SUPPLEMENTARY DATA

Supplementary Table 1. Baseline characteristics of non-diabetic participants in the IRAS by ethnicity

	Caucasians	African Americans	Hispanics	p-value
BCAA (μMols/L)	332 ± 62.8	320 ± 61.6	327 ± 60.2	0.15
Valine (μMols/L)	178 ± 35.6	171 ± 33.5	176 ± 33.7	0.10
Leucine (μMols/L)	113 ± 21.3	109 ± 22.2	110 ± 21.9	0.22
Isoleucine (μMols/L)	41.2 ± 9.21	40.3 ± 10.2	40.3 ± 9.0	0.42
Insulin sensitivity ($x10^{-4}$ min^{-1} $[\mu U/l]^{-1}$)	1.9 (1.12–3.37)	1.42 (0.85–2.44)	1.37 (0.69–2.64)	<0.0001
Fasting insulin (pmol/l)	11 (8–16)	13 (9.5–19)	15 (10–21)	<0.0001
Acute insulin response (μU/ml)	42 (23.5–69)	63.3 (31.5–94.3)	59.5 (38–99.5)	<0.0001
Metabolic clearance of insulin (l/min)	5.77 (4.39–7.57)	4.80 (3.79–6.21)	4.86 (3.60–6.56)	<0.0001

Data in means ± standard deviations or percentages or medians (interquartile ranges)

Supplementary Table 2. Baseline characteristics of non-diabetic participants in the IRAS by distribution of S_I

	Distribution of S_I			
	Lowest third	Middle third	Upper third	p-value
BCAA (μMols/L)	345 ± 61.8	329 ± 58.2	308 ± 59.6	<0.0001
Age (years)	55.3 ± 8.47	55.0 ± 8.29	54.1 ± 8.56	0.14
Male (%)	48.1	41.9	44.1	0.26
Ethnicity (%) Caucasians African Americans Hispanics	 30.0 29.4 40.7	 41.0 28.3 30.7	 49.3 20.1 30.6	 <0.001
Current smoker (%)	15.4	14.8	18.3	0.73
Current drinker (%)	75.5	71.1	76.3	0.50
Energy expenditure (kcal/kg/d)	37.7 (35.1–42.2)	38.4 (35.5–43.3)	39.1 (36.1–44.6)	0.0036
Family history of diabetes (%)	44.5	42.5	30.6	<0.001
Impaired glucose tolerance (%)	53.1	34.6	11.4	<0.001
Body mass index (kg/m^2)	31.9 ± 6.35	28.1 ± 4.33	25.3 ± 3.81	<0.0001
Waist-hip ratio	0.90 ± 0.076	0.86 ± 0.084	0.83 ± 0.084	<0.0001
Energy intake (kcal/day)	1966 ± 877	1848 ± 818	1849 ± 718	0.099
Protein intake (g/day)	79.4 ± 36.8	77.2 ± 35.7	76.3 ± 29.8	0.49
Incident diabetes (%)	26.7	16.0	4.6	<0.001

Data in means ± standard deviations or percentages or medians (interquartile ranges)

SUPPLEMENTARY DATA

Supplementary Table 3.Spearman correlation analysis among plasma BCAAs

	Total BCAA		Valine		Leucine	
	rho	p-value	rho	p-value	rho	p-value
Valine	0.95	<0.0001				
Leucine	0.92	<0.0001	0.76	<0.0001		
Isoleucine	0.90	<0.0001	0.77	<0.0001	0.89	<0.0001

Data shown is rho (r)

Supplementary Table 4. Spearman correlation analysis between plasma BCAAs with measures of insulin metabolism

	Fasting insulin	S_I	MCRI	AIR	FBG	2h pc BG
All participants	0.26**	-0.26**	-0.30**	0.068	0.23*	0.13**
Caucasians	0.31**	-0.35**	-0.36**	0.12*	0.23*	0.24**
African Americans	0.18*	-0.12	-0.24*	0.016	0.16*	-0.063
Hispanics	0.32**	-0.29**	-0.34**	0.095	0.30**	0.15*
Caucasians + Hispanics	0.29**	-0.31**	-0.33**	0.091*	0.27**	0.20**

