Supplementary Table 1: MR analyses of anthropometric and metabolic conditions as exposures and corrected insulin response (CIR) as outcome

Method	β	Standard Error	p	Egger-Intercept	p_{Egger}	Cochrane's Q	Q df	p_Q	I^2
Body Mass Index									
MR Egger	0.008	0.177	0.963	0.001	0.8	447.574	440	0.391	1.692
Weighted median	0.001	0.111	0.992						
Inverse variance weighted	0.05	0.068	0.461			447.639	441	0.403	1.483
Simple mode	0.048	0.31	0.876						
Weighted mode	-0.036	0.182	0.844						
Coronary Artery Disease									
MR Egger	-0.096	0.132	0.476	0.014	0.388	22.015	16	0.143	27.321
Weighted median	-0.046	0.067	0.499						
Inverse variance weighted	0.009	0.057	0.875			23.099	17	0.146	26.403
Simple mode	0.007	0.11	0.948						
Weighted mode	-0.028	0.068	0.688						
High-Density Lipoprotein									
MR Egger	-0.056	0.135	0.677	-0.001	0.762	127.501	107	0.086	16.079
Weighted median	-0.022	0.136	0.871						
Inverse variance weighted	-0.087	0.089	0.327			127.611	108	0.096	15.367
Simple mode	0.177	0.306	0.565						
Weighted mode	0.011	0.122	0.928						
Hypertension									
MR Egger	-9.604	4.53	0.05	0.056	0.03	11.858	16	0.754	-34.93
Weighted median	-0.196	1.33	0.883						
Inverse variance weighted	0.929	1.021	0.363			17.545	17	0.418	3.104
Simple mode	-0.766	2.097	0.719						

Weighted mode	-0.575	1.909	0.767						
Leg Fat Percent Left									
MR Egger	-0.732	0.716	0.309	0.006	0.439	119.988	132	0.765	-10.011
Weighted median	-0.461	0.271	0.089						
Inverse variance weighted	-0.197	0.191	0.304			120.589	133	0.772	-10.292
Simple mode	-0.418	0.734	0.57						
Weighted mode	-0.549	0.538	0.31						
Leg Fat Percent Right									
MR Egger	-0.409	0.568	0.473	0.004	0.474	132.247	128	0.381	3.212
Weighted median	-0.172	0.328	0.599						
Inverse variance weighted	-0.024	0.188	0.9			132.78	129	0.392	2.847
Simple mode	-0.25	0.753	0.741						
Weighted mode	-0.283	0.423	0.505						
Liver Fat									
MR Egger									
Weighted median									
Inverse variance weighted	-0.035	0.321	0.914			0.157	1	0.692	-537.273
Simple mode									
Weighted mode									
Type 2 Diabetes									
MR Egger	-0.358	0.091	<0.001	0.012	0.088	155.47	95	0	38.895
Weighted median	-0.231	0.066	<0.001						
Inverse variance weighted	-0.218	0.041	<0.001			160.344	96	0	40.129
Simple mode	0.13	0.172	0.451						
Weighted mode	-0.237	0.074	0.002						
Triglycerides									

MR Egger	-0.133	0.154	0.389	0.004	0.306	127.283	99	0.029	22.221
Weighted median	-0.137	0.143	0.339						
Inverse variance weighted	-0.012	0.099	0.906			128.642	100	0.028	22.265
Simple mode	-0.672	0.327	0.042						
Weighted mode	-0.11	0.125	0.378						
BMI-Adjusted Waist-Hip Ratio									
MR Egger	-0.127	0.32	0.691	0.006	0.355	172.572	140	0.032	18.874
Weighted median	0.344	0.165	0.037						
Inverse variance weighted	0.151	0.112	0.177			173.633	141	0.032	18.794
Simple mode	0.608	0.417	0.147						
Weighted mode	0.582	0.408	0.155						

Supplementary Table 2: Phenome wide association study for GIPR variant rs11671664

