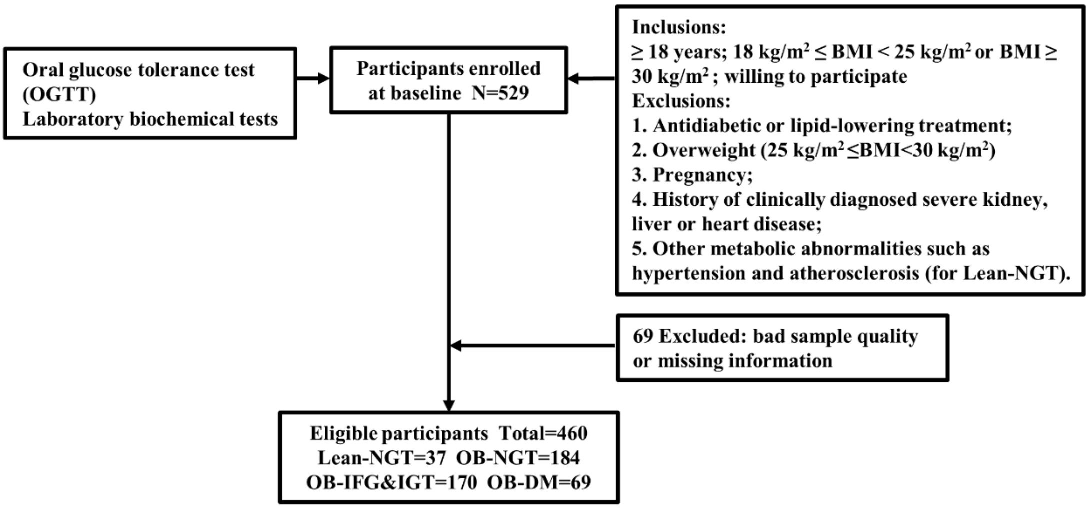
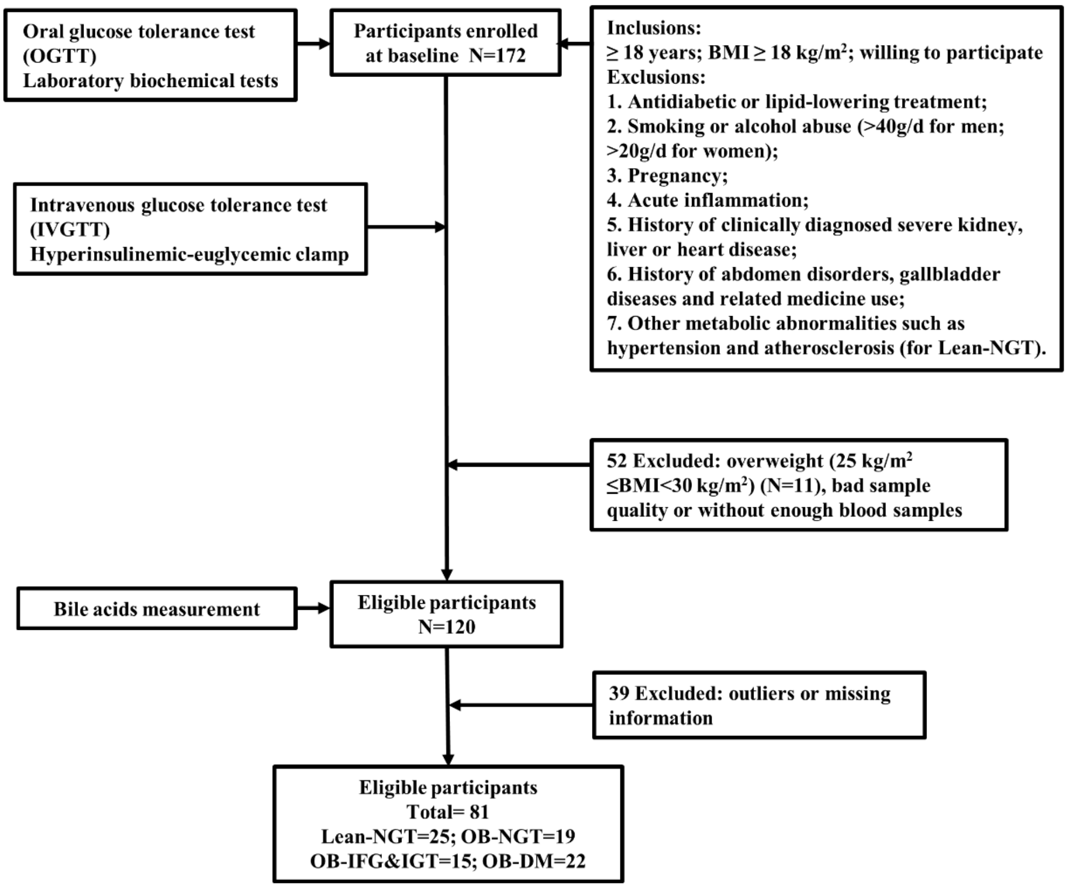
Supplementary Fig. 1 Flow diagram of participant enrollment and study design

