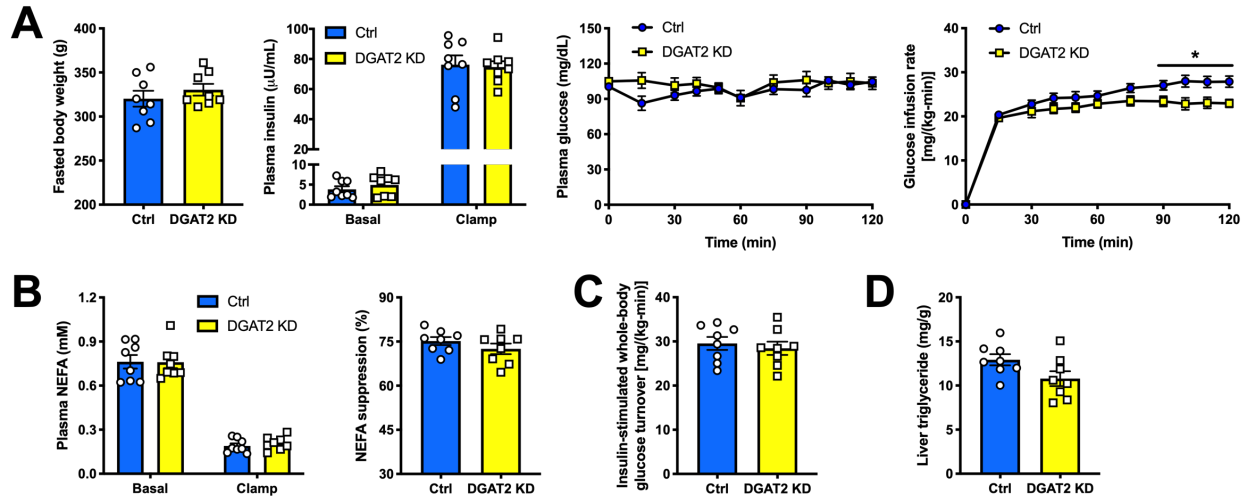


## Supplemental Information

### Figure S1



**Figure S1. Related to Figure 1**

(A) Fasted body weight, fasting and clamp insulin levels, plasma glucose and glucose infusion rate during hyperinsulinemic-euglycemic clamp in Ctrl vs DGAT2 KD rats.

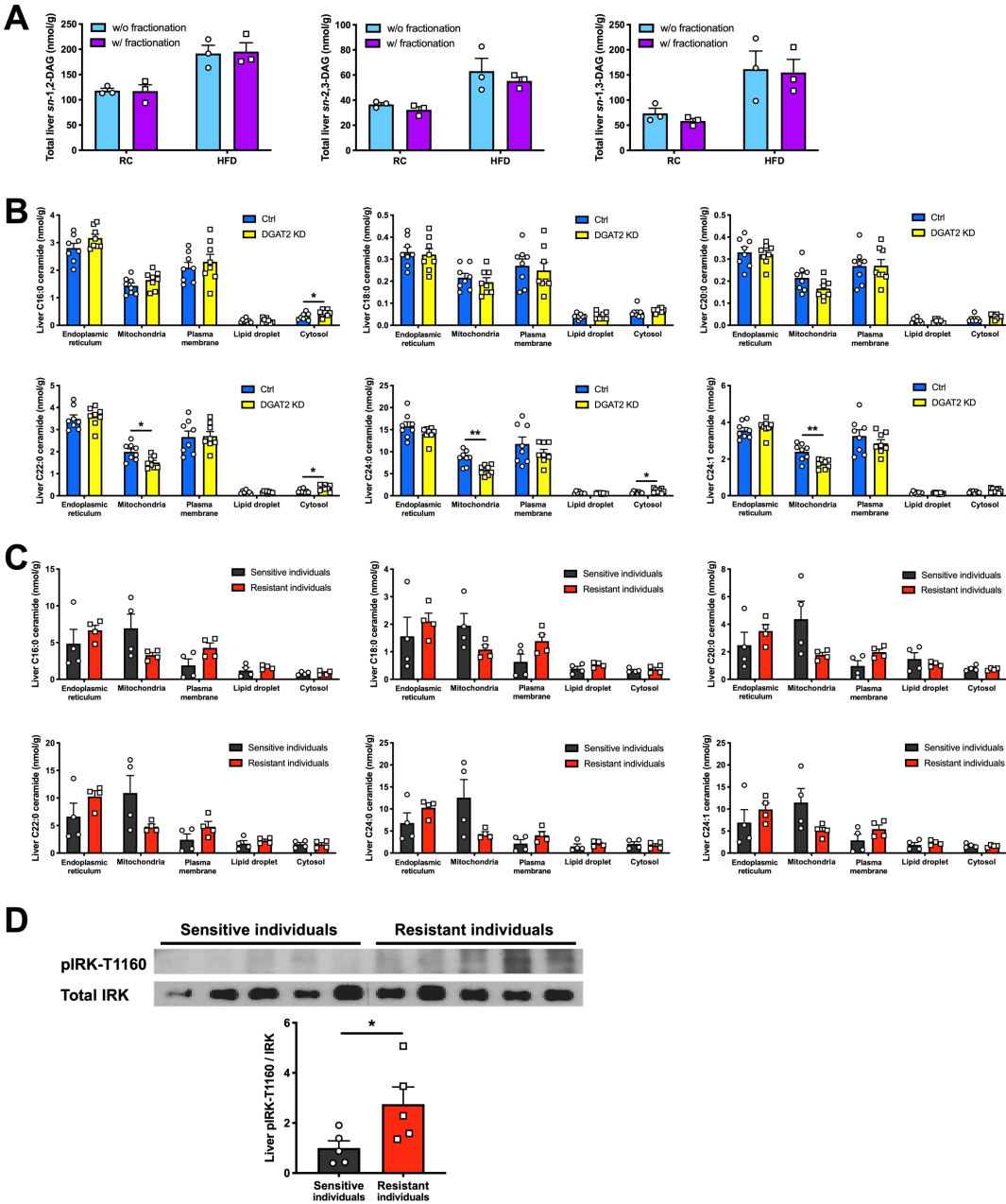
(B) Plasma NEFA and its suppression by insulin during clamp.

