

SUPPLEMENTARY DATA

Supplementary Table 1. Observed associations between instrumental variables and insulin sensitivity.

Instrumental variable	Beta (95% CI)	P – value
Age adjusted		
rs17300539	0.096 (0.014, 0.179)	0.022
rs3774261	0.074 (0.028, 0.121)	1.9×10^{-3}
rs6444175	0.091 (0.041, 0.141)	3.7×10^{-4}
Allele score	0.242 (0.101, 0.384)	8.0×10^{-4}
Age, BMI and waistR adjusted		
rs17300539	0.048 (-0.019, 0.115)	0.157
rs3774261	0.036 (-0.002, 0.073)	0.061
rs6444175	0.053 (0.012, 0.093)	0.011
Allele score	0.119 (0.005, 0.234)	0.042

BMI, body mass index; waistR, waist residual, i.e. BMI-adjusted waist circumference.

Supplementary Table 2. Secondary analyses including individuals with type 2 diabetes (N = 1,057), age-adjusted results.

Instrumental variable	First stage F statistic	Instrumental variable estimate		Observational estimate		Endogeneity† P-value
		Beta (95% CI)	P-value	Beta (95% CI)	P-value	
rs17300539	49.8	0.549 (0.179, 0.920)	3.7×10^{-3}	0.612 (0.533, 0.690)	1.7×10^{-47}	0.736
rs3774261	33.4	0.620 (0.171, 1.068)	6.9×10^{-3}			0.972
rs6444175	31.6	0.722 (0.260, 1.185)	2.2×10^{-3}			0.632
Allele score*	55.9	0.591 (0.241, 0.942)	9.7×10^{-4}			0.908

*The allele score was created using genotypes for rs17300539 and rs3774261 ($R^2 = 0.137$).

†Endogeneity was assessed by Durbin-Wu-Hausman test and reflects whether the difference between the IV estimate and the observational estimate was statistically significant.

Supplementary Table 3. Association between instrumental variables and body mass index (BMI).

	Age adjusted		Age and adiponectin adjusted	
	Beta (95% CI)	P-value	Beta (95% CI)	P-value
rs17300539	-0.47 (-1.00, 0.06)	0.084	0.06 (-0.46, 0.58)	0.815
rs3774261	-0.42 (-0.72, -0.12)	0.006	-0.15 (-0.44, 0.15)	0.330
rs6444175	-0.44 (-0.77, -0.12)	0.008	-0.15 (-0.47, 0.16)	0.337
Allele score	-1.32 (-2.24, -0.41)	0.005	-0.29 (-1.20, -0.61)	0.522

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Supplementary Table 4. Comparison of instrumental variable estimated and observed association between adiponectin and insulin sensitivity, stratified by overweight status defined by median BMI.

Instrumental variable	First stage F statistic	Instrumental variable estimate		Observational estimate		Endogeneity† P-value
		Beta (95% CI)	P-value	Beta (95% CI)	P-value	
Normal weight (BMI < 25.7 kg/m ²), N = 471						
rs17300539	25.4	0.459 (0.061, 0.858)	0.024	0.228 (0.140, 0.316)	5.9 × 10 ⁻⁷	0.230
rs3774261	16.0	0.199 (-0.285, 0.684)	0.420			0.902
rs6444175	13.2	0.476 (-0.073, 1.025)	0.090			0.354
Allele score*	27.5	0.309 (-0.066, 0.684)	0.107			0.662
Overweight (BMI ≥ 25.7 kg/m ²), N = 471						
rs17300539	16.2	0.244 (-0.418, 0.907)	0.470	0.526 (0.407, 0.645)	7.5 × 10 ⁻¹⁷	0.386
rs3774261	14.9	0.746 (0.060, 1.432)	0.033			0.517
rs6444175	15.4	0.719 (0.048, 1.390)	0.036			0.562
Allele score	22.2	0.564 (0.006, 1.121)	0.048			0.892

*The allele score was created using genotypes for rs17300539 and rs3774261 ($R^2 = 0.137$). †Endogeneity was assessed by Durbin-Wu-Hausman test and reflects whether the difference between the IV estimate and the observational estimate was statistically significant.