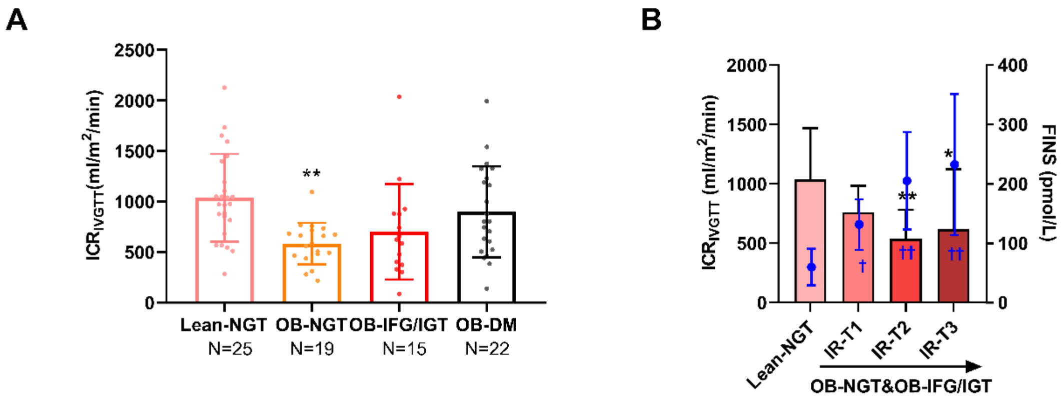
Cohort 1



Cohort 2



Supplementary Fig. 2 Insulin clearance rate during IVGTT in cohort 2



A: Insulin clearance rate measured from IVGTT among Lean-NGT, OB-NGT, OB-IFG/IGT and OB-DM groups in cohort 2. **P<0.01 vs. Lean-NGT. B: Insulin clearance rate measured from IVGTT among Lean-NGT subjects and the tertiles of nondiabetic obese subjects based on the level of insulin resistance (GIR) in cohort 2. *P<0.05, **P<0.01 vs. Lean-NGT. Blue dots represent fasting insulin levels of each tertile. †P<0.05, ††P<0.01 vs. Lean-NGT.

Supplementary Table 1. Abbreviations of Bile Acids

Bile Acids	Abbreviations
Cholic acid	CA
Chenodeoxycholic acid	CDCA
Ursocholic acid	UCA
Deoxycholic acid	DCA
Ursodeoxycholic acid	UDCA
Lithocholic acid	LCA
Isolithocholic acid	isoLCA
Hyocholic acid	HCA
Hyodeoxycholic acid	HDCA
Nor cholic acid	NorCA
Nordeoxycholic acid	NorDCA
3-dehydrocholic acid	3-DHCA
7-dehydrocholic acid	7-DHCA
Chenodeoxycholic acid-3-glucuronide	CDCA-3Gln
β-ursocholic acid	βUCA
β-ursodeoxycholic acid	βUDCA
β-chenodeoxycholic acid	βCDCA
β-cholic acid	βCA
β-Deoxycholic acid	βDCA
β-muricholic acid	βMCA
Isolithocholic acid	isoLCA
Dehydrolithocholic acid	dehydroLCA
6-ketolithocholic acid	6-ketoLCA
7-ketolithocholic acid	7-ketoLCA
12-ketolithocholic acid	12-ketoLCA
Allocholic acid	ACA
Glycocholic acid	GCA
Glycochenodeoxycholic acid	GCDCA
Glycodeoxycholic acid	GDCA
Glycohyocholic acid	GHCA
Glycolithocholic acid sulfate	GLCA-S
Glycoursodeoxycholic acid	GUDCA
Glycolithocholic acid	GLCA
Taurocholic acid	TCA
Taurochenodeoxycholic acid	TCDCA
Taurohyocholic acid	THCA
Taurodeoxycholic acid	TDCA