Reported Trait	Study N Initial	Study N Replication	P-Value	Beta	Beta CI Lower	Beta CI Upper	PMID
Body mass index	158,284	337,300	3.00E-42	-0.040	-0.046	-0.034	28892062
Body mass index	27,715	55,333	6.00E-14	-4.220	-5.322	-3.118	22344219
Body mass index (SNP x SNP interaction)	26,620	35,625	7.00E-14	-0.046	-0.058	-0.034	22344221
Body mass index	86,739	47,352	3.00E-12	-0.041	-0.052	-0.029	24861553
Type 2 diabetes	183,651	82,027	3.00E-12	0.076	0.055	0.097	28869590
2h-glucose post OGTT[a]	11,268	30,620	1.98E-15	0.094	0.082	0.106	20081857
2h-glucose post OGTT (adjusted fasting-glucose)[a]	11,066	29,762	2.56E-20	0.107	0.095	0.118	20081857

[a]Beta provided is for the insulin-reducing allele, GIPR-A, for rs10423928. The insulin-increasing allele of rs10423928, GIPR-T, is in LD with rs11671664 with r^2=0.39: (https://ldlink.nci.nih.gov/?var=rs11671664&pop=GBR&genome_build=grch37&r2_d=r2&window=500000&collapseTranscript=true&tab=ldproxy, accessed January 22, 2022)

SNP = single nucleotide polymorphism; OGTT = oral glucose tolerance test

Supplementary Table 3: Phenome wide association study for CDKAL1 variant rs7756992

Reported Trait	Study N Initial	Study N Replication	P-Value	Beta	Beta CI Lower	Beta CI Upper	Odds Ratio	Odds Ratio CI Lower	Odds Ratio CI Upper	PMID
Type 2 diabetes	1114458		6.00E-128	0.12	0.11	0.13				32541925
Type 2 diabetes	898130		2.00E-88				1.15	1.13	1.17	30297969
Type 2 diabetes	659316		6.00E-62				1.14	1.12	1.16	30054458
Type 2 diabetes (adjusted for BMI)	298957		1.33E-61				1.11	1.10	1.13	29632382
Type 2 diabetes	298957		1.22E-41				1.11	1.09	1.13	29632382
Type 2 diabetes	459000		5.00E-31							30595370
Type 2 diabetes	110452	77138	2.00E-26				1.20	1.16	1.24	24509480
Birth weight (MTAG)	182902		3.00E-25	-0.04	-0.05	-0.04				31681408
Psoriasis or type 2 diabetes (trans-disease meta-analysis)	925490		2.00E-20				1.11	1.09	1.13	33385400
Birth length (MTAG)	182902		1.00E-19	-0.06	-0.07	-0.05				31681408
Glycated hemoglobin levels	88355		3.00E-12	0.01	0.01	0.02				28898252
Type 2 diabetes	8686	9461	8.00E-09				1.20	1.13	1.28	17460697
Type 2 diabetes [additive model]	117775		1.00E-08				1.15	1.10	1.21	26961502
Infant head circumference (MTAG)	182902		2.00E-08	-0.07	-0.09	-0.04				31681408

Supplementary Table 4: Instrument used for corrected insulin response adjusted for insulin sensitivity (CIRadjISI)

SNP	Gene	Effect Allele	Other Allele	EAF	beta	se
rs7756992	*CDKAL1*	G	A	0.27	-0.11	0.016
rs1111875	HHEX	C	T	0.59	-0.1	0.015
rs4502156	*C2CD4A/ NLF1/ VPS13C*	T	C	0.57	-0.092	0.015

SNP=single nucleotide polymorphism, Gene=nearest gene, EAF=effect allele frequency, beta=regression coefficient, se=standard error of regression coefficient

Supplementary Table 5: MR analyses of corrected insulin response adjusted for insulin sensitivity (CIRadjISI) as exposure and anthropometric and metabolic traits as outcomes

