL/6 or FVB backgrounds. 8-week-old wild-type and FXR KO female mice were maintained on a Western diet for 16 weeks. *p<0.05, **p<0.01 & ***p<0.001



Supplemental Figure 4. **Hepatic expression of FXR targets and enzymes involved in bile acid synthesis in FVB FXR KO mice.** mRNA levels of hepatic A) FXR, B) SHP, C) SR-BI, D) CYP8B1, E) CYP27A1 and D) CYP7B1 in FXR KO mice on C57BL/6 or FVB backgrounds. 8-week-old wild-type and FXR KO female mice were maintained on a Western diet for 16 weeks. *p<0.05, **p<0.01 & ***p<0.001

Supplemental Table 1. CKD increases levels of serum bile acids in humans

	Normal kidney function	Chronic kidney disease
CA	40.96 ± 9.89	100.18 ± 50.24
UDCA	33.59 ± 19.93	22.99 ± 16.58
HDCA	26.72 ± 21.86	18.65 ± 11.38
CDCA	53.14 ± 9.67	174.25 ± 89.74
DCA	125.99 ± 36.52	300.32 ± 89.50
LCA	9.89 ± 2.10	12.42 ± 4.23
GCA	94.70 ± 32.44	189.06 ± 67.06
GUDCA	22.58 ± 6.70	50.33 ± 19.47
GCDCA	105.55 ± 17.24	250.52 ± 57.92
GDCA	102.34 ± 34.30	371.61 ± 113.46
TCA	7.97 ± 3.17	29.48 ± 17.85
TUDCA	0.31 ± 0.12	2.93 ± 1.03
THDCA	21.44 ± 8.42	21.69 ± 21.32
TCDCA	17.53 ± 3.36	181.38 ± 111.48
TDCA	9.86 ± 2.64	81.65 ± 38.90
TLCA	0.56 ± 0.13	2.61 ± 0.94
Total BA	676.96 ± 116.35	1826.42 ± 337.65
eGFR (mL/min/1.73m^2)	80.00 ± 12.00	34.00 7.00
Age	57.00 ± 7.00	59.00 14.00

Levels of bile acids were analyzed in the serum from patients (N=10) with chronic kidney disease and age-matched patients (N=10) with normal kidney function.
CA; cholic acid, UDCA; ursodeoxycholic acid, HDCA; hyodeoxycholic acid, CDCA; chenodeoxycholic acid, DCA; deoxycholic acid, LCA; lithocholic acid
GCA; glycocholic acid, GUDCA; glycoursodeoxycholic acid, GCDCA; glycochenodeoxychol
GDCA; glycodeoxycholic acid, TCA; taurocholic acid, TUDCA; tauroursodeoxycholic acid
THDCA; taurohyodeoxycholic acid, TCDCA; taurochenodeoxycholic acid,
TDCA; taurodeoxycholic acid, TLCA; taurolithocholic acid.

Supplemental Table 2.
CKD increases levels of serum bile acids in LDLR KO mice

ng/ml	NKD	CKD
α-MCA	25.15 ± 13.50	25.9227 ± 29.80
β-MCA	167.47 ± 57.78	244.944 ± 86.41
CA	145.80 ± 59.68	346.217 ± 15.64
UDCA	20.16 ± 8.11	43.3114 ± 18.15
CDCA	28.50 ± 9.34	61.3828 ± 18.65
DCA	98.24 ± 25.30	335.797 ± 67.57
LCA	12.54 ± 2.36	10.8883 ± 3.67
α-TMCA	22.35 ± 6.02	28.1201 ± 22.97
β-TMCA	149.26 ± 46.46	304.542 ± 92.92
TCA	115.69 ± 22.46	309.1 ± 124.91
TUDCA	78.44 ± 19.27	77.0552 ± 21.18
TCDCA	55.58 ± 8.67	318.004 ± 52.08
TDCA	56.19 ± 5.99	157.255 ± 18.49
(μg/dl)		
Creatinine	103.21 ± 13.83	387.33 ± 23.48