Bile Acids	Abbreviations
Tauroursodeoxycholic acid	TUDCA
Taurolithocholic acid	TLCA
Tauro-α-muricholic acid	TαMCA

Supplementary Table 2. Correlations among different insulin clearance measurements in cohort 2

	ICR_{Clamp}	ICR_{IVGTT}	$CpAUC_{120}/InsAUC_{120}$ (OGTT)	$CpAUC_{60}/InsAUC_{60}$ (IVGTT)
ICR_{Clamp}*	-	r=0.465	r=0.579	r=0.496
ICR_{IVGTT}*	P<0.0001	-	r=0.443	r=0.690
$CpAUC_{120}/InsAUC_{120}$† (OGTT)	P<0.0001	P=0.0006	-	r=0.654
$CpAUC_{60}/InsAUC_{60}$* (IVGTT)	P<0.0001	P<0.0001	P<0.0001	-

*Data were calculated from the IVGTT or hyperinsulinemic-euglycemic clamp (N=81).

†Data were calculated from the 4-time point OGTT (N=56).

Supplementary Table 3. Relationships between insulin clearance and main clinical parameters

Metabolic parameters	**$CpAUC_{120}/InsAUC_{120}$ (Cohort 1, N=460)**		**ICR_{Clamp} (Cohort 2, N=81)**	
	Correlation coefficients	P value	Correlation coefficients	P value
Age	**0.119***	**0.011**	-0.102	0.364
Sex	-0.029	0.529	0.020	0.859
BMI	**-0.410****	**<0.0001**	**-0.450****	**<0.0001**
ALT	**-0.331****	**<0.0001**	**-0.305****	**0.006**
AST	**-0.208****	**<0.0001**	**-0.228***	**0.040**
TC	-0.032	0.493	-0.198	0.076
TG	**-0.177****	**<0.0001**	**-0.229***	**0.040**
HDL-C	**0.234****	**<0.0001**	**0.255***	**0.022**
LDL-C	-0.027	0.567	**-0.272***	**0.014**
Lp(a)	0.031	0.511	**0.276***	**0.013**
FPG	**-0.107***	**0.022**	-0.017	0.877
2h-PG	-0.024	0.605	-0.144	0.201
FINS	**-0.515****	**<0.0001**	**-0.605****	**<0.0001**
FCP	**-0.512****	**<0.0001**	**-0.532****	**<0.0001**
GluAUC	0.008	0.860	**-0.372****	**0.001**
InsAUC	**-0.773****	**<0.0001**	**-0.507****	**0<0.0001**
CpAUC	**-0.652****	**<0.0001**	**-0.488****	**<0.0001**
$InsAUC_{30}/GluAUC_{30}$	**-0.690****	**<0.0001**	**/**	**/**
FPIR	/	/	-0.191	0.087
Matsuda index	**0.760****	**<0.0001**	/	/
GIR	/	/	**0.486****	**<0.0001**
DI	0.019	0.681	0.119	0.292

All non-normally distributed variables were Ln- transformed before analysis.

Correlation coefficients and P values were calculated by Pearson correlation analysis.

*P<0.05, **P<0.01.

BMI, body mass index; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TC, total cholesterol; TG, total triglyceride; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; Lp(a), lipoprotein (a); HbA1c, hemoglobin A1c; FPG, fasting plasma glucose; 2h-PG, 2-h postload plasma glucose; FINS, fasting serum insulin; FCP, fasting serum C-peptide; GluAUC, InsAUC and CpAUC, total areas under the curves of glucose, insulin and C-peptide during the 2-h OGTT (Cohort 1) and 1-h IVGTT (Cohort 2); FPIR, first-phase insulin response; ICR, insulin clearance rate; GIR, glucose infusion rate; DI, disposition index.

