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**Supplementary Table 1:** Rationale for categorizing 30 T2D-associated single-nucleotide polymorphisms (SNP) as affecting  $\beta$ -cell function or insulin resistance, based on known gene function or specific metabolic phenotypes in the Meta-Analysis of Glucose and Insulin-related traits Consortium (MAGIC).

						<b>Physiology based on MAGIC analyses</b>						
SNP	Locus	Chr	Risk allele	T2D effect	HOMA- $\beta$		HOMA- $\beta$ effect		AIR	Proinsulin	Physiology clustering	
					effect	<i>p</i>	<-0.008	<i>p</i> <0.05				<i>p</i> <0.05
<b><math>\beta</math>-cell function</b>	rs10830963	<i>MTNR1B</i>	11	G	0.0414	-0.0394	8.6E-23	xx	xx			
	rs10203174	<i>THADA</i>	2	C	0.0569	-0.0262	9.8E-06	x			x	
	rs6819243	<i>MAEA</i>	4	T	0.0294	-0.0249	9.5E-03	x				
	rs7903146	<i>TCF7L2</i>	10	T	0.1399	-0.0200	1.4E-07	x	x		x	
	rs11717195	<i>ADCY5</i>	3	T	0.0492	-0.0181	2.7E-05	x			x	
	rs1552224	<i>ARAP1</i>	11	A	0.0374	-0.0166	9.4E-05	x	x		x	
	rs3802177	<i>SLC30A8</i>	8	G	0.0531	-0.0160	2.0E-05	x	x	x	x	
	rs10758593	<i>GLIS3</i>	9	A	0.0253	-0.0145	1.3E-05	x				
	rs10278336	<i>GCK</i>	7	A	0.0374	-0.0128	2.1E-04	x	x			
	rs17168486	<i>DGKB</i>	7	T	0.0374	-0.0126	3.0E-03	x	x		x	
	rs2075423	<i>PROX1</i>	1	G	0.0294	-0.0125	3.9E-04	x	x		x	
	rs4402960	<i>IGF2BP2</i>	3	T	0.0531	-0.0115	1.2E-03	x	x	x		
	rs4502156	<i>VPS13C</i>	15	T	0.0212	-0.0099	3.6E-03	x				
	rs7756992	<i>CDKAL1</i>	6	G	0.0607	-0.0095	7.5E-03	x	xx	x	x	
	rs11257655	<i>CDC123</i>	10	T	0.0334	-0.0091	2.5E-02	x	x			
	rs1496653	<i>UBE2E2</i>	3	A	0.0374	-0.0088	1.9E-02	x				
	rs163184	<i>KCNQ1</i>	11	G	0.0374	-0.0086	1.6E-02	x		x		
	rs10811661	<i>CDKN2A/B</i>	9	T	0.0755	-0.0085	5.1E-02	x	x	x	x	
	rs1111875	<i>HHEX/IDE</i>	10	C	0.0374	-0.0042	2.0E-01		xx	x	x	
rs5215	<i>KCNJ11</i>	11	C	0.0294	0.0009	7.8E-01			x			
						HOMA-IR effect	<i>p</i>	HOMA-IR <i>p</i> <0.05	FI <i>p</i> <10 <sup>-8</sup>	Obesity <i>p</i> <10 <sup>-8</sup>	IR lipid profile	Physiology clustering
<b>Insulin resistance</b>	rs12970134	<i>MC4R</i>	18	A	0.0334	0.0084	7.6E-02			x		x
	rs13233731	<i>KLF14</i>	7	G	0.0043	0.0077	5.1E-02	x			x	
	rs13389219	<i>GRB14</i>	2	C	0.0374	0.0124	2.2E-03	x	x			
	rs1801282	<i>PPARG</i>	3	C	0.0453	0.0161	5.6E-03	x	x		x	
	rs2261181	<i>HMG A2</i>	12	T	0.0414	0.0135	4.9E-02	x				
	rs2943640	<i>IRS1</i>	2	C	0.0414	0.0086	3.6E-02	x	x		x	
	rs459193	<i>ANKRD55</i>	5	G	0.0414	0.0115	1.1E-02	x				
	rs780094	<i>GCKR</i>	2	C	0.0334	0.0201	7.6E-07	x	x		x	
	rs8182584	<i>PEPD</i>	19	T	0.0212	0.0122	3.9E-03	x	x			
rs9936385	<i>FTO</i>	16	C	0.0531	0.0148	3.3E-04	x		x		x	