(C) Insulin-stimulated whole-body glucose turnover during clamp.

(D) Liver triglyceride content in Ctrl vs DGAT2 KD rats.

In all panels, data are the mean  $\pm$  S.E.M. of  $n = 8$  per group.

# Figure S2



**Figure S2. Related to Figure 2**

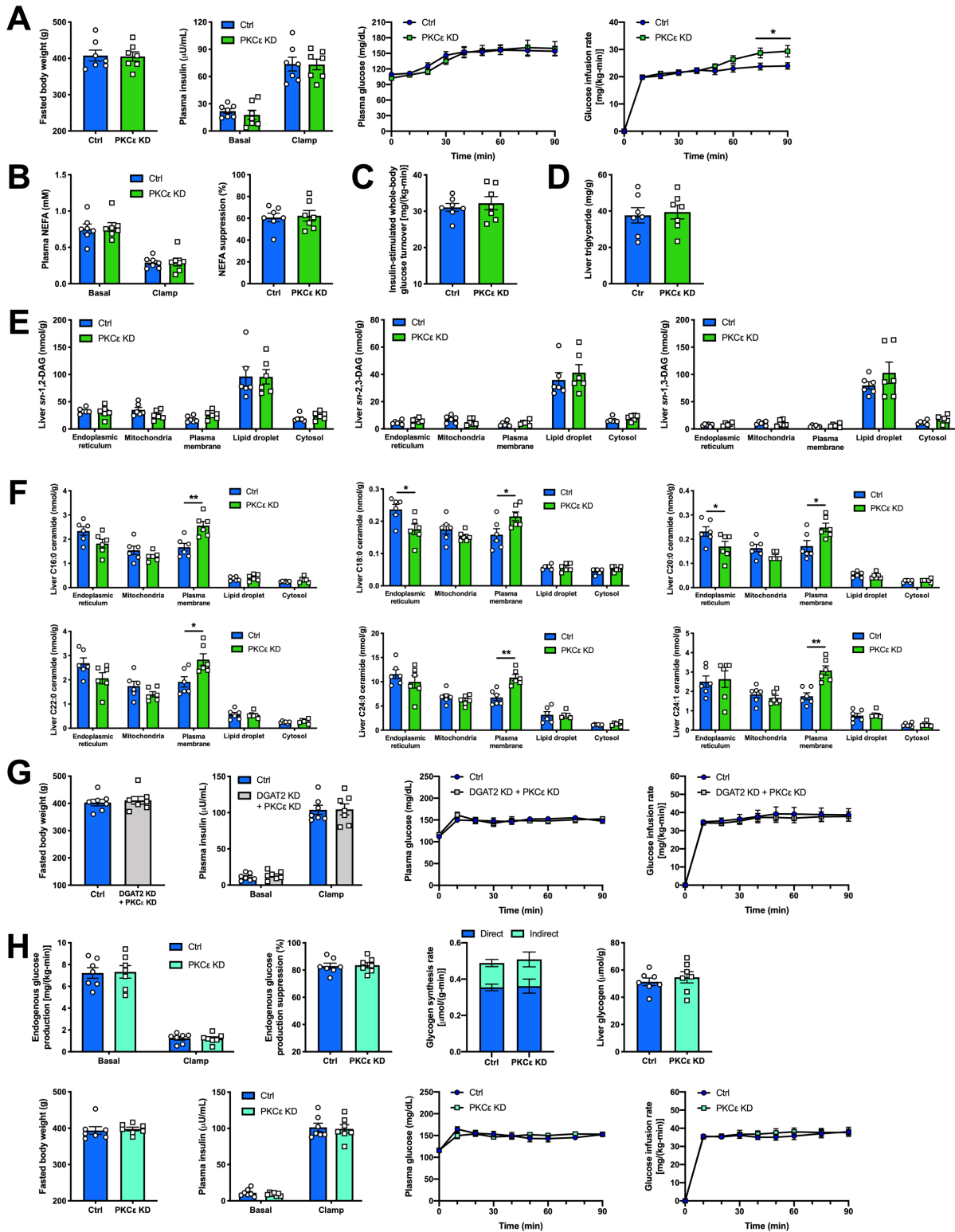
(A) Liver DAG stereoisomer content measured with and without the fractionation method to determine the lipid content recovery of the fractionation method.