Data shown is rho (r), **p<0.0001, *p<0.05

Supplementary Table 5. Spearman correlation analysis of individual BCAAs with measures of insulin sensitivity, secretion and clearance

	Valine		Leucine		Isoleucine	
	rho	p-value	rho	p-value	rho	p-value
Fasting insulin	0.26	<0.0001	0.23	<0.0001	0.23	<0.0001
S_I	-0.26	<0.0001	-0.22	<0.0001	-0.23	<0.0001
MCRI	-0.30	<0.0001	-0.26	<0.0001	-0.27	<0.0001
AIR	0.095	0.013	0.019	0.6	0.034	0.4

Supplementary Table 6. Estimated regression coefficients (95% confidence intervals) on the association between plasma BCAAs and S_I, stratified by ethnicity

	Beta-coefficients (95% CI)	p-value
Caucasians		
Unadjusted	-0.0031 (-0.0040, -0.0022)	<0.001
Model 1	-0.0034 (-0.0044, -0.0024)	<0.001
Model 2	-0.0028 (-0.0038, -0.0018)	<0.001
Model 3	-0.0017 (-0.0026, -0.00074)	<0.001
Hispanics		
Unadjusted	-0.0024 (-0.0035, -0.0012)	<0.001
Model 1	-0.0025 (-0.0037, -0.0012)	<0.001
Model 2	-0.0018 (-0.0030, -0.00059)	0.004
Model 3	-0.0012 (-0.0023, 0.000014)	0.053

Model 1 – adjusted for age, sex, ethnicity, study center
Model 2 – Model 1 + smoking, alcohol consumption, caloric expenditure, family history of diabetes, dietary kcal, dietary protein, fasting blood glucose
Model 3 – Model 2 + BMI

SUPPLEMENTARY DATA

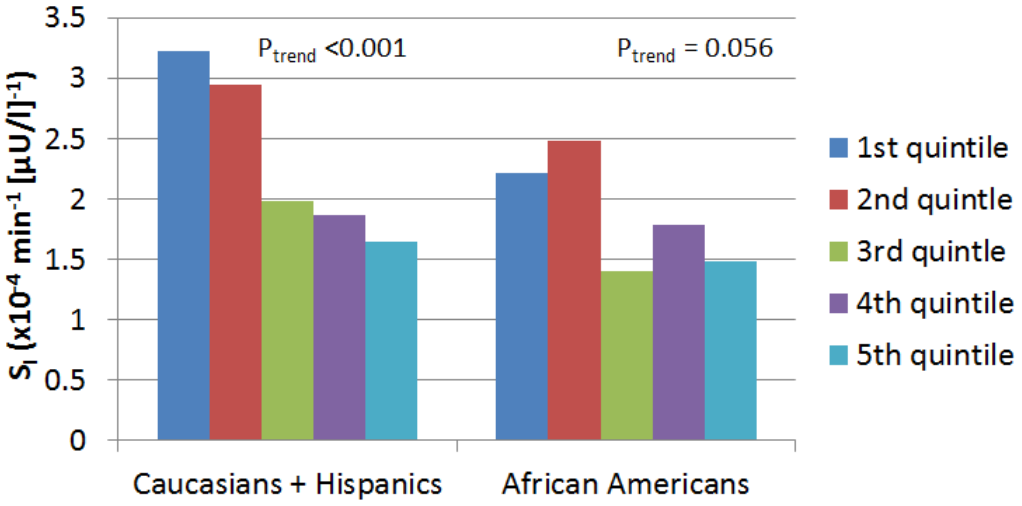
Supplementary Table 7. Estimated odds ratios (95% confidence intervals) on the association between plasma BCAAs distribution and incident diabetes