Eight-week-old male LDLR KO mice were subjected to sham operation (NKD) or 5/6 nephrectomy (CKD). Animals were fed a Western diet for 16 weeks. Values in red are statistically significant ($p<0.05$, Student's t-test)
MCA; murocholic acid, CA; cholic acid, UDCA; ursodeoxycholic acid,
CDCA; chenodeoxycholic acid, DCA; deoxycholic acid,
LCA; lithocholic acid, TMCA; tauromuricholic acid
TCA; taurocholic acid, TUDCA; tauroursodeoxycholic acid,
TCDCA; taurochenodeoxycholic acid,TDCA; taurodeoxycholic acid,

Supplemental Table 3. CKD increases levels of serum bile acids in DBA/2J mice

ng/ml	NKD	CKD
α-MCA	10.11 ± 4.06	10.31 ± 2.43
β-MCA	102.66 ± 28.08	120.58 ± 67.29
CA	15.54 ± 6.10	98.05 ± 16.87
UDCA	24.56 ± 12.00	11.12 ± 3.38
CDCA	40.83 ± 1.21	46.65 ± 5.44
DCA	16.47 ± 9.88	169.09 ± 55.53
LCA	7.86 ± 3.32	13.44 ± 4.96
α-TMCA	71.45 ± 21.50	48.41 ± 11.87
β-TMCA	419.25 ± 64.81	369.52 ± 35.91
TCA	311.92 ± 56.72	550.51 ± 180.60
TUDCA	129.16 ± 49.17	68.63 ± 35.78
TCDCA	201.98 ± 42.87	187.69 ± 36.07
TDCA	96.42 ± 23.46	301.73 ± 33.73
Total	1444.71 ± 119.82	2368.21 ± 318.20
(μg/dl)		
Creatinine	99.20 ± 6.00	311.00 ± 21.24

Eight-week-old male DBA mice were subjected to sham-operation or 5/6nephrectomy. Animals were fed a western diet for 16 weeks. Values in red are sttistically significant ($p<0.05$ student t-test)

Supplemental Table 4.
Biochemical parameters in CKD LDLRKO mice treated with FXR agonists

		Vehicle NKD	Vehicle CKD	Px20606 CKD
Triglyceride	mg/dl	459.7 ± 16.2	285.8 ± 27.3	56.5 ± 5.9
Cholesterol	mg/dl	2198.7 ± 138.1	1594.9 ± 161.1	465.2 ± 51.2
Glucose	mg/dl	268 ± 6.8	222.1 ± 27.5	169.3 ± 22.9
Calcium	mg/dl	9.5 ± 0.3	9.9 ± 0.3	10.0 ± 0.2
Phosphorus	mg/dl	9.1 ± 0.8	12.5 ± 1.8	10.3 ± 0.5
Creatinine	μg/dl	93.4 ± 14.1	379.3 ± 29.0	404.2 ± 31.9

Eight-week-old male LDLR KO mice were subjected to sham-operation (NKD) or 5/6 nephrectomy (CKD).
CKD mice were fed a Western diet or a Western diet containing Px20606 (5 mg/kg) for 12 weeks.
Blood was withdrawnafter a 4 hours-fasting. Data expressed as Mean ± SEM.
Red indicates a statistical significance ($p<0.05$ vs. NKD-vehicle)
Blue indicates a statistical significance ($p<0.05$ vs. CKD-vehicle)

