SUPPLEMENTARY DATA

Supplementary Table 1. Associations of *IRS1* variants with HOMA-IR and fasting insulin in the GOLDN and BPRHS populations[1].

			GOLDN				BPRHS				Meta-analysis [2]	
Trait	SNP	Genotype	Mean ± SEM (n)	Beta (SEM)	*P* [1]		Mean ± SEM (n)	Beta (SEM)	*P* [1]		Z-score	*P*
HOMA-IR	rs7578326	AG+GG	3.44 ± 0.11 (446)	-0.013 (0.005)	0.010		5.74 ± 0.33 (501)	-0.009 (0.005)	0.069		-3.102	0.002
		AA	3.82 ± 0.14 (374)				6.06 ± 0.41 (336)					
	rs2943641	CT+TT	3.46 ± 0.10 (482)	-0.013 (0.005)	0.020		5.54 ± 0.33 (469)	-0.010 (0.005)	0.043		-3.080	0.002
		CC	3.84 ± 0.15 (338)				6.24 ± 0.39 (373)					
Insulin, mU/L	rs7578326	AG+GG	13.4 ± 0.3 (446)	-0.010 (0.003)	0.003		17.6 ± 0.7 (501)	-0.009 (0.004)	0.028		-3.648	0.0003
		AA	14.9 ± 0.5 (374)				18.7 ± 0.9 (336)					
	rs2943641	CT+TT	13.5 ± 0.3 (482)	-0.008 (0.004)	0.019		17.4 ± 0.8 (469)	-0.007 (0.004)	0.071		-2.932	0.003
		CC	14.9 ± 0.5 (338)				18.7 ± 0.9 (373)					

[1] Values are means ± SEM; SNP, single-nucleotide polymorphism; HOMA-IR, homeostasis model assessment of insulin resistance. *P*-values in GOLDN were adjusted for age, sex, waist circumference, study center, smoking status, alcohol drinking, type 2 diabetes, physical activity and family relationships. *P*-values in the BPRHS were adjusted for age, sex, waist circumference, smoking status, alcohol drinking, type 2 diabetes, physical activity, and population structure.

[2] Meta-analysis was used to combine Z statistics across GOLDN and the BPRHS, weighted by the sample size.

SUPPLEMENTARY DATA

Supplementary Table 2. Associations between *IRS1* haplotypes and risk of type 2 diabetes, impaired fasting glucose/type 2 diabetes and metabolic syndrome in GOLDN and the BPRHS[1].

Haplotype [2] (carriers vs non-carriers)	Frequency	Type 2 diabetes		IFG/T2D		Metabolic syndrome	
		Pooled odds ratio (95% CI)	*P* [3]	Pooled odds ratio (95% CI)	*P* [3]	Pooled odds ratio (95% CI)	*P* [3]
A-T	0.043	0.74 (95% CI: 0.47-1.18)	0.205	0.53 (95% CI: 0.36-0.80)	0.002	0.76 (95% CI: 0.52-1.10)	0.141
A-C	0.629	1.62 (95% CI: 1.10-2.38)	0.014	1.46 (95% CI: 1.06-2.01)	0.020	1.46 (95% CI: 1.09-1.96)	0.012
G-T	0.312	0.86 (95% CI: 0.66-1.13)	0.283	1.04 (95% CI: 0.82-1.31)	0.743	0.98 (95% CI: 0.79-1.21)	0.862
G-C	0.016	1.23 (95% CI: 0.82-1.84)	0.312	1.40 (95% CI: 0.93-2.11)	0.103	0.99 (95% CI: 0.68-1.45)	0.954

[1] Values are OR and 95% CI; IFG/T2D, impaired fasting glucose/type 2 diabetes.

[2] *IRS1* haplotypes were estimated based on 2 single-nucleotide polymorphisms in the following order: rs7578326 and rs2943641.