(B) and (C) Liver ceramide species content in five subcellular compartments.

(D) Human liver IRK-T1160 phosphorylation as measured by western blot (top) and with its quantification (bottom).

In all panels, data are the mean±S.E.M. In (A),  $n = 3$  per group. In (B),  $n = 8$  per group. In (C),  $n = 4$  per group. In (D),  $n = 5$  per group. \* $P < 0.05$  and \*\* $P < 0.01$ .

# Figure S3



**Figure S3. Related to Figure 3**

(A) Fasted body weight, fasting and clamp insulin levels, plasma glucose and glucose infusion rate during clamp in HFD-fed Ctrl vs hepatic PKC $\epsilon$  KD rats.

(B) Plasma NEFA and its suppression by insulin during clamp in HFD-fed Ctrl vs hepatic PKC $\epsilon$  KD rats.

(C) Insulin-stimulated whole-body glucose turnover during clamp in HFD-fed Ctrl vs hepatic PKC $\epsilon$  KD rats.

(D) Liver triglyceride content in HFD-fed Ctrl vs hepatic PKC $\epsilon$  KD rats.

(E) Liver DAG stereoisomer content in five subcellular compartments in HFD-fed Ctrl vs hepatic PKC $\epsilon$  KD rats.

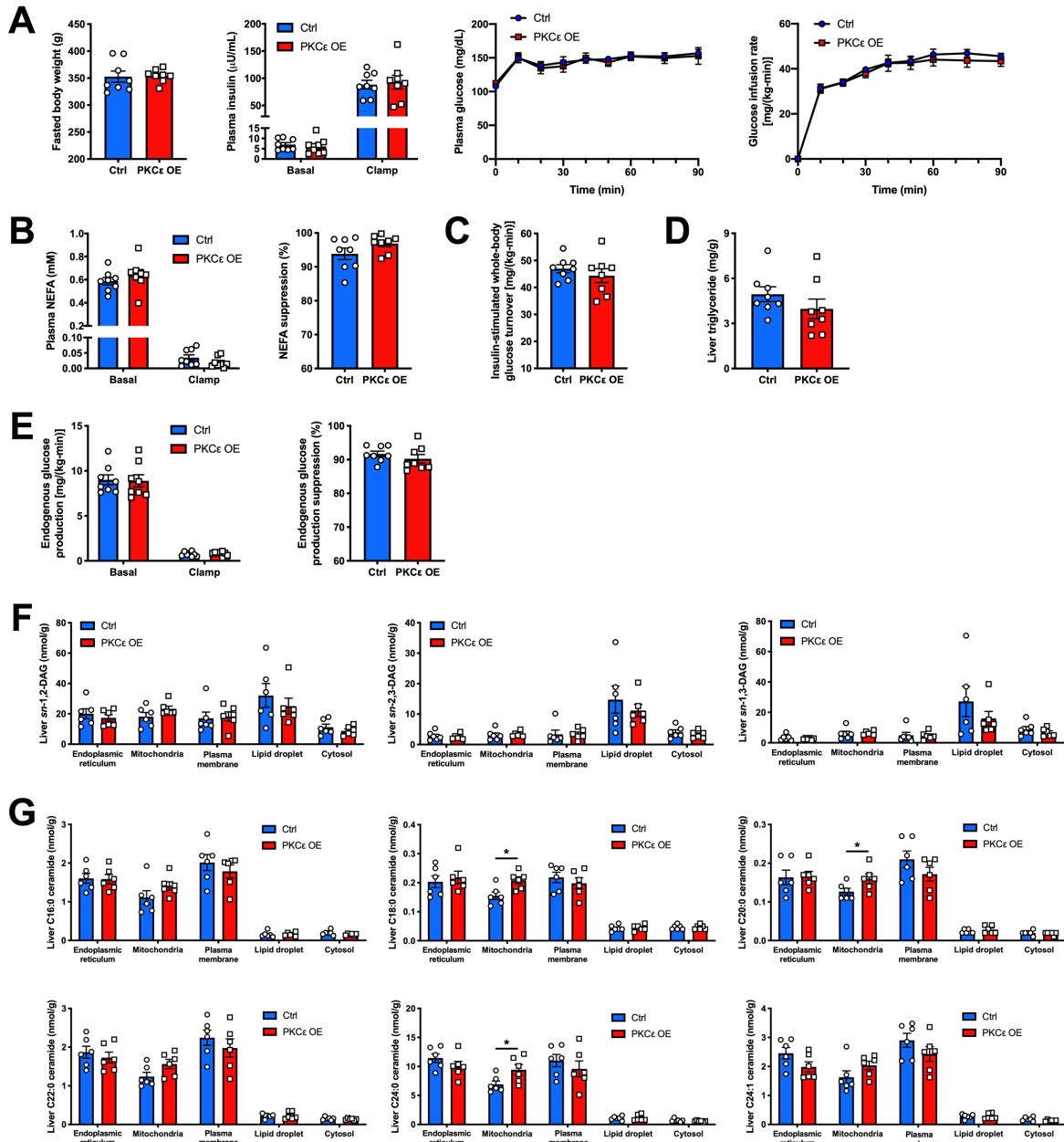
(F) Liver ceramide species content in five subcellular compartments in HFD-fed Ctrl vs hepatic PKC $\epsilon$  KD rats.