Supplemental Table 5. CKD increases levels of serum bile acids in LDLR KO mice

ng/ml	NKD	CKD	CKD
		Vehicle	Px26060
α-MCA	22.3 ± 2.3	20.5 ± 11.9	72.2 ± 19.9
β-MCA	158.8 ± 28.4	138.2 ± 87.9	976.0 ± 283.9
CA	165.0 ± 39.8	371.8 ± 51.7	27.0 ± 12.2
UDCA	25.2 ± 27.6	23.7 ± 22.0	223.8 ± 76.5
CDCA	43.7 ± 10.3	67.4 ± 7.8	124.5 ± 20.1
DCA	94.0 ± 24.4	316.3 ± 42.4	0.5 ± 0.6
LCA	11.3 ± 4.8	10.5 ± 3.3	19.9 ± 3.9
α-TMCA	27.6 ± 13.2	40.7 ± 6.5	100.6 ± 52.1
β-TMCA	163.0 ± 34.4	294.8 ± 56.5	1222.0 ± 98.6
TCA	154.2 ± 53.6	275.7 ± 67.3	39.5 ± 16.3
TUDCA	53.8 ± 4.0	54.5 ± 4.9	96.9 ± 32.3
TCDCA	57.8 ± 19.1	180.2 ± 16.0	537.6 ± 38.9
TDCA	55.6 ± 22.8	207.7 ± 56.9	2.4 ± 0.8
Px26060	0.0 ± 0.0	0.0 ± 0.0	39.1 ± 3.7
INT-747	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Creatinine	106.2 ± 6.0	359.0 ± 30.1	349.3 ± 23.3

Eight-week-old male LDLR KO mice were subjected to sham-operation or 5/6 nephrectomy. Animals were fed a western diet containg Px26060 (5mg/kg) for 12 weeks. Values in red (vs NKD) and blue (vs. CKD + vehicle) are statistically significant ($p<0.05$ student t-test).

Supplemental Table 6. CKD increases levels of serum bile acids in DBA2/J mice

Kidney condition	NKD	CKD	CKD	CKD
ng/ml	**vehicle**	**vehicle**	**Px26060**	**INT-747**
a-MCA	12.3 ± 4.1	13.4 ± 4.3	18.3 ± 5.0	19.4 ± 5.55
b-MCA	111.2 ± 18.3	132.1 ± 12.3	644.1 ± 20.5	621.3 ± 34.9
CA	12.3 ± 7.0	114.6 ± 18.1	5.1 ± 1.3	7.9 ± 3.1
UDCA	15.6 ± 12.7	14.9 ± 2.6	26.8 ± 3.5	28.5 ± 3.6
CDCA	48.7 ± 3.4	49.8 ± 6.7	85.3 ± 4.6	88.3 ± 10.8
DCA	15.7 ± 3.7	180.3 ± 25.5	1.4 ± 0.8	10.4 ± 3.0
LCA	8.8 ± 3.0	10.3 ± 3.1	19.8 ± 2.3	22.4 ± 4.1
a-TMCA	64.0 ± 16.3	59.4 ± 15.6	68.3 ± 13.3	70.3 ± 3.4
b-TMCA	383.5 ± 37.4	398.1 ± 40.4	559.4 ± 21.3	527.9 ± 56.9
TCA	356.1 ± 48.9	689.3 ± 32.9	40.9 ± 5.8	57.5 ± 7.0
TUDCA	120.1 ± 14.4	107.3 ± 43.2	139.3 ± 36.7	143.8 ± 9.0
TCDCA	222.4 ± 32.3	199.3 ± 30.1	349.6 ± 24.5	300.8 ± 35.2
TDCA	89.7 ± 14.8	405.1 ± 28.5	3.9 ± 1.6	25.5 ± 1.5
Px26060	0.0 ± 0.0	0.0 ± 0.0	100.3 ± 9.8	0.0 ± 0.0
INT-747	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	103.2 ± 7.4
Creatinine	106.2 ± 6.0	365.1 ± 30.1	371.2 ± 23.3	361.3 ± 24.8

Eight-week-old male DBA2/J mice were subjected to sham-operation or 5/6nephrectomy. Animals were fed a western diet for 12 weeks.
Values in red (vs NKD) and blue (vs. CKD + vehicle) are statistically significant ($p<0.05$ student t-test).