	Odds ratios (95% CI) per 1 SD increase in BCAAs	p-value
All participants		
Model 1	1.49 (1.19, 1.87)	0.001
Model 2	1.30 (1.00, 1.69)	0.050
Model 3	1.23 (0.94, 1.60)	0.131
Model 4	1.26 (0.96, 1.65)	0.094
Caucasians		
Model 1	2.15 (1.46, 3.15)	<0.001
Model 2	1.96 (1.26, 3.05)	0.003
Model 3	1.66 (1.06, 2.59)	0.027
Model 4	1.64 (1.05, 2.58)	0.031
African Americans		
Model 1	0.84 (0.52, 1.35)	0.462
Model 2	0.69 (0.36, 1.32)	0.258
Model 3	0.71 (0.37, 1.37)	0.314
Model 4	0.72 (0.37, 1.41)	0.343
Hispanics		
Model 1	1.62 (1.07, 2.46)	0.024
Model 2	1.41 (0.86, 2.33)	0.174
Model 3	1.34 (0.82, 2.22)	0.261
Model 4	1.50 (0.89, 2.53)	0.132
Caucasians + Hispanics		
Model 1	1.85 (1.41, 2.44)	<0.001
Model 2	1.67 (1.21, 2.29)	0.002
Model 3	1.52 (1.10, 2.10)	0.011
Model 4	1.57 (1.13, 2.17)	0.007

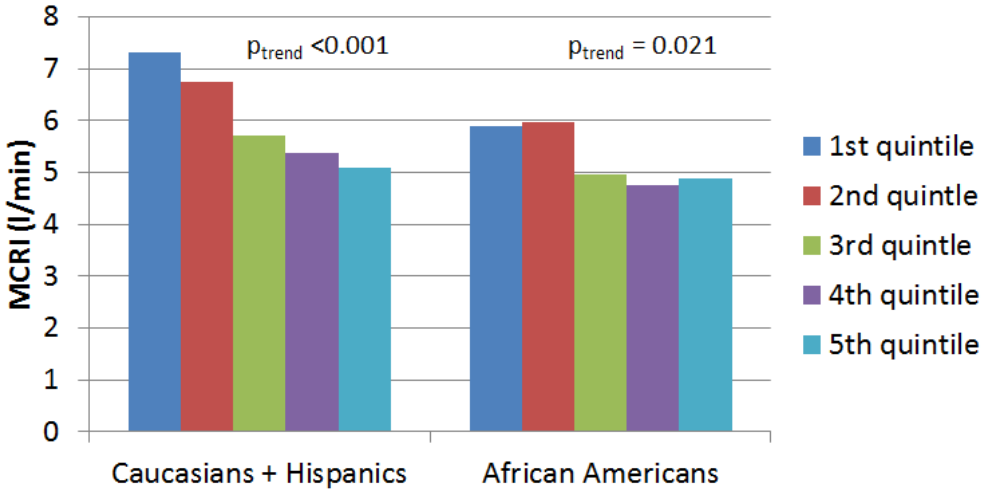
Model 1 – adjusted for age, sex, ethnicity, study center
Model 2 – Model 1 + smoking, alcohol consumption, caloric expenditure, family history of diabetes, dietary kcal, dietary protein, fasting blood glucose, BMI (fully-adjusted model)
Model 3 – Model 2 + S_I
Model 4 – Model 3 + MCRI