Supplementary Table 4. Multivariable linear regression analysis between ICR_{Clamp} and serum BAs in cohort 2

	Model 1		**Model 2**		**Model 3**		**Model 4**	
Bile Acids	Coefficients	P value	Coefficients	P value	Coefficients	P value	Coefficients	P value
GDCA	**-0.351**	**0.001**	**-0.333**	**0.001**	**-0.296**	**0.006**	**-0.335**	**0.004**
TDCA	**-0.351**	**0.001**	**-0.350**	**0.000**	**-0.329**	**0.002**	**-0.333**	**0.003**
βCA	**0.236**	**0.034**	0.158	0.129	0.150	0.165	0.106	0.328
GCDCA	**-0.236**	**0.034**	**-0.236**	**0.027**	**-0.216**	**0.048**	**-0.271**	**0.013**
TCDCA	**-0.250**	**0.024**	**-0.264**	**0.012**	**-0.280**	**0.010**	**-0.329**	**0.003**
βCDCA	0.269	**0.015**	0.202	0.052	**0.232**	**0.031**	0.171	0.107
TαMCA	**-0.251**	**0.024**	**-0.223**	**0.028**	-0.185	0.079	-0.147	0.171
βMCA	0.180	0.108	0.132	0.201	0.158	0.129	0.126	0.224
UDCA	0.148	0.189	0.120	0.244	0.131	0.210	0.097	0.342
βUDCA	0.207	0.064	0.153	0.142	0.161	0.125	0.147	0.155
GHCA	**-0.262**	**0.018**	**-0.229**	**0.025**	-0.193	0.063	-0.196	0.066
THCA	**-0.270**	**0.015**	**-0.235**	**0.022**	**-0.232**	**0.027**	**-0.223**	**0.042**
3_DHCA	**0.258**	**0.020**	0.166	0.112	0.183	0.095	0.199	0.063
7_DHCA	0.189	0.091	0.170	0.095	0.212	0.054	0.188	0.079
GLCA	-0.194	0.083	-0.167	0.101	-0.091	0.443	-0.068	0.587
TLCA	**-0.304**	**0.006**	**-0.308**	**0.002**	**-0.332**	**0.006**	**-0.357**	**0.005**
GLCA_S	-0.217	0.052	-0.139	0.184	-0.070	0.538	-0.072	0.538
7_ketoLCA	0.172	0.124	0.136	0.187	0.154	0.147	0.138	0.173
βUCA	-0.019	0.863	0.071	0.500	0.077	0.506	-0.023	0.842

	Model 1		Model 2		Model 3		Model 4	
Bile Acids	Coefficients	P value	Coefficients	P value	Coefficients	P value	Coefficients	P value
UCA	-0.027	0.808	0.079	0.456	0.078	0.511	-0.029	0.977
GUDCA	-0.134	0.234	-0.089	0.411	-0.076	0.487	-0.141	0.205
GCA	-0.119	0.290	-0.125	0.226	-0.145	0.163	-0.175	0.090
TUDCA	-0.149	0.185	-0.119	0.280	-0.150	0.182	-0.211	0.057
TCA	-0.170	0.128	-0.153	0.138	**-0.213**	**0.043**	**-0.244**	**0.020**
dehydroLCA	-0.042	0.712	-0.081	0.436	0.010	0.931	0.039	0.738
isoLCA	-0.065	0.564	-0.032	0.757	0.069	0.542	0.128	0.272
LCA	-0.076	0.501	-0.057	0.582	0.002	0.985	0.032	0.773
NorDCA	-0.103	0.361	-0.135	0.188	-0.043	0.701	0.056	0.633
12_ketoLCA	-0.134	0.232	-0.125	0.223	-0.060	0.587	-0.009	0.940
CDCA	0.123	0.275	0.054	0.604	0.069	0.527	0.058	0.583
DCA	-0.115	0.306	-0.085	0.413	-0.028	0.789	0.004	0.967
LCA_S	-0.041	0.713	-0.058	0.572	0.020	0.856	0.049	0.651
6_ketoLCA	0.009	0.937	-0.012	0.911	0.094	0.382	0.065	0.538
βDCA	-0.032	0.774	-0.019	0.851	0.069	0.526	0.086	0.427
HDCA	0.052	0.642	-0.036	0.725	0.082	0.481	0.049	0.683
NorCA	-0.147	0.190	-0.042	0.685	-0.034	0.759	-0.140	0.181
HCA	-0.010	0.928	-0.003	0.979	0.027	0.804	0.046	0.668
ACA	0.084	0.458	0.040	0.702	0.082	0.454	0.152	0.148
CA	0.112	0.321	0.034	0.744	0.045	0.687	0.088	0.413
CDCA_3Gln	-0.080	0.476	-0.102	0.323	-0.099	0.345	-0.115	0.262