(G) Fasted body weight, fasting and clamp insulin levels, plasma glucose and glucose infusion rate during clamp in Ctrl vs hepatic DGAT2 + PKC $\epsilon$  KD rats.

(H) EGP, EGP's suppression by insulin and hepatic glycogen synthesis rate during a hyperinsulinemic-hyperglycemic clamp and post-clamp hepatic glycogen content, fasted body weight, fasting and clamp insulin levels, plasma glucose and glucose infusion rate during clamp in regular chow diet-fed Ctrl vs hepatic PKC $\epsilon$  KD rats.

In all panels, data are the mean $\pm$ S.E.M. In (E) and (F),  $n = 6$  per group. In all the other panels,  $n = 7$  per group. \* $P < 0.05$  and \*\* $P < 0.01$ .

# Figure S4



**Figure S4. Related to Figure 4**

- (A) Fasted body weight, fasting and clamp insulin levels, plasma glucose and glucose infusion rate during clamp in Ctrl vs hepatic PKC $\epsilon$  OE rats.
- (B) Plasma NEFA and its suppression by insulin during clamp.
- (C) Insulin-stimulated whole-body glucose turnover during clamp.
- (D) Liver triglyceride in Ctrl vs hepatic PKC $\epsilon$  OE rats.
- (E) EGP and its suppression by insulin during clamp.
- (F) Liver DAG stereoisomer content in five subcellular compartments in Ctrl vs hepatic OE rats.
- (G) Liver ceramide species content in five subcellular compartments in Ctrl vs hepatic OE rats.

In all panels, data are the mean $\pm$ S.E.M. In (F) and (G),  $n = 6$  per group. In all the other panels,  $n = 8$  per group. \* $P < 0.05$ .

# Table S1

	Hepatic Insulin Sensitive		Hepatic Insulin Resistant		<i>P</i>
	mean	SD	mean	SD	
Women/men (n)	4/4	-	2/5	-	-
Age (years)	49	14	51	10	0.347
BMI (kg/m <sup>2</sup> )	40.6	4.5	50.1	7.7	0.011
Body fat content (%)	43	6	47	8	0.292
Liver fat content (%)	3.6	1.3	16.2	5.8	0.001
Fasting plasma glucose (mmol/L)	4.7	0.3	5.9	0.7	0.001
Fasting plasma insulin (pmol/L)	100	36	221	49	<0.001
Fasting plasma triglycerides (%)	1.36	0.47	1.60	0.77	0.482
Basal EGP (μmol/kg/min)	7.1	0.9	7.5	0.9	0.377
Insulin-mediated EGP suppression (% of basal)	81	7	55	5	<0.001
Insulin-stimulated glucose Rd (% of basal)	506	137	232	67	<0.001

**Table S1. Baseline characteristics of human subjects, Related to Figure 2**