[3] Meta-analysis was used to combine the effect size estimates (beta coefficients) from GOLDN and the BPRHS, weighted by the inverse of the corresponding standard errors. *P*-values in GOLDN were adjusted for age, sex, study center, smoking status, alcohol drinking, physical activity and family relationships for metabolic syndrome, and were further adjusted for waist circumference for type 2 diabetes and IFG/T2D. *P*-values in the BPRHS were adjusted for age, sex, smoking status, alcohol drinking, physical activity, and population structure for metabolic syndrome, and were further adjusted for waist circumference for type 2 diabetes and IFG/T2D.

SUPPLEMENTARY DATA

Supplementary Table 3. Associations between *IRS1* haplotypes and HOMA-IR and fasting insulin in the GOLDN and BPRHS populations[1].

	Haplotype		GOLDN			BPRHS			Meta-analysis [2]	
			Mean ± SEM (n)	Beta (SEM)	*P*	Mean ± SEM (n)	Beta (SEM)	*P*	Z-score	*P*
HOMA-IR	A-T	Non-carriers	3.61 ± 0.09 (752)	-0.005 (0.009)	0.576	5.97 ± 0.27 (760)	0.008 (0.008)	0.338	0.290	0.772
		Carriers	3.72 ± 0.27 (68)			4.76 ± 0.53 (84)				
	A-C	Non-carriers	3.20 ± 0.18 (113)	-0.004 (0.007)	0.514	4.54 ± 0.37 (143)	-0.012 (0.007)	0.074	-1.731	0.084
		Carriers	3.68 ± 0.10 (707)			6.11 ± 0.29 (701)				
	G-T	Non-carriers	3.80 ± 0.14 (386)	0.013 (0.005)	0.012	5.97 ± 0.35 (426)	0.007 (0.005)	0.139	2.817	0.005
		Carriers	3.45 ± 0.11 (434)			5.72 ± 0.37 (418)				
	G-C	Non-carriers	3.63 ± 0.09 (795)	0.005 (0.011)	0.679	5.97 ± 0.29 (712)	0.011 (0.007)	0.121	1.395	0.163
		Carriers	3.20 ± 0.35 (25)			5.16 ± 0.47 (132)				
Insulin, mU/L	A-T	Non-carriers	14.0 ± 0.3 (752)	-0.006 (0.006)	0.329	18.1 ± 0.6 (760)	0.004 (0.007)	0.534	-0.242	0.809
		Carriers	14.5 ± 0.9 (68)			16.6 ± 1.5 (84)				
	A-C	Non-carriers	12.5 ± 0.6 (113)	-0.006 (0.005)	0.258	15.7 ± 1.1 (143)	-0.012 (0.005)	0.029	-2.349	0.019
		Carriers	14.3 ± 0.3 (707)			18.4 ± 0.6 (701)				
	G-T	Non-carriers	14.8 ± 0.5 (386)	0.009 (0.003)	0.005	18.2 ± 0.8 (426)	0.006 (0.004)	0.119	3.072	0.002
		Carriers	13.4 ± 0.4 (434)			17.7 ± 0.8 (418)				
	G-C	Non-carriers	14.1 ± 0.3 (795)	0.008 (0.010)	0.431	18.3 ± 0.6 (712)	0.012 (0.006)	0.030	2.098	0.036
		Carriers	12.9 ± 1.5 (25)			16.0 ± 1.1 (132)				

[1] Values are means ± SEM; *IRS1* haplotypes were estimated based on 2 single-nucleotide polymorphisms in the following order: rs7578326 and rs2943641. *P*-values in GOLDN were adjusted for age, sex, waist circumference, study center, smoking status, alcohol drinking, type 2 diabetes, physical activity and family relationships. *P*-values in the BPRHS were adjusted for age, sex, waist circumference, smoking status, alcohol drinking, type 2 diabetes, physical activity, and population structure.

[2] Meta-analysis was used to combine Z statistics across GOLDN and the BPRHS, weighted by the sample size.

SUPPLEMENTARY DATA

Supplementary Table 4. Interaction of *IRS1* haplotype G-T with diet on HOMA-IR and risk of metabolic syndrome in the GOLDN population[1].