Physiology clustering as  $\beta$ -cell function or insulin resistance based on MAGIC analyses(1). Fasting insulin (FI) *p*-values based on body-mass index\*gene analyses in (2). Obesity defined as association with risk of increased body-mass index in Genetic Investigation of ANthropometric Traits (GIANT) data(3). Insulin resistance (IR) lipid profile defined as

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high triglyceride and low HDL levels as reported in (2). AIR—acute insulin response; Chr—chromosome; FI: fasting insulin; HOMA—homeostasis model of assessment; IGI—insulinogenic index; MAGIC—Meta-Analysis of Glucose and Insulin-related traits Consortium; SNP—single-nucleotide polymorphism; T2D—type 2 diabetes.

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**Supplementary Table 2: Mean  $\beta$ -cell ( $GRS_{\beta}$ ) and insulin resistance ( $GRS_{IR}$ ) genotype risk scores in the Framingham Offspring and CARDIA Studies**

	Total	BMI<30 kg/m <sup>2</sup>	BMI≥30 kg/m <sup>2</sup>
<b><math>GRS_{\beta}</math></b>			
<b>FOS</b>	21.6 (3.0)	21.6 (3.0)	21.6 (2.9)
T2D	22.6 (3.0)	23.2 (3.1)	22.4 (2.6)
No T2D	21.6 (3.0)	21.6 (3.0)	21.6 (2.9)
<b>CARDIA Whites</b>	21.2 (3.1)	21.2 (3.1)	21.0 (3.2)
T2D	22.1 (3.3)	22.3 (3.4)	21.6 (2.9)
No T2D	21.2 (3.1)	21.2 (3.1)	20.7 (3.3)
<b>CARDIA Blacks</b>	21.3 (2.4)	21.4 (2.4)	21.1 (2.4)
T2D	21.6 (2.5)	21.6 (2.5)	21.7 (2.5)
No T2D	21.3 (2.4)	21.3 (2.4)	20.8 (2.3)
<b><math>GRS_{IR}</math></b>			
<b>FOS</b>	10.4 (2.0)	10.4 (2.0)	10.5 (2.0)
T2D	10.3 (2.4)	10.3 (2.3)	10.3 (2.7)
No T2D	10.4 (2.0)	10.4 (2.0)	10.5 (2.0)
<b>CARDIA Whites</b>	10.4 (2.0)	10.4 (2.0)	10.3 (2.1)
T2D	10.6 (1.9)	10.5 (1.9)	10.8 (2.0)
No T2D	10.4 (2.0)	10.4 (2.0)	10.1 (2.1)
<b>CARDIA Blacks</b>	11.1 (1.9)	11.1 (1.9)	11.0 (1.8)
T2D	11.4 (1.8)	11.5 (1.8)	11.3 (1.7)
No T2D	11.0 (1.9)	11.0 (1.9)	10.9 (1.9)

Data are mean (SD) weighted genotype risk scores (GRS) consisting of 20 single-nucleotide polymorphisms (SNP) associated with  $\beta$ -cell dysfunction ( $GRS_{\beta}$ ) and 10 SNP associated with insulin resistance ( $GRS_{IR}$ ) in the overall FOS and CARDIA cohorts and in participants with and without type 2 diabetes (T2D). Among FOS and CARDIA whites, GRS are weighted by the effects sizes from the DIAGRAM v3 meta-analysis(4). GRS are unweighted among CARDIA blacks.

