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Supplemental Table 1. Variants in insulin-30 instrument sets										
SNP rsID	Chr	Position (bp)	Nearest gene	Insulin raising allele	Other allele	beta	p-value	Insulin-30-stringent	Insulin-30-relaxed	GSIS-stringent
rs1111875	10	94452862	HHEX	T	C	0.095	7.50E-11	Yes	Yes	Yes
rs2287019	19	50894012	QPCTL	C	T	0.12	1.49E-09	Yes	Yes	Yes
rs742642	6	20773060	CDKAL1	G	A	0.12	7.69E-09	Yes	Yes	Yes
rs6943153	7	50759073	GRB10	T	C	0.082	5.48E-08		Yes	
rs10830963	11	92348358	MTNR1B	C	G	0.085	2.04E-07		Yes	Yes
rs6006427	22	28999993	OSM	C	T	0.11	3.86E-06		Yes	
rs4942511	13	45798649	C13orf18	C	T	0.33	7.85E-06		Yes	
rs10233248	7	49445212	VWC2	A	T	0.11	8.90E-06		Yes	
rs17044912	3	6462627	AF279782	C	T	0.25	1.06E-05		Yes	
rs2274611	9	89532495	CTSL	C	T	0.093	1.32E-05		Yes	
rs6740210	2	65017249	SLC1A4	T	C	0.17	1.59E-05		Yes	
rs2865851	19	58907560	MIR519D	G	A	0.15	1.68E-05		Yes	
rs7581860	2	204940565	PARD3B	A	G	0.2	1.69E-05		Yes	
rs918689	16	74755148	CNTNAP4	G	A	0.099	1.77E-05		Yes	
rs11240131	1	145751075	NBPF1 /KIAA1693	C	T	0.13	1.98E-05		Yes	
rs2388417	15	92192224	LINC01579	T	C	0.36	2.14E-05		Yes	
rs1239081	2	78683501	AC092660	G	A	0.1	2.14E-05		Yes	
rs10834748	11	25668301	LUZP2	A	T	0.13	2.17E-05		Yes	
rs3759356	12	5020623	KCNA5	A	G	0.11	2.35E-05		Yes	

rs13152357	4	153091882	RP11-73G16	C	T	0.4	2.37E-05		Yes	
rs1265052	6	31188450	C6ORF15	C	T	0.092	2.39E-05		Yes	
rs210328	14	53135415	AL163953	C	T	0.11	2.44E-05		Yes	
rs7607980	2	165259447	COBLL1	T	C	0.097	2.49E-05		Yes	
rs11768772	7	12881672	RN7SKP228	G	C	0.26	2.54E-05		Yes	
rs12549902	8	41628416	NKX6-3	G	A	0.045	2.66E-05		Yes	Yes
rs2909874	5	85371948	NBPF22P	A	G	0.099	2.92E-05		Yes	
rs7046518	9	19409446	ACER2	A	G	0.11	2.94E-05		Yes	
rs4918546	10	112384883	RN7SL686P	G	T	0.14	3.23E-05		Yes	
rs368664	1	218953658	C1orf115	A	C	0.28	3.77E-05		Yes	
rs1073923	16	77416394	WVOX	T	C	0.19	3.77E-05		Yes	
rs11675522	2	3130664	AC019118	T	C	0.099	3.83E-05		Yes	
rs925820	3	2843988	CNTN4	T	G	0.099	3.99E-05		Yes	
rs16877965	8	31371846	WRN	A	G	0.21	4.01E-05		Yes	
rs9364646	6	162629938	PARK2	A	G	0.14	4.13E-05		Yes	
rs7573433	2	165835109	SCN2A	A	G	0.15	4.25E-05		Yes	
rs6601952	10	5403634	UCN3	C	A	0.097	4.52E-05		Yes	
rs7100825	10	125309032	CR607950	T	C	0.18	4.80E-05		Yes	
rs10223660	6	2966865	NQO2	C	T	0.11	4.81E-05		Yes	
rs987192	2	23286093	hCG_1783917	T	C	0.27	4.86E-05		Yes	
rs10811661	9	22124094	CDKN2BAS	C	T	0.079	5.00E-05		Yes	
rs933360	7	50725739	ANK1	G	A	0.033	1.40E-04			Yes
rs4502156	15	60170447	GRB10	C	T	0.045	2.10E-03			Yes

Beta refers to the association of each variant with log-insulin 30. Abbreviations: Chr, chromosome; SNP, single nucleotide polymorphism.