Method	β	Standard Error	p	Egger-Intercept	p_{Egger}	Cochrane's Q	Q df	p_Q	I^2
Body Mass Index									
MR Egger	0.622	0.134	0.135	-0.059	0.142	0.262	1	0.609	-281.853
Weighted median	0.031	0.016	0.062						
Inverse variance weighted	0.033	0.03	0.268			19.756	2	<0.001	89.876
Simple mode	0.049	0.026	0.206						
Weighted mode	0.039	0.026	0.27						
High-Density Lipoprotein									
MR Egger	0.266	0.542	0.709	-0.023	0.746	11.444	1	<0.001	91.261
Weighted median	0.027	0.018	0.145						
Inverse variance weighted	0.038	0.03	0.204			13.482	2	<0.001	85.166
Simple mode	0.021	0.028	0.524						
Weighted mode	0.019	0.026	0.551						
Leg Fat Percent Left									
MR Egger	0.087	0.106	0.562	-0.006	0.683	0.855	1	0.355	-16.96
Weighted median	0.029	0.01	0.002						
Inverse variance weighted	0.03	0.008	0			1.15	2	0.563	-73.925
Simple mode	0.031	0.012	0.129						
Weighted mode	0.028	0.012	0.15						
Leg Fat Percent Right									
MR Egger	0.09	0.107	0.554	-0.006	0.672	0.441	1	0.507	-126.996
Weighted median	0.028	0.01	0.004						
Inverse variance weighted	0.03	0.008	<0.001			0.761	2	0.683	-162.701

Simple mode	0.027	0.012	0.159						
Weighted mode	0.026	0.012	0.164						
Liver Fat									
MR Egger	-0.224	2.028	0.93	0.019	0.941	9.867	1	0.002	89.865
Weighted median	0.045	0.069	0.509						
Inverse variance weighted	-0.036	0.103	0.728			9.953	2	0.007	79.905
Simple mode	0.073	0.078	0.448						
Weighted mode	0.07	0.078	0.462						
Triglycerides									
MR Egger	-0.769	0.268	0.213	0.069	0.237	2.572	1	0.109	61.121
Weighted median	-0.084	0.018	<0.001						
Inverse variance weighted	-0.085	0.037	0.023			19.44	2	<0.001	89.712
Simple mode	-0.12	0.024	0.038						
Weighted mode	-0.119	0.031	0.063						
BMI-Adjusted Waist-Hip Ratio									
MR Egger	-0.855	0.658	0.418	0.081	0.437	21.609	1	<0.001	95.372
Weighted median	-0.072	0.018	<0.001						
Inverse variance weighted	-0.053	0.053	0.316			53.886	2	<0.001	96.288
Simple mode	-0.101	0.018	0.03						
Weighted mode	-0.099	0.018	0.032						

Supplementary Table 6: MR analyses of corrected insulin response adjusted for insulin sensitivity (CIRadjISI) as exposure and categorical traits (Coronary Artery Disease, Hypertension, Type 2 Diabetes) as outcomes

Method	β	Standard Error	p	Odds Ratio (95% CI)	Egger-Intercept	p_{Egger}	Cochrane's Q	Q df	p_Q	I^2
Coronary Artery Disease										
MR Egger	-2.206	1.186	0.314	0.110 (0.011, 1.127)	0.206	0.333	0.497	1	0.481	-101.023
Weighted median	-0.228	0.113	0.044	0.796 (0.641, 0.989)						
Inverse variance weighted	-0.156	0.112	0.163	0.063 (0.855, 0.687)			3.497	2	0.174	42.812
Simple mode	-0.26	0.148	0.221	0.771 (0.581, 1.024)						
Weighted mode	-0.258	0.156	0.24	0.772 (0.578, 1.033)						
Hypertension										
MR Egger	-0.091	0.176	0.696	0.913 (0.646, 1.289)	0.009	0.702	9.899	1	0.002	89.898
Weighted median	-0.004	0.007	0.562	0.996 (0.983, 1.009)						
Inverse variance weighted	-0.003	0.01	0.801	0.997 (0.978, 1.017)			12.425	2	0.002	83.904
Simple mode	-0.008	0.01	0.521	0.992 (0.972, 1.012)						
Weighted mode	-0.007	0.011	0.576	0.993 (0.971, 1.015)						
Type 2 Diabetes										
MR Egger	-4.897	0.948	0.122	0.007, (0.001, 0.048)	0.404	0.147	2.554	1	0.11	60.851