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**Supplementary Table 3: Odds ratios for  $GRS_{\beta}$  and  $GRS_{IR}$  in prediction models for incident type 2 diabetes in the Framingham Offspring Study**

	$GRS_{\beta}$ model	$GRS_{IR}$ model	$GRS_{\beta} + GRS_{IR}$ model
<b>Demographic model</b>			
$GRS_{\beta}$	1.11 (1.08, 1.15)*	---	1.11 (1.08, 1.15)*
$GRS_{IR}$	---	1.04 (1.00, 1.10)	1.05 (1.00, 1.10)
<b>Clinical model</b>			
$GRS_{\beta}$	1.10 (1.06, 1.14)*	---	1.10 (1.06, 1.14)*
$GRS_{IR}$	---	0.98 (0.93, 1.04)	0.99 (0.93, 1.04)

Data are odds ratios from pooled logistic regression models for incident type 2 diabetes and correspond to a 1-allele increase in the GRS. Demographic models are adjusted for age and sex. Clinical models are adjusted for age, sex, parental history of diabetes (yes vs. no), body-mass index, systolic blood pressure, fasting plasma glucose, high-density lipoprotein (HDL), and fasting triglycerides.  $GRS_{\beta}$  and  $GRS_{IR}$  models include only the  $GRS_{\beta}$  and  $GRS_{IR}$ , respectively. The  $GRS_{\beta} + GRS_{IR}$  model contains both terms. \* $p < 0.001$

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**Supplementary Table 4: Hazard ratios for  $GRS_{\beta}$  and  $GRS_{IR}$  in prediction models for incident type 2 diabetes among whites in the CARDIA Study**

	$GRS_{\beta}$ model	$GRS_{IR}$ model	$GRS_{\beta} + GRS_{IR}$ model
<b>Demographic model</b>			
$GRS_{\beta}$	1.09 (1.02, 1.16)*	---	1.09 (1.02, 1.16)**
$GRS_{IR}$	---	1.06 (0.96, 1.17)	1.06 (0.96, 1.17)
<b>Clinical model</b>			
$GRS_{\beta}$	1.09 (1.02, 1.17)**	---	1.09 (1.02, 1.17)**
$GRS_{IR}$	---	1.01 (0.91, 1.12)	1.01 (0.91, 1.11)

Data are hazard ratios from Cox regression models for incident type 2 diabetes and correspond to a 1-allele increase in the GRS. Demographic models are adjusted for age and sex. Clinical models are adjusted for age, sex, parental history of diabetes (yes vs. no), body-mass index, systolic blood pressure, fasting plasma glucose, log-transformed high-density lipoprotein (HDL), and log-transformed fasting triglycerides.  $GRS_{\beta}$  and  $GRS_{IR}$  models include only the  $GRS_{\beta}$  and  $GRS_{IR}$ , respectively. The  $GRS_{\beta} + GRS_{IR}$  model contains both terms. \* $p < 0.05$ , \*\* $p < 0.01$

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**Supplementary Table 5: Hazard ratios for  $GRS_{\beta}$  and  $GRS_{IR}$  in prediction models for incident type 2 diabetes among blacks in the CARDIA Study**

	$GRS_{\beta}$ model	$GRS_{IR}$ model	$GRS_{\beta} + GRS_{IR}$ model
<b>Demographic model</b>			
$GRS_{\beta}$	1.06 (0.98, 1.14)	---	1.06 (0.98, 1.14)
$GRS_{IR}$	---	1.09 (1.00, 1.20)	1.10 (1.00, 1.20)
<b>Clinical model</b>			
$GRS_{\beta}$	1.06 (0.99, 1.15)	---	1.07 (0.99, 1.15)
$GRS_{IR}$	---	1.05 (0.96, 1.15)	1.05 (0.96, 1.16)

Data are hazard ratios from Cox regression models for incident type 2 diabetes and correspond to a 1-allele increase in the GRS. Demographic models are adjusted for age and sex. Clinical models are adjusted for age, sex, parental history of diabetes (yes vs. no), body-mass index, systolic blood pressure, fasting plasma glucose, log-transformed high-density lipoprotein (HDL), and log-transformed fasting triglycerides.  $GRS_{\beta}$  and  $GRS_{IR}$  models include only the  $GRS_{\beta}$  and  $GRS_{IR}$ , respectively. The  $GRS_{\beta} + GRS_{IR}$  model contains both terms.