SUPPLEMENTARY DATA

Supplementary Figure 1. Quintile distribution of SI by ethnic groups

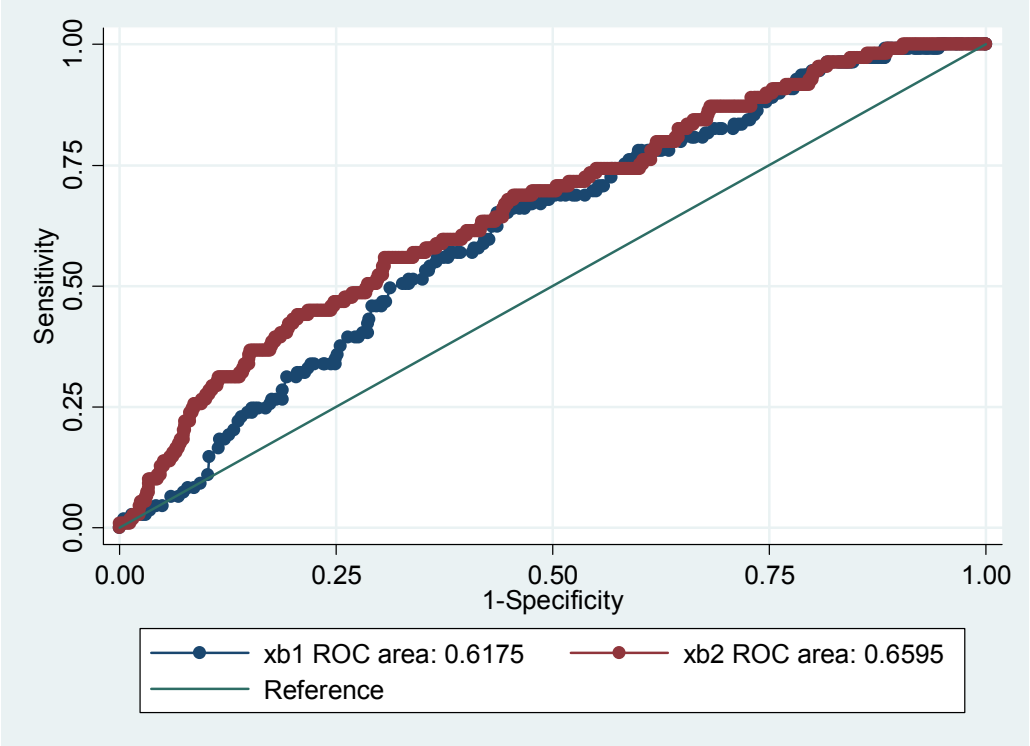


Supplementary Figure 2. Quintile distribution of MCRI by ethnic groups



SUPPLEMENTARY DATA

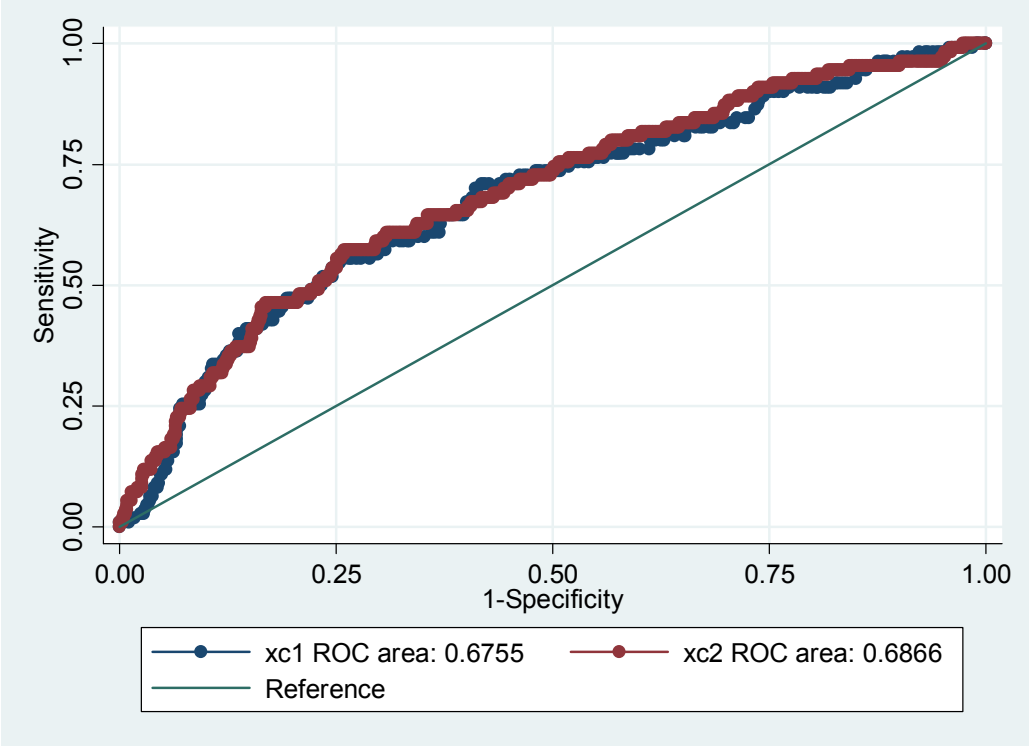
Supplementary Figure 3. Area under the receive operator characteristic curve for metabolic syndrome with or without BCAA