Weighted median	-0.72	0.095	<0.001	0.487 (0.403, 0.589)						
Inverse variance weighted	-0.887	0.21	<0.001	0.412 (0.273, 0.621)			48.472	2	<0.001	95.874
Simple mode	-1.041	0.187	0.031	0.353 (0.244, 0.510)						
Weighted mode	-0.49	0.129	0.063	0.613 (0.491, 0.765)						

Supplementary Table 7. MR analyses of anthropometric and metabolic conditions as exposures and corrected insulin response adjusted for insulin sensitivity (CIRadjISI) as outcome

Method	β	Standard Error	p	Egger-Intercept	p_{Egger}	Cochrane's Q	Q df	p_Q	I^2
Body Mass Index									
MR Egger	0.039	0.187	0.835	0	0.998	443.688	440	0.442	0.831
Weighted median	-0.051	0.124	0.68						
Inverse variance weighted	0.039	0.071	0.59			443.688	441	0.455	0.606
Simple mode	-0.153	0.319	0.631						
Weighted mode	-0.071	0.201	0.725						
Coronary Artery Disease									
MR Egger	-0.148	0.158	0.364	0.018	0.362	28.509	16	0.027	43.876
Weighted median	-0.076	0.072	0.29						
Inverse variance weighted	-0.015	0.069	0.833			30.077	17	0.026	43.478
Simple mode	0.012	0.113	0.914						
Weighted mode	-0.062	0.073	0.402						
High-Density Lipoprotein									
MR Egger	-0.099	0.137	0.472	0.001	0.814	118.475	107	0.211	9.686
Weighted median	0.021	0.139	0.879						
Inverse variance weighted	-0.075	0.09	0.41			118.537	108	0.23	8.889
Simple mode	0.107	0.308	0.729						
Weighted mode	-0.002	0.128	0.985						
Hypertension									
MR Egger	-8.389	4.82	0.101	0.053	0.05	10.698	16	0.828	-49.557
Weighted median	1.143	1.421	0.421						
Inverse variance weighted	1.569	1.075	0.144			15.19	17	0.582	-11.915
Simple mode	0.38	2.21	0.865						

Weighted mode	0.061	2.13	0.978						
Leg Fat Percent Left									
MR Egger	-0.772	0.759	0.311	0.007	0.373	121.152	132	0.741	-8.954
Weighted median	-0.115	0.289	0.691						
Inverse variance weighted	-0.119	0.203	0.558			121.949	133	0.744	-9.062
Simple mode	-0.302	0.756	0.69						
Weighted mode	-0.227	0.593	0.703						
Leg Fat Percent Right									
MR Egger	-0.596	0.591	0.315	0.007	0.286	129.508	129	0.471	0.392
Weighted median	-0.182	0.34	0.592						
Inverse variance weighted	0.001	0.196	0.996			130.659	130	0.467	0.505
Simple mode	-0.466	0.674	0.491						
Weighted mode	-0.278	0.469	0.554						
Liver Fat									
MR Egger									
Weighted median									
Inverse variance weighted	-0.065	0.34	0.847			0.026	1	0.873	-3820.94
Simple mode									
Weighted mode									
Type 2 Diabetes									
MR Egger	-0.369	0.089	<0.001	0.012	0.074	130.029	95	0.01	26.939
Weighted median	-0.215	0.07	0.002						
Inverse variance weighted	-0.226	0.04	<0.001			134.482	96	0.006	28.615
Simple mode	-0.108	0.168	0.522						
Weighted mode	-0.183	0.074	0.015						
Triglycerides									

MR Egger	-0.113	0.146	0.44	0.003	0.506	102.388	100	0.415	2.332
Weighted median	-0.025	0.145	0.865						
Inverse variance weighted	-0.038	0.093	0.681			102.844	101	0.43	1.793
Simple mode	-0.161	0.296	0.589						
Weighted mode	-0.04	0.124	0.747						
BMI-adjusted Waist-Hip Ratio									
MR Egger	-0.382	0.323	0.239	0.009	0.175	156.341	140	0.163	10.452
Weighted median	0.102	0.166	0.541						
Inverse variance weighted	0.031	0.113	0.782			158.419	141	0.15	10.996
Simple mode	0.536	0.461	0.247						
Weighted mode	0.358	0.409	0.383						