Diet	Total energy, %	HOMA-IR					Metabolic syndrome		
		G-T carriers (n)	G-T non-carriers (n)	*P*-trend[2]	*P*-interaction[2]		Odds ratio (95% CI) (G-T carriers vs non-carriers)	*P*-trend[3]	*P*-interaction[3]
MUFA	≤ 13.2	3.24 ± 0.13 (212)	3.82 ± 0.21 (197)	0.002	0.051		0.66 (95% CI: 0.42-1.01)	0.058	0.057
	> 13.2	3.66 ± 0.17 (220)	3.77 ± 0.19 (189)	0.759			1.27 (95% CI: 0.77-2.08)	0.347	
SFA	≤ 11.8	3.23 ± 0.14 (210)	3.92 ± 0.19 (199)	0.001	0.031		0.67 (95% CI: 0.44-1.02)	0.063	0.056
	> 11.8	3.66 ± 0.16 (222)	3.67 ± 0.20 (187)	0.856			1.17 (95% CI: 0.75-1.82)	0.486	
Total fat	≤ 35.7	3.16 ± 0.12 (209)	3.78 ± 0.18 (200)	0.003	0.067		0.61 (95% CI: 0.40-0.95)	0.029	0.032
	> 35.7	3.73 ± 0.18 (223)	3.82 ± 0.22 (186)	0.795			1.26 (95% CI: 0.77-2.06)	0.358	
Carbohydrate	≤ 49.1	3.70 ± 0.17 (230)	3.78 ± 0.23 (179)	0.691	0.007		1.38 (95% CI: 0.84-2.25)	0.204	0.008
	> 49.1	3.18 ± 0.12 (202)	3.82 ± 0.17 (207)	0.0005			0.57 (95% CI: 0.38-0.86)	0.008	
SFA-to-carbohydrate ratio	≤ 0.24	3.10 ± 0.12 (201)	3.86 ± 0.17 (208)	0.0001	0.005		0.51 (95% CI: 0.34-0.79)	0.002	0.002
	> 0.24	3.77 ± 0.17 (231)	3.73 ± 0.23 (178)	0.572			1.49 (95% CI: 0.89-2.49)	0.126	

[1] Values are means ± SEM or OR and 95% CI; MUFA, monounsaturated fatty acid; SFA, saturated fatty acid. *IRS1* haplotypes were estimated based on 2 single-nucleotide polymorphisms in the following order: rs7578326 and rs2943641.

[2] *P*-values were adjusted for age, sex, waist circumference, study center, smoking status, alcohol drinking, type 2 diabetes, physical activity and family relationships.

[3] *P*-values were adjusted for age, sex, study center, smoking status, alcohol drinking, physical activity and family relationships.

SUPPLEMENTARY DATA

Supplementary Table 5. Interaction of *IRS1* haplotype A-C with dietary glycemic load and glycemic index on risk of metabolic syndrome in the GOLDN and BPRHS populations [1].

	Diet	Odds ratio (95% CI) (A-C non-carriers vs carriers)	*P*-trend	*P*-interaction
GOLDN	Low glycemic load (≤ 111.5)	0.38 (95% CI: 0.18-0.63)	0.0002	0.006
	High glycemic load (> 111.5)	1.36 (95% CI: 0.10-2.84)	0.419	
	Low glycemic index (≤ 49.1)	0.58 (95% CI: 0.19-1.10)	0.094	0.918
	High glycemic index (> 49.1)	0.63 (95% CI: 0.18-1.17)	0.143	
BPRHS	Low glycemic load (≤ 141.2)	0.70 (95% CI: 0.39-1.26)	0.235	0.77
	High glycemic load (> 141.2)	0.78 (95% CI: 0.46-1.33)	0.364	
	Low glycemic index (≤ 57.1)	0.50 (95% CI: 0.28-0.87)	0.014	0.034
	High glycemic index (> 57.1)	1.15 (95% CI: 0.65-2.03)	0.641	

[1] Values are odds ratio and 95% CI; *IRS1* haplotypes were estimated based on 2 single-nucleotide polymorphisms in the following order: rs7578326 and rs2943641. *P*-values in GOLDN were adjusted for age, sex, study center, smoking status, alcohol drinking, physical activity and family relationships. *P*-values in the BPRHS were adjusted for age, sex, smoking status, alcohol drinking, physical activity, and population structure.