Supplemental Table 2, Variants in BMI instrument set							
SNP	Chr	Position	Nearest gene	BMI increasing allele	Other allele	beta	P-value
rs1558902	16	52361075	FTO	A	T	0.0818	7.51E-153
rs6567160	18	55980115	MC4R	C	T	0.0556	3.93E-53
rs13021737	2	622348	TMEM18	G	A	0.0601	1.113E-50
rs10938397	4	44877284	GNPDA2	G	A	0.0402	3.205E-38
rs543874	1	176156103	SEC16B	G	A	0.0482	2.618E-35
rs2207139	6	50953449	TFAP2B	G	A	0.0447	4.126E-29
rs11030104	11	27641093	BDNF	A	G	0.0414	5.557E-28
rs3101336	1	72523773	NEGR1	C	T	0.0334	2.661E-26
rs7138803	12	48533735	BCDIN3D	A	G	0.0315	8.153E-24
rs10182181	2	25003800	ADCY3	G	A	0.0307	8.777E-24
rs3888190	16	28796987	ATP2A1	A	C	0.0309	3.14E-23
rs1516725	3	187306698	ETV5	C	T	0.0451	1.886E-22
rs12446632	16	19842890	GPRC5B	G	A	0.0403	1.477E-18
rs2287019	19	50894012	QPCTL	C	T	0.036	4.585E-18
rs16951275	15	65864222	MAP2K5	T	C	0.0311	1.911E-17
rs3817334	11	47607569	MTCH2	T	C	0.0262	5.145E-17
rs2112347	5	75050998	POC5	T	G	0.0261	6.191E-17
rs12566985	1	74774781	FPGT	G	A	0.0242	3.282E-15
rs3810291	19	52260843	ZC3H4	A	G	0.0283	4.812E-15
rs7141420	14	78969207	NRXN3	T	C	0.0235	1.23E-14
rs13078960	3	85890280	CADM2	G	T	0.0297	1.737E-14
rs10968576	9	28404339	LINGO2	G	A	0.0249	6.607E-14

rs17024393	1	109956211	GNAT2	C	T	0.0658	7.029E-14
rs12429545	13	53000207	OLFM4	A	G	0.0334	1.094E-12
rs13107325	4	103407732	SLC39A8	T	C	0.0477	1.825E-12
rs11165643	1	96696685	PTBP2	T	C	0.0218	2.07E-12
rs17405819	8	76969139	HNF4G	T	C	0.0224	2.07E-11
rs1016287	2	59159129	LINC01122	T	C	0.0229	2.253E-11
rs4256980	11	8630515	TRIM66	G	C	0.0209	2.9E-11
rs12401738	1	78219349	FUBP1	A	G	0.0211	1.145E-10
rs205262	6	34671142	C6orf106	G	A	0.0221	1.753E-10
rs12016871	13	26915782	MTIF3	T	C	0.0298	2.291E-10
rs12940622	17	76230166	RPTOR	G	A	0.0182	2.494E-09
rs11847697	14	29584863	PRKD1	T	C	0.0492	3.99E-09
rs2075650	19	50087459	TOMM40	A	G	0.0258	1.247E-08
rs2121279	2	142759755	LRP1B	T	C	0.0245	2.313E-08
rs29941	19	39001372	KCTD15	G	A	0.0182	2.407E-08
rs6091540	20	50521269	ZFP64	C	T	0.0188	8.024E-08
rs7715256	5	153518086	GALNT10	G	T	0.0163	1.695E-07
rs2176040	2	226801046	LOC646736	A	G	0.0141	0.000006058
rs657452	1	49362434	AGBL4	A	G	0.0227	5.482E-13
rs12286929	11	114527614	CADM1	G	A	0.0217	1.31E-12
rs7903146	10	114748339	TCF7L2	C	T	0.0234	1.112E-11
rs10132280	14	24998019	STXBP6	C	A	0.023	1.141E-11
rs17094222	10	102385430	HIF1AN	C	T	0.0249	5.942E-11
rs7599312	2	213121476	ERBB4	G	A	0.022	1.173E-10
rs2365389	3	61211502	FHIT	C	T	0.02	1.629E-10
rs2820292	1	200050910	NAV1	C	A	0.0195	1.834E-10