STROBE-MR checklist of recommended items to address in reports of Mendelian randomization studies[1]

Item No.	Section	Checklist item	Page No.	Relevant text from manuscript
1	**TITLE and ABSTRACT**	Indicate Mendelian randomization (MR) as the study's design in the title and/or the abstract if that is a main purpose of the study		Pg. 1: Title "Insulin response to oral glucose and cardiometabolic disease: A Mendelian randomization study to assess potential causality"
	INTRODUCTION			
2	**Background**	Explain the scientific background and rationale for the reported study. What is the exposure? Is a potential causal relationship between exposure and outcome plausible? Justify why MR is a helpful method to address the study question		Pg. 3: Obesity is a growing problem worldwide and is associated with cardiometabolic disease. Post-prandial hyperinsulinemia has been linked to weight gain. Two sample MR can be used to infer causality between an exposure and an outcome using genetic variants associated with the exposure as an instrument. A previous MR study supported a causal association between insulin levels at 30-minutes post glucose challenge and body mass index. Whether this translates to increased cardiometabolic disease is not established.
3	**Objectives**	State specific objectives clearly, including pre-specified causal hypotheses (if any). State that MR is a method that, under specific assumptions, intends to estimate causal effects		Pg. 3-4: We have undertaken bi-directional MR analysis on summary level data from participants of European descent to assess potential causal relationships between CIR, BMI and cardiometabolic phenotypes.
	METHODS			
4	**Study design and data sources**	Present key elements of the study design early in the article. Consider including a table listing sources of data for all phases of the study. For each data source contributing to the analysis, describe the following:		
	a)	Setting: Describe the study design and the underlying population, if possible. Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection, when available.		Pg. 4-5: Bi-directional MR was used to assess causal associations between CIR (based on 8 genome-wide significant SNPs in the MAGIC cohort of up to 26,037 participants without T2D) and BMI from published summary statistics from GIANT-UK Biobank cohort. We also assessed whether CIR affects WHR (adjusted and unadjusted for BMI), leg fat (assessed by impedance), liver fat (assessed by MR), T2D, plasma TG and HDL, hypertension and CAD. Cohort details are provided in Table 1.
	b)	Participants: Give the eligibility criteria, and the sources and methods of selection of participants. Report the sample size, and whether any power or sample size calculations were carried out prior to the main analysis		Pg. 4-5: PMID for original GWAS/cohorts provided in Table 1.
	c)	Describe measurement, quality control and selection of genetic variants		Pg. 4-5: Genetic variants that were significant at p-value threshold of 5x10-8 in meta-GWAS were used in the instrument; effect size and standard error was also calculated from these meta-GWAS.
	d)	For each exposure, outcome, and other relevant variables, describe methods of assessment and diagnostic criteria for diseases		Pg. 4-5: As describe above in (a).
	e)	Provide details of ethics committee approval and participant informed consent, if relevant		Not applicable.
5	**Assumptions**	Explicitly state the three core IV assumptions for the main analysis (relevance, independence and exclusion restriction) as well assumptions for any additional or sensitivity analysis		Pg. 5: The first assumption is that the instrument is associated with the exposure, therefore we used SNPs that were associated with the exposure at genome-wide significance. Second that the instrument does not influence the outcome via another pathway other than the outcome (horizontal pleiotropy). Third, there are no confounders associated with the instrument.
6	**Statistical methods: main analysis**	Describe statistical methods and statistics used		