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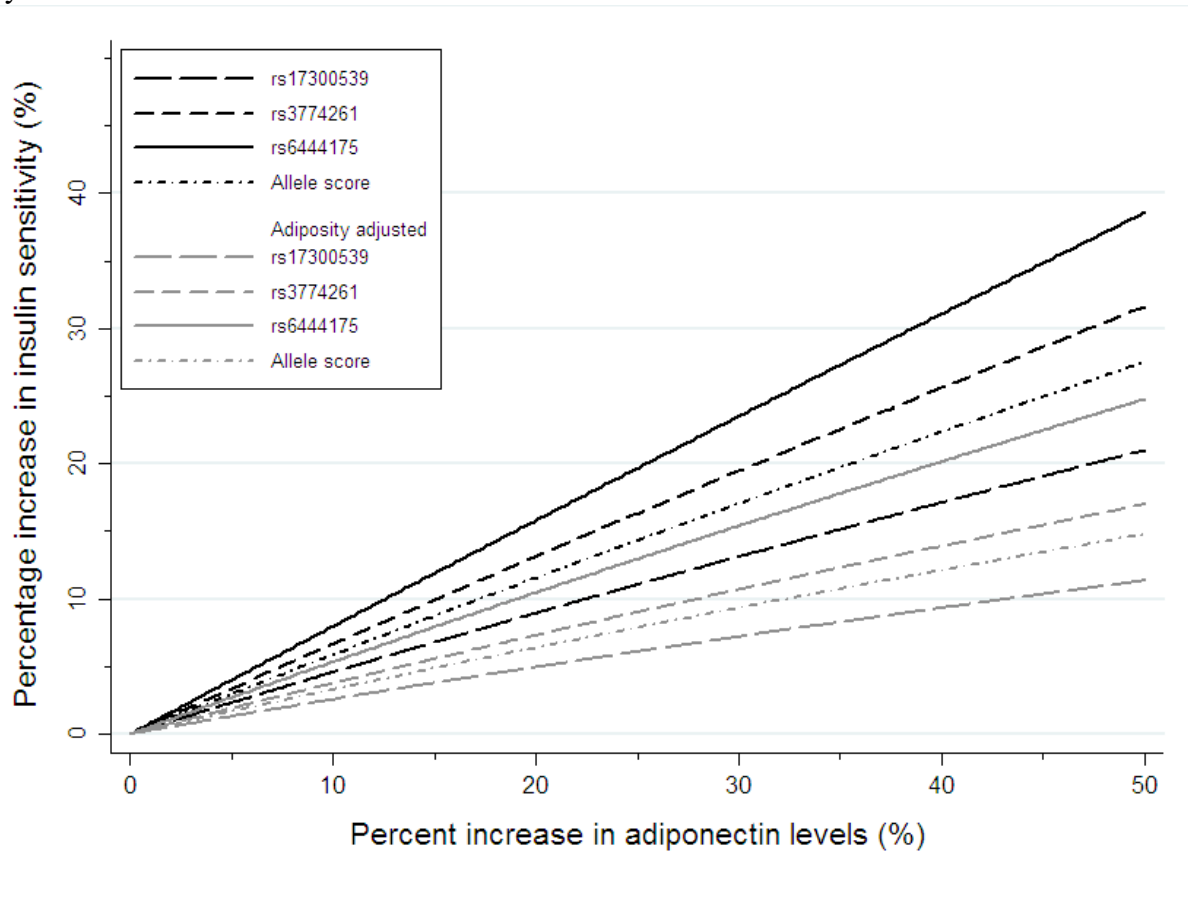
Supplementary Table 5. Effect size comparison between ULSAM cohort and other studies for the SNPs used as instrumental variables.

SNP	N	Effect allele	Effect* (95% CI)	P-value	Adjustment	Reference
rs17300539	942	A	0.205 (0.144, 0.267)	1.1×10^{-10}	Age adjusted	Current study
			0.188 (0.128, 0.247)	8.1×10^{-10}	Age, BMI and waistR adjusted	
	1,919	A	0.155 (0.077, 0.233)	9.3×10^{-5}	Age, sex and BMI adjusted	[1]
rs3774261	941	A	0.109 (0.074, 0.144)	1.3×10^{-9}	Age adjusted	Current study
			0.092 (0.059, 0.126)	8.0×10^{-8}	Age, BMI and waistR adjusted	
	11,519	A	0.04 (no CI reported)	4.7×10^{-8}	Not mentioned	[2]
rs6444175	942	A	0.113 (0.076, 0.151)	5.3×10^{-9}	Age adjusted	Current study
			0.098 (0.061, 0.134)	1.5×10^{-7}	Age, BMI and waistR adjusted	
	14,733	G	-0.08 (-0.1, -0.07)	1.2×10^{-21}	Age, sex and BMI adjusted	[3]

* All the results reported are based on natural log-transformed adiponectin.

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Supplementary Figure 1. Instrumental variable estimated percent change in insulin sensitivity with varying percent change in adiponectin levels. The instrumental variable point estimates were used to calculate the change in insulin sensitivity when adiponectin changes by a certain percentage. The black lines are based on age adjusted results: rs17300539, black long dash; rs3774261, black dash; rs6444175, black solid; allele score, black short dash with dot. Grey lines are the results further adjusted for adiposity.



- [1] Henneman, P., Y. S. Aulchenko, et al. (2010). "Genetic architecture of plasma adiponectin overlaps with the genetics of metabolic syndrome-related traits." *Diabetes Care* 33(4): 908-913.
- [2] Warren, L. L., L. Li, et al. (2012). "Deep Resequencing Unveils Genetic Architecture of ADIPOQ and Identifies a Novel Low-Frequency Variant Strongly Associated With Adiponectin Variation." *Diabetes* 61(5): 1297-1301.
- [3] Abecasis, G. R., J. B. Richards, et al. (2009). "A Genome-Wide Association Study Reveals Variants in ARL15 that Influence Adiponectin Levels." *PLoS Genetics* 5(12): e1000768.