rs12885454	14	28806589	PRKD1	C	A	0.0207	1.943E-10
rs16851483	3	142758126	RASA2	T	G	0.0483	3.548E-10
rs1167827	7	75001105	HIP1	G	A	0.0202	6.333E-10
rs758747	16	3567359	NLRC3	T	C	0.0225	7.473E-10
rs1928295	9	119418304	TLR4	T	C	0.0188	7.91E-10
rs9925964	16	31037396	KAT8	A	G	0.0192	8.108E-10
rs11126666	2	26782315	KCNK3	A	G	0.0207	1.332E-09
rs2650492	16	28240912	SBK1	A	G	0.0207	1.915E-09
rs6804842	3	25081441	RARB	G	A	0.0185	2.476E-09
rs4740619	9	15624326	C9orf93	T	C	0.0179	4.564E-09
rs13191362	6	162953340	PARK2	A	G	0.0277	7.339E-09
rs3736485	15	49535902	DMXL2	A	G	0.0176	7.412E-09
rs17001654	4	77348592	SCARB2	G	C	0.0306	7.76E-09
rs11191560	10	104859028	NT5C2	C	T	0.0308	8.446E-09
rs1528435	2	181259207	UBE2E3	T	C	0.0178	1.196E-08
rs1000940	17	5223976	RABEP1	G	A	0.0192	1.284E-08
rs2033529	6	40456631	TDRG1	G	A	0.019	1.388E-08
rs11583200	1	50332407	ELAVL4	C	T	0.0177	1.479E-08
rs9400239	6	109084356	FOXO3	C	T	0.0188	1.613E-08
rs10733682	9	128500735	LMX1B	A	G	0.0174	1.83E-08
rs11688816	2	62906552	EHBP1	G	A	0.0172	1.893E-08
rs11057405	12	121347850	CLIP1	G	A	0.0307	2.019E-08
rs11727676	4	145878514	HHIP	T	C	0.0358	2.55E-08
rs3849570	3	81874802	GBE1	A	C	0.0188	2.601E-08
rs6477694	9	110972163	EPB41L4B	C	T	0.0174	2.673E-08
rs7899106	10	87400884	GRID1	G	A	0.0395	2.96E-08

rs2176598	11	43820854	HSD17B12	T	C	0.0198	2.971E-08
rs2245368	7	76446079	DTX2P1	C	T	0.0317	3.187E-08
rs17724992	19	18315825	PGPEP1	A	G	0.0194	3.415E-08
rs7243357	18	55034299	GRP	T	G	0.0217	3.857E-08
rs1808579	18	19358886	C18orf8	C	T	0.0167	4.169E-08
rs2033732	8	85242264	RALYL	C	T	0.0192	4.889E-08
rs1441264	13	78478920	MIR548A2	A	G	0.0175	6.037E-08
rs2080454	16	47620091	CBLN1	C	A	0.0168	6.547E-08
rs7164727	15	70881044	LOC100287559	T	C	0.018	6.829E-08
rs17203016	2	207963763	CREB1	G	A	0.021	8.145E-08
rs977747	1	47457264	TAL1	T	G	0.0167	8.652E-08
rs9914578	17	1951886	SMG6	G	C	0.0201	8.99E-08
rs9374842	6	120227364	LOC285762	T	C	0.0187	9.673E-08
rs16907751	8	81538012	ZBTB10	C	T	0.035	1.255E-07
rs9540493	13	65103705	MIR548X2	A	G	0.0172	1.416E-07
rs7239883	18	38401669	LOC284260	G	A	0.0164	1.633E-07
rs13201877	6	137717234	IFNGR1	G	A	0.0233	2.348E-07
rs2836754	21	39213610	ETS2	C	T	0.0164	4.161E-07
rs492400	2	219057996	USP37	C	T	0.0158	4.167E-07
rs9641123	7	93035668	CALCR	C	G	0.0191	0.0000005
rs1460676	2	164275935	FIGN	C	T	0.0197	8.982E-07
rs4787491	16	29922838	INO80E	G	A	0.0159	0.000002241
rs6465468	7	95007450	ASB4	T	G	0.0166	0.000002318

Beta refers to the association of each variant with body mass index. Abbreviations: BMI, body mass index; Chr, chromosome; SNP, single nucleotide polymorphism.