Supplemental Table 7. Serum biochemical parameters in CKD LDLRKO and and FXRKO; LDLRKO mice

		LDLRKO	FXRKO; LDLRKO
Triglyceride	mg/dl	255 ± 3.5	551.5 ± 6.38
Cholesterol	mg/dl	1943.3 ± 57.3	3012.1 ± 91.0
Calcium	mg/dl	8.5 ± 0.1	9.3 ± 0.04
Phosphorus	mg/dl	12.2 ± 0.1	14.4 ± 0.3
Creatinine	ng/dl	350.0 ± 60.5	341.5 ± 30.5

Eight-week-old male FXRKO; LDLR KO mice were subjected to sham-operation or 5/6nephrectomy. Animals were fed a western diet for 16 weeks.
Values in red are sttistically significant ($p<0.05$ student t-test)

Supplemental Table 8. CKD increases levels of serum bile acids in LDLR KO mice

ng/ml	LDLRKO	FXRKO; LDLRKO
α-MCA	27.47 ± 6.84	27.67 ± 20.91
β-MCA	403.91 ± 137.62	646.54 ± 1216.74
CA	337.55 ± 60.79	1332.61 ± 684.10
UDCA	31.12 ± 14.93	40.17 ± 44.67
CDCA	58.32 ± 19.52	84.61 ± 73.74
DCA	377.42 ± 142.75	1314.78 ± 386.59
LCA	18.53 ± 6.38	27.50 ± 14.11
α-TMCA	48.41 ± 29.06	172.08 ± 104.98
β-TMCA	329.52 ± 64.26	332.04 ± 1964.64
TCA	321.51 ± 208.08	6364.86 ± 4941.77
TUDCA	68.63 ± 87.63	183.89 ± 144.51
TCDCA	271.02 ± 86.92	312.44 ± 184.49
TDCA	151.73 ± 105.47	1091.65 ± 1372.67

Eight-week-old male FXRKO; LDLR KO mice were subjected to sham-operation or 5/6nephrectomy. Animals were fed a western diet for 16 weeks.

Values in red are sttistically significant ($p<0.05$ student t-test)

Supplemental Table 9. Serum bile acid levels in C57Bl6 and FVB FXRKO mice

	WT		FXRKO	
ng/ml	C57BL6	FVB	C57BL6	FVB
α-MCA	88.0 ± 18.4	38.0 ± 13.9	240.8 ± 32.0	252.2 ± 11.5
β-MCA	187.6 ± 22.0	63.4 ± 13.4	210.3 ± 17.7	376.0 ± 70.5
CA	276.1 ± 42.3	73.4 ± 15.2	2882.4 ± 338.1	2993.7 ± 441.0
UDCA	19.2 ± 4.9	5.6 ± 0.7	14.5 ± 5.8	8.1 ± 2.2
CDCA	41.2 ± 13.6	25.1 ± 3.4	44.7 ± 6.9	47.0 ± 15.8
DCA	32.8 ± 6.4	98.6 ± 5.7	496.3 ± 92.9	2362.5 ± 180.2
LCA	11.0 ± 0.4	11.3 ± 0.7	11.3 ± 0.4	14.3 ± 2.0
α-TMCA	51.1 ± 12.3	16.3 ± 4.4	89.2 ± 28.1	62.1 ± 11.0
β-TMCA	189.4 ± 21.6	54.9 ± 12.5	310.4 ± 107.3	235.6 ± 20.3
TCA	887.4 ± 83.1	767.1 ± 59.7	20731.7 ± 565.4	9442.8 ± 335.3
TUDCA	51.1 ± 3.2	16.3 ± 4.4	119.2 ± 28.1	62.1 ± 11.0
TCDCA	47.3 ± 8.2	42.6 ± 6.0	143.5 ± 15.2	147.2 ± 20.9
TDCA	35.5 ± 9.3	151.3 ± 30.9	1115.8 ± 158.3	1088.9 ± 231.3

Eight-week-old FXRKO mice were were fed a western diet for 16 weeks.
Values in blue are statistically significant ($p<0.05$ student t-test vs C57B6 WT)
Values in red are statistically significant ($p<0.05$ student t-test vs C57B6 FXR KO)