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**Supplementary Table 6: Racial differences in the associations between GRS and incident type 2 diabetes**

	<b>GRS<sub>t</sub></b>	<b>GRS<sub>β</sub></b>	<b>GRS<sub>IR</sub></b>
<b>Demographic model</b>			
Whites	1.077 (1.059, 1.095)	1.109 (1.079, 1.139)	1.047 (1.003, 1.093)
Blacks	1.046 (1.005, 1.088)	1.058 (0.982, 1.140)	1.095 (0.997, 1.202)
<i>p</i>	0.19	0.25	0.39
<b>Clinical model</b>			
Whites	1.060 (1.040, 1.080)	1.098 (1.063, 1.133)	0.990 (0.945, 1.038)
Blacks	1.046 (1.003, 1.090)	1.063 (0.986, 1.147)	1.049 (0.957, 1.151)
<i>p</i>	0.57	0.45	0.28

Data are effect sizes of the association between each GRS and incident T2D among FOS and CARDIA whites (meta-analyzed) and CARDIA blacks. Demographic models are adjusted for age and sex. Clinical models are adjusted for age, sex, parental history of diabetes (yes vs. no), body-mass index, systolic blood pressure, fasting plasma glucose, log-transformed high-density lipoprotein (HDL), and log-transformed fasting triglycerides. *P* values correspond to *t*-tests comparing the effect sizes between whites and blacks.

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**Supplementary Table 7:  $P$ -values for  $GRS_{\beta}$  and  $GRS_{IR}$  regression terms in prediction models for incident type 2 diabetes in the Framingham Offspring Study, stratified by body-mass index (BMI)**

	$GRS_{\beta}$ model	$GRS_{IR}$ model	$GRS_{\beta} + GRS_{IR}$ model
<b>BMI<math>\geq</math>30 kg/m<sup>2</sup></b>			
$GRS_{\beta}$	<0.001	---	<0.001
$GRS_{IR}$	---	0.427	0.426
<b>BMI&lt;30 kg/m<sup>2</sup></b>			
$GRS_{\beta}$	<0.001	---	<0.001
$GRS_{IR}$	---	0.223	0.199

Data are  $p$ -values from pooled logistic regression models for incident type 2 diabetes, stratified by BMI category. Models are adjusted for age and sex.  $GRS_{\beta}$  and  $GRS_{IR}$  models include only the  $GRS_{\beta}$  and  $GRS_{IR}$ , respectively. The  $GRS_{\beta} + GRS_{IR}$  model contains both terms.



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**Supplementary Table 8:  $P$ -values for  $GRS_{\beta}$  and  $GRS_{IR}$  regression terms in prediction models for incident type 2 diabetes in the overall CARDIA Study, stratified by body-mass index (BMI)**

	$GRS_{\beta}$ model	$GRS_{IR}$ model	$GRS_{\beta} + GRS_{IR}$ model
<b>BMI<math>\geq</math>30 kg/m<sup>2</sup></b>			
$GRS_{\beta}$	0.018	---	0.021
$GRS_{IR}$	---	0.221	0.263
<b>BMI&lt;30 kg/m<sup>2</sup></b>			
$GRS_{\beta}$	0.015	---	0.013
$GRS_{IR}$	---	0.084	0.070

Data are  $p$ -values from Cox regression models for incident type 2 diabetes, stratified by BMI category. Models are adjusted for age, sex, and race.  $GRS_{\beta}$  and  $GRS_{IR}$  models include only the  $GRS_{\beta}$  and  $GRS_{IR}$ , respectively. The  $GRS_{\beta} + GRS_{IR}$  model contains both terms.