Bile Acids	Model 1		Model 2		Model 3		Model 4	
	Coefficients	P value	Coefficients	P value	Coefficients	P value	Coefficients	P value
PBA/SBA	-0.095	0.339	-0.126	0.226	-0.193	0.076	-0.180	0.093
UnConBA/ConBA	**0.367**	**0.001**	**0.313**	**0.003**	**0.322**	**0.003**	**0.335**	**0.002**
12α OH/non-12αOH BA	-0.028	0.806	-0.027	0.797	-0.007	0.946	0.004	0.970

All non-normally distributed variables were Ln- transformed before regression analysis. Regression coefficients and P values were calculated from multivariable linear regression analysis between ICR_{Clamp} and BAs.

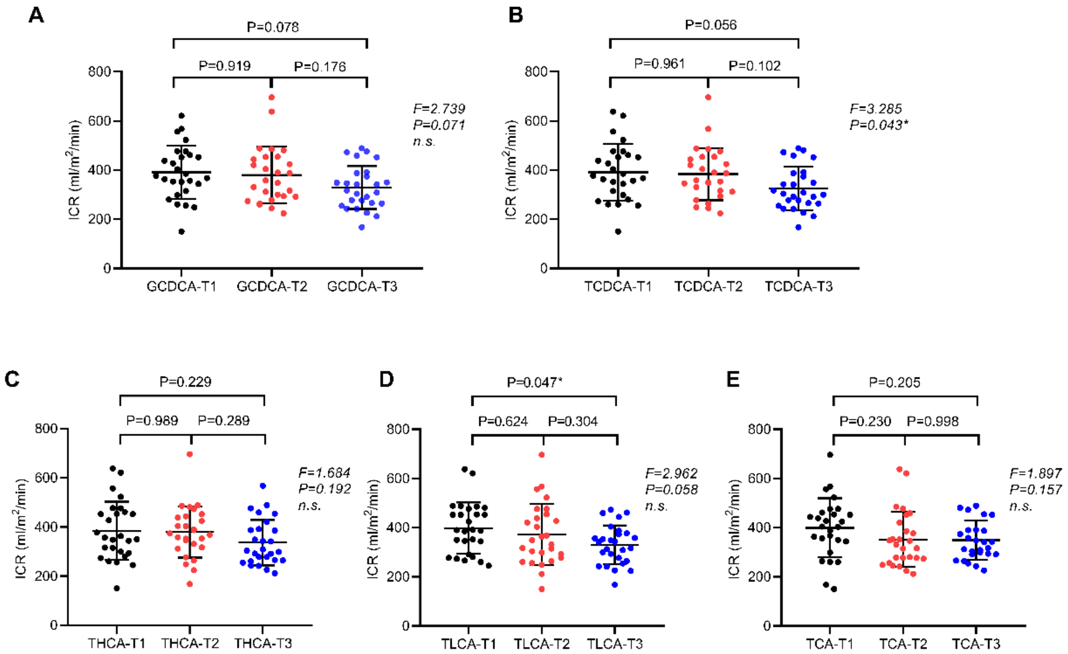
Model 1: univariable analysis with ICR_{Clamp} as dependent variable and specific BA as independent variable;

Model 2: Model 1 + age, sex and BMI adjusted;

Model 3: Model 2 + ALT, AST, and serum lipids (TG, TC, LDL-C, HDL-C and Lp(a)) adjusted;

Model 4: Model 3 + glucose metabolic parameters (FPG, FINS, FCP, GluAUC, InsAUC, CpAUC, FPIR and GIR) adjusted.

Supplementary Fig. 3 Tertile analysis between ICR_{Clamp} and correlated BAs



ICR_{Clamp} was compared across tertiles of GCDCA (A), TCDCA (B), THCA(C), TLCA (D) and TCA (E). BAs concentrations were ranked from low to high as T1 to T3. The statistical comparison was performed by one-way ANOVA and Tukey's post hoc test. *P<0.05.