Supplemental Table 3. Individual variant association in CAMP-MGH cohort with insulin-30						
SNP	Nearest gene	Insulin raising allele	Other allele	beta	SE	P-value
rs1111875	HHEX	T	C	0.06	0.02	0.01
rs2287019	QPCTL	C	T	0.05	0.03	0.08
rs742642	CDKAL1	G	A	0.09	0.03	0.01
rs6943153	GRB10	T	C	-0.03	0.02	0.17
rs10830963	MTNR1B	C	G	0.06	0.03	0.03
rs6006427	OSM	C	T	0.01	0.03	0.82
rs4942511	C13orf18	C	T	-0.13	0.08	0.12
rs10233248	VWC2	A	T	-0.03	0.03	0.27
rs17044912	AF279782	C	T	0.05	0.09	0.57
rs2274611	CTSL	C	T	0.04	0.02	0.09
rs6740210	SLC1A4	T	C	0.04	0.04	0.36
rs2865851	MIR519D	G	A	-0.01	0.02	0.71
rs7581860	PARD3B	A	G	0.07	0.04	0.12
rs918689	CNTNAP4	G	A	0.03	0.03	0.19
rs11240131	NBPF1 /KIAA1693	C	T	-0.03	0.03	0.41
rs2388417	LINC01579	T	C	0.10	0.10	0.29
rs1239081	AC092660	G	A	-0.04	0.02	0.09
rs10834748	LUZP2	A	T	0.00	0.03	0.90
rs3759356	KCNA5	A	G	-0.02	0.03	0.46
rs13152357	RP11- 73G16	C	T	0.05	0.06	0.42
rs1265052	C6ORF15	C	T	0.05	0.02	0.03
rs210328	AL163953	C	T	0.04	0.03	0.14
rs7607980	COBLL1	T	C	0.01	0.03	0.74
rs11768772	RN7SKP228	G	C	0.02	0.05	0.72
rs2909874	NKX6-3	A	G	0.02	0.02	0.47
rs7046518	NBPF22P	A	G	0.01	0.03	0.75
rs4918546	ACER2	G	T	-0.01	0.03	0.84
rs368664	RN7SL686P	A	C	0.07	0.06	0.28
rs1073923	C1orf115	T	C	0.00	0.05	0.98
rs11675522	WVOX	T	C	0.02	0.02	0.50
rs925820	AC019118	T	G	0.02	0.02	0.33
rs16877965	CNTN4	A	G	0.02	0.06	0.73
rs9364646	WRN	A	G	0.02	0.03	0.58
rs7573433	PARK2	A	G	-0.01	0.04	0.87
rs6601952	SCN2A	C	A	0.00	0.02	0.84
rs7100825	UCN3	T	C	0.04	0.04	0.30
rs987192	CR607950	T	C	-0.02	0.05	0.68
rs10811661	NQO2	C	T	0.01	0.03	0.86
rs12549902	ANK1	G	A	0.02	0.02	0.52
rs933360	GRB10	G	A	-0.03	0.03	0.32
rs4502156	C2CD4A	C	T	0.01	0.02	0.69

Beta refers to the association of each variant with log-insulin 30. Abbreviations: SE, standard error.

Supplemental table 4.

Summary of bidirectional Mendelian randomization analyses.

Instrument Set	Exposure Data	Outcome Data	MR Beta	MR SE	MR P-value	Het. P-value	Egger Test P-value
Insulin-30 Stringent	MAGIC	GIANT	0.095	0.013	1.8E-12	2.7E-07	5.9E-01
Insulin-30 Stringent	MAGIC	UK Biobank	0.104	0.016	1.3E-10	2.2E-05	4.4E-01
Insulin-30 Stringent	MAGIC	Combined	0.098	0.010	2.2E-21	7.6E-12	5.3E-01
GSIS Stringent	MAGIC	GIANT	0.055	0.011	8.5E-07	2.7E-11	2.5E-01
GSIS Stringent	MAGIC	UK Biobank	0.054	0.013	6.6E-05	8.8E-11	3.1E-01
GSIS Stringent	MAGIC	Combined	0.054	0.009	3.4E-10	3.6E-22	2.7E-01
Insulin-30 Relaxed	MAGIC	GIANT	0.010	0.004	2.0E-02	5.3E-10	8.7E-01
Insulin-30 Relaxed	MAGIC	UK Biobank	0.004	0.004	3.1E-01	1.9E-09	9.0E-01
Insulin-30 Relaxed	MAGIC	Combined	0.007	0.003	1.8E-02	7.3E-23	9.2E-01
Insulin-30 Sensitivity	MAGIC	GIANT	0.042	0.017	1.1E-02	8.3E-01	NA
Insulin-30 Sensitivity	MAGIC	UK Biobank	0.050	0.020	1.4E-02	2.3E-01	NA
Insulin-30 Sensitivity	MAGIC	Combined	0.045	0.013	4.2E-04	3.4E-01	NA
BMI	GIANT	MAGIC	0.115	0.145	4.3E-01	1.3E-01	1.7E-01

MR-Beta refers to the effect of genetically-raised insulin-30 on BMI for the insulin-30 instrument sets, and the effect of genetically-raised BMI on insulin-30. Abbreviations: het., heterogeneity; GIANT, Genetic Investigation of ANthropometric Traits consortium, MAGIC, Meta-Analysis of Glucose- and Insulin-related traits Consortium; MR, Mendelian randomization; SE, standard error.

Figure legend

Supplemental Figure 1. SNP-trait effect estimates for insulin-30-stringent instruments. Scatterplot of association of each variant with insulin-30 and with body mass index. The dashed line represents the slope of the MR effect estimate of genetically-raised insulin 30 on BMI using all 3 instruments; the dotted line is the MR effect estimate excluding the outlier, QPCTL/GIPR. Abbreviations: MR, Mendelian randomization; SD, standard deviation; SE, standard error; SNP, single nucleotide polymorphism.