		a)	Describe how quantitative variables were handled in the analyses (i.e., scale, units, model)	Pg. 6-9: Betas are provided for continuous variables and odds ratios for binary traits.
		b)	Describe how genetic variants were handled in the analyses and, if applicable, how their weights were selected	Pg. 4: Genetic variants were weighted based on effect size in prior meta-GWAS.
		c)	Describe the MR estimator (e.g. two-stage least squares, Wald ratio) and related statistics. Detail the included covariates and, in case of two-sample MR, whether the same covariate set was used for adjustment in the two samples	Pg. 5-6: Univariable MR using an inverse variance weighted (IVW) approach, i.e. meta-analysis of the individual Wald ratio for each SNP was conducted to assess potential causality between traits.
		d)	Explain how missing data were addressed	Pg. 5: If the SNP was not matched directly, LD pruning was used to select a proxy (r2>0.8).
		e)	If applicable, indicate how multiple testing was addressed	Pg. 10: These tests were hypothesis driven and the traits are correlated. A Bonferroni correction is likely over-conservative (p-value threshold of 0.0042 for 12 tests), where only increased CIR and reduced T2D/TG remain significant. The other data should be interpreted with caution.
7	**Assessment of assumptions**		Describe any methods or prior knowledge used to assess the assumptions or justify their validity	Pg. 3: Pre-clinical studies have indicated that hyperinsulinemia may cause cardiometabolic disease. Prior MR also suggested post-prandial hyperinsulinemia increases BMI.
8	**Sensitivity analyses and additional analyses**		Describe any sensitivity analyses or additional analyses performed (e.g. comparison of effect estimates from different approaches, independent replication, bias analytic techniques, validation of instruments, simulations)	Pg. 5-6: Sensitivity analyses included MR Egger, weighted median and weighted mode as well as tests of heterogeneity (Cochrane's Q test) and leave-one-out analyses.
9	**Software and pre-registration**			
		a)	Name statistical software and package(s), including version and settings used	TwoSampleMR package in R (R studio® v1.3.1073 and R® v4.0.3), with January 2020 update
		b)	State whether the study protocol and details were pre-registered (as well as when and where)	The study was not pre-registered.
	RESULTS			
10	**Descriptive data**			
		a)	Report the numbers of individuals at each stage of included studies and reasons for exclusion. Consider use of a flow diagram	Cohort details in Table 1.
		b)	Report summary statistics for phenotypic exposure(s), outcome(s), and other relevant variables (e.g. means, SDs, proportions)	Cohort details in Table 1.
		c)	If the data sources include meta-analyses of previous studies, provide the assessments of heterogeneity across these studies	Cohort details in Table 1: PMID to original GWAS studies are provided.
		d)	For two-sample MR: i. Provide justification of the similarity of the genetic variant-exposure associations between the exposure and outcome samples	Cohort details in Table 1: exposure and outcome samples have similar mean age and %female.

		ii.	Provide information on the number of individuals who overlap between the exposure and outcome studies	Pg. 4-5: MAGIC included 13 discovery GWAS, of which 24.5% of exposure cohort were also part of the GIANT consortium (2.8%) and some UK ~2000 participants, ~0.4% may potentially have participated in the UK Biobank study.
11	**Main results**			
		a)	Report the associations between genetic variant and exposure, and between genetic variant and outcome, preferably on an interpretable scale	Pg. 6-9: Associations were reported as exposure increases or reduces the outcome.
		b)	Report MR estimates of the relationship between exposure and outcome, and the measures of uncertainty from the MR analysis, on an interpretable scale, such as odds ratio or relative risk per SD difference	Pg. 6-9: MR estimates were provided as beta +/- standard error with p-value for continuous variables (Table 3). For binary variables, odds ratio was also provided (Table 4).
		c)	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable.
		d)	Consider plots to visualize results (e.g. forest plot, scatterplot of associations between genetic variants and outcome versus between genetic variants and exposure)	Scatter, funnel, forest and leave-one-out plots were provided for significant associations (Figures 1-5).
12	**Assessment of assumptions**			
		a)	Report the assessment of the validity of the assumptions	MR-Egger intercept with p-value was reported as a measure of horizontal pleiotropy for all significant associations (Tables 3-4).
		b)	Report any additional statistics (e.g., assessments of heterogeneity across genetic variants, such as I^2, Q statistic or E-value)	Pg. 6-9: Cochrane's Q statistic and I2 values were provided for significant associations (Tables 3-4).
13	**Sensitivity analyses and additional analyses**			
		a)	Report any sensitivity analyses to assess the robustness of the main results to violations of the assumptions	Pg. 6-9: MR-Egger, weighted-median and weighted-mode analyses were also conducted (Tables 3-4).
		b)	Report results from other sensitivity analyses or additional analyses	Pg. 6-9: Visualization of the scatter and funnel plots, and leave-one-out analyses were also completed (Figures 1-5).
		c)	Report any assessment of direction of causal relationship (e.g., bidirectional MR)	Pg. 6-7: Bidirectional MR was completed for CIR and BMI, with only a significant causal association for CIR on BMI.
		d)	When relevant, report and compare with estimates from non-MR analyses	Not applicable.
		e)	Consider additional plots to visualize results (e.g., leave-one-out analyses)	Figures 1-5.
	DISCUSSION			Pg. 10: Our data suggests that increased CIR may modestly increase BMI, may promote favourable fat distribution (increased leg fat mass with no change in WHR or liver fat), reduce T2D and improve lipids (reduced TG and increased HDL) with neutral effects on hypertension and coronary artery disease.
14	**Key results**		Summarize key results with reference to study objectives	
15	**Limitations**		Discuss limitations of the study, taking into account the validity of the IV assumptions, other sources of potential bias, and imprecision. Discuss both direction and magnitude of any potential bias and any efforts to address them	Pg. 13: Findings may not apply to other ethnic groups and we did not undertake analysis by sex. Unlike other complex traits, relatively few SNPs have been associated with post-OGTT insulin and a larger sample size may permit more robust inferences given the pleiotropic effects of some SNPs in the MR instrument. Further, we do not have longitudinal data on participants. We also did not assess the interaction between dietary macronutrient intake and CIR.