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**Supplementary Table 9: Prediction models for incident type 2 diabetes in the Framingham Offspring Study, examining the interaction between genotype risk score and obesity**

	<b>GRS model</b>	<b>GRS + obesity model</b>	<b>GRS*obesity interaction model</b>
<b>GRS<sub>t</sub> model</b>			
GRS <sub>t</sub>	1.08 (1.06, 1.10)	1.08 (1.06, 1.10)	1.09 (1.07, 1.12)
Obesity	---	4.46 (3.66, 5.43)	22.39 (1.66, 301.34)
GRS <sub>t</sub> *obesity interaction	---	---	0.98 (0.94, 1.01)
<b>GRS<sub>β</sub> model</b>			
GRS <sub>β</sub>	1.11 (1.08,1.15)	1.13 (1.09, 1.16)	1.14 (1.09, 1.19)
Obesity	---	4.46 (3.66, 5.43)	8.44 (1.97, 36.16)
GRS <sub>β</sub> *obesity interaction	---	---	0.97 (0.91, 1.04)
<b>GRS<sub>IR</sub> model</b>			
GRS <sub>IR</sub>	1.04 (1.00, 1.10)	1.03 (0.98, 1.09)	1.04 (0.98, 1.11)
Obesity	---	4.31 (3.54, 5.25)	5.11 (1.82, 14.36)
GRS <sub>IR</sub> *obesity interaction	---	---	0.98 (0.89, 1.08)

Data are odds ratios (OR) from pooled logistic regression models for type 2 diabetes per weighted allele increase in 62-SNP GRS (GRS<sub>t</sub>), β-cell GRS (GRS<sub>β</sub>), and insulin resistance GRS (GRS<sub>IR</sub>), or for obesity (BMI ≥ 30 kg/m<sup>2</sup>). All models are adjusted for age and sex. The GRS models include the corresponding GRS. GRS + obesity models include both the corresponding GRS and a term for obesity. GRS\*obesity interaction models include the corresponding GRS, an obesity term, and an interaction term between GRS and obesity.

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**Supplementary Table 10: Prediction models for incident type 2 diabetes in the overall CARDIA Study, examining the interaction between genotype risk score and obesity**

	<b>GRS model</b>	<b>GRS + obesity model</b>	<b>GRS*obesity interaction model</b>
<b>GRS<sub>t</sub> model</b>			
GRS <sub>t</sub>	1.06 (1.03, 1.09)	1.07 (1.04, 1.10)	1.07 (1.03, 1.10)
Obesity	---	6.11 (4.52, 8.26)	9.99 (0.19, 517.69)
GRS <sub>t</sub> *obesity interaction	---	---	0.99 (0.94, 1.05)
<b>GRS<sub>β</sub> model</b>			
GRS <sub>β</sub>	1.09 (1.02, 1.16)	1.09 (1.04, 1.14)	1.07 (1.01, 1.14)
Obesity	---	6.17 (4.56, 8.34)	2.60 (0.28, 23.81)
GRS <sub>β</sub> *obesity interaction	---	---	1.04 (0.94, 1.15)
<b>GRS<sub>IR</sub> model</b>			
GRS <sub>IR</sub>	1.08 (1.01, 1.15)	1.08 (1.01, 1.15)	1.10 (1.01, 1.19)
Obesity	---	5.94 (4.40, 8.02)	9.61 (2.01, 45.85)
GRS <sub>IR</sub> *obesity interaction	---	---	0.96 (0.83, 1.10)

Data are odds ratios (OR) from Cox regression models for type 2 diabetes per weighted allele increase in 62-SNP GRS (GRS<sub>t</sub>), β-cell GRS (GRS<sub>β</sub>), and insulin resistance GRS (GRS<sub>IR</sub>), or for obesity (BMI<sub>≥</sub>30 kg/m<sup>2</sup>). All models are adjusted for age, sex, and race. The GRS models include the corresponding GRS. GRS + obesity models include both the corresponding GRS and a term for obesity. GRS\*obesity interaction models include the corresponding GRS, an obesity term, and an interaction term between GRS and obesity.

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