Xb1: age, sex, ethnicity, metabolic syndrome
Xb2: age, sex, ethnicity, metabolic syndrome, BCAA
p=0.10 comparing xb1 vs. xb2

SUPPLEMENTARY DATA

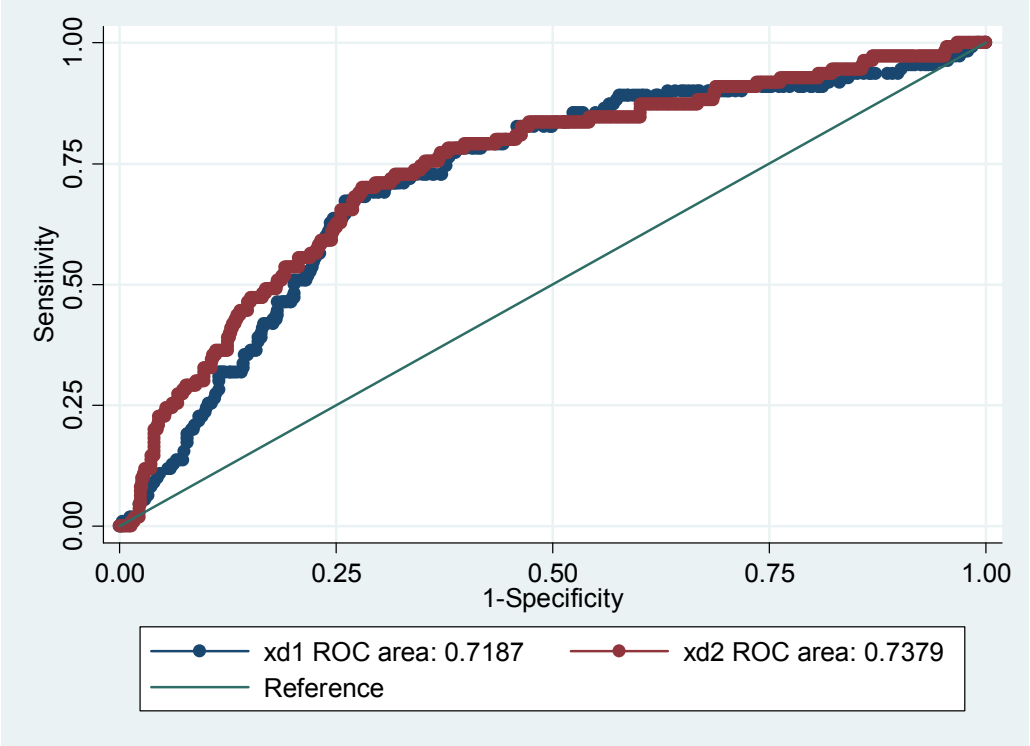
Supplementary Figure 4. Area under the receive operator characteristic curve for BMI with or without BCAA



Xc1: age, sex, ethnicity, BMI
Xc2: age, sex, ethnicity, BMI, BCAA
p=0.34 comparing xc1 vs. xc2

SUPPLEMENTARY DATA

Supplementary Figure 5. Area under the receive operator characteristic curve for IFG with or without BCAA



Xd1: age, sex, ethnicity, IFG
Xd2: age, sex, ethnicity, IFG, BCAA
p=0.25 comparing xd1 vs. xd2