16	**Interpretation**		
	a)	Meaning: Give a cautious overall interpretation of results in the context of their limitations and in comparison with other studies	Pg. 12: We suggest that post-prandial hyperinsulinemia per se is likely not deleterious to cardiometabolic health in the absence of compromised adipose storage/increased lipid flux and/or hyperglycemia. The data does not support a causal role for CIR in cardiometabolic disease. There may be some metabolically beneficial effects of increased CIR but given multiple testing, we have explicitly stated that caution should be applied in interpreting the results.
	b)	Mechanism: Discuss underlying biological mechanisms that could drive a potential causal relationship between the investigated exposure and the outcome, and whether the gene-environment equivalence assumption is reasonable. Use causal language carefully, clarifying that IV estimates may provide causal effects only under certain assumptions	In the discussion (pg. 9-12), we have discussed potential mechanisms including potential effects mediated by horizontal pleiotropy by analyses of individual SNPs in the instrument, as well as the evidence from prior studies.
	c)	Clinical relevance: Discuss whether the results have clinical or public policy relevance, and to what extent they inform effect sizes of possible interventions	Not applicable. As we did not assess dietary exposure, implications re: public policy/clinical management decisions can not be made.
17	**Generalizability**	Discuss the generalizability of the study results (a) to other populations, (b) across other exposure periods/timings, and (c) across other levels of exposure	Pg. 13: The study provides insight into the effects of hyperinsulinemia on cardiometabolic disease, however is limited in its generalizability due to: small sample size, only European ethnicity, non-diabetic population and lack of macronutrient data as detailed in the limitations. We also do not have longer-term outcomes. Many people with increased weight can transition from metabolically healthy to unhealthy status over time.
	OTHER INFORMATION		
18	**Funding**	Describe sources of funding and the role of funders in the present study and, if applicable, sources of funding for the databases and original study or studies on which the present study is based	Pg. 14: SD is funded by CIHR, Heart & Stroke Foundation of Canada, Diabetes Canada and Banting & Best Diabetes Centre (DH Gales Family Charitable Foundation New Investigator Award and a Reuben & Helene Dennis Scholar in Diabetes Research).
19	**Data and data sharing**	Provide the data used to perform all analyses or report where and how the data can be accessed, and reference these sources in the article. Provide the statistical code needed to reproduce the results in the article, or report whether the code is publicly accessible and if so, where	All data used in this study is public access. PMID/GWAS id for cohorts are provided in Table 1. TwoSampleMR R code is also publicly available.
20	**Conflicts of Interest**	All authors should declare all potential conflicts of interest	No conflicts of interests.

1. Skrivankova VW, Richmond RC, Woolf BAR, et al. Strengthening the Reporting of Observational Studies in Epidemiology using Mendelian Randomisation (STROBE-MR): Explanation and Elaboration. BMJ. 2021;375:n2233.