Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods. Construction of the Obesity Genetic Risk Score (GRS)

We selected single-nucleotide polymorphisms (SNPs) for investigation that were associated with an obesity-related phenotype at a threshold of $P < 1 \times 10^{-5}$ in genome-wide association studies (GWAS) of European-descent individuals. We grouped the selected SNPs into linkage disequilibrium (LD) blocks using a linkage threshold of $R^2 \geq 0.95$ and data from the International HapMap Consortium's CEU sample.[1] We retained LD blocks that included an SNP associated with an obesity-related phenotype at $P < 1 \times 10^{-8}$ in at least 1 GWAS or that included SNPs associated with an obesity-related phenotype at $P < 1 \times 10^{-5}$ in at least 2 GWAS. This analysis yielded 32 LD blocks. We selected 1 tag SNP from each LD block to include in the GRS. To construct the GRS, we weighted the obesity-associated alleles for each GRS SNP by the effect size reported for the SNP or its closest LD proxy in meta-analyses of body mass index (BMI) GWAS.[2, 3] We then summed the weighted counts of obesity-associated alleles for each SNP to compute the GRS. An additive model was assumed on the basis of prior research documenting additive contributions to BMI for many of the GRS SNPs.[4, 5]

eTable 1. Single Nucleotide Polymorphisms Included in the Genetic Risk Score[a]

Chr	Nearest Gene	rs	Alleles	BMI-Increasing Allele	Frequency of BMI-Increasing Allele	GWAS Effect-Size for BMI
1	NEGR1	rs2568958	A/G	A	60%	0.13
	TNNI3K	rs1514177	C/G	G	43%	0.07
	PTBP2	rs11165643	C/T	T	63%	0.06
	SEC16B	rs10913469	C/T	C	21%	0.21
2	TMEM18	rs7567570	C/T	C	82%	0.31
	ADCY3, RBJ	rs10182181	A/G	G	51%	0.14
	FANCL	rs887912	A/G	A	29%	0.10
3	CADM2	rs7640855	A/G	A	20%	0.10
	ETV5	rs7647305	C/T	C	79%	0.12
4	SLC39A8	rs13107325	C/T	T	8%	0.19
5	FLJ35779	rs2112347	G/T	T	65%	0.10
	ZNF608	rs6864049	A/G	G	55%	0.07
6	TFAP2B	rs2206277	A/G	A	18%	0.13
9	LRRN6C	rs1412235	C/G	C	31%	0.11
	LMX1B	rs867559	A/G	G	21%	0.24
11	STK33, RPL27A	rs4929949	C/T	C	52%	0.06
	BDNF	rs6265	A/G	G	52%	0.18
	MTCH2	rs10838738	A/G	G	34%	0.05
12	BCDIN3, FAIM2	rs7138803	A/G	A	36%	0.12
13	MTIF3	rs1475219	C/T	C	20%	0.09
14	PRKD1	rs11847697	C/T	T	3%	0.17
	NRXN3	rs10150332	C/T	C	23%	0.13
15	MAP2K5	rs2241423	A/G	G	78%	0.13
16	GPRC5B	rs12446554	G/T	G	87%	0.17
	SH2B1	rs4788102	A/G	A	39%	0.15
	FTO	rs9939609	A/T	A	36%	0.38
18	MC4R	rs921971	C/T	C	28%	0.21
19	KCTD15	rs29941	C/T	C	67%	0.06
	ZC3H4, TMEM160	rs3810291	A/G	A	68%	0.09

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); Chr, chromosome; GWAS, genome-wide associated studies.

[a]Alleles are reported from the forward strand. Nearest gene is reported for the locus identified in the meta-analysis of BMI GWAS by the Genetic Investigation of Anthropometric Traits (GIANT) Consortium.[2] GWAS effect sizes are the per-allele change in BMI estimated in meta-analyses of BMI GWAS by the GIANT Consortium[2] and Thorleifsson and colleagues.[3] The following 3 SNPs failed quality controls in the Dunedin sample and were not included in the genetic risk score: rs11083779 near *QPCTL*; rs12641981 near *GNPDA2*; and rs2121279 near *LRP1B*.

eTable 2. The Genetic Risk Score and the Family History Score Have Independent Effects on Growth and Obesity Risk[a]

|	Life Course Growth			Obesity			
	Model Intercept	Childhood Slope	Adulthood Slope	Teens	20s	30s	Chronic
Panel A. Bivariate Associations							
		Beta/ P Value		Relative Risk (95% Confidence Interval)			
Genome Risk Score	0.38	0.03	0.02	1.42	1.37	1.23	1.37
	p<0.001	p<0.001	p=0.014	(1.10, 1.83)	(1.13, 1.67)	(1.08, 1.39)	(1.09, 1.73)
Family History Score	0.63	0.05	0.04	1.63	1.72	1.49	1.83
	p<0.001	p<0.001	p<0.001	(1.36, 1.95)	(1.51, 1.97)	(1.35, 1.63)	(1.58, 2.13)
Panel B. Independent Associations							
		Beta/ P value		Relative Risk (95% Confidence Interval)			
Genome Risk Score	0.31	0.02	0.01	1.31	1.27	1.17	1.26
	p<0.001	p=0.004	p=0.065	(1.01, 1.70)	(1.04, 1.55)	(1.03, 1.32)	(1.00, 1.59)
Family History Score	0.60	0.05	0.04	1.58	1.67	1.46	1.78
	p<0.001	p<0.001	p<0.001	(1.31, 1.90)	(1.46, 1.92)	(1.32, 1.61)	(1.52, 2.09)

[a]Panel A presents bivariate effect sizes for the genetic risk score and the family history score from the life course growth model and obesity prediction models. Panel B presents the independent effects of the genetic risk score and the family history score on life-course growth and obesity risk. Independent effects were estimated from multivariate growth models (life-course growth) and multivariate Poisson regression models (obesity). The genetic risk score and the family history score were standardized to have means of 0 and SDs of 1 for analyses. All analyses were adjusted for sex.

eTable 3. Indirect Effects of the Genetic Risk Score on Adult Obesity Outcomes Mediated by Weight Gain From Birth Through 3 Years of Age and the Adiposity Rebound[a]

Developmental Phenotype	Obesity Outcome							
	Teens		20s		30s		Chronic	
	Indirect Effect Expressed as a Relative Risk (95% Confidence Intervals)							
Birth-Age 3 y Weight Gain	1.06	(1.01, 1.12)	1.03	(1.00, 1.06)	1.01	(0.99, 1.04)	1.04	(1.01, 1.08)
Adiposity Rebound	1.32	(1.17, 1.52)	1.19	(1.11, 1.31)	1.12	(1.06, 1.19)	1.20	(1.11, 1.32)

[a]Indirect effects were estimated using the structural equation described by MacKinnon & Dwyer[6] implemented with Poisson regression models. Indirect effect estimates were exponentiated to compute risk ratios. Indirect effect estimates for the adiposity rebound reflect the combined indirect effects of age and BMI at adiposity rebound. Analyses were adjusted for sex. Confidence intervals were estimated from 5000 bootstrap repetitions.

eFigure 1. Distribution of the Genetic Risk Score. The transparent bars show the distribution of the count of risk alleles across the 29 single-nucleotide polymorphisms included in the genetic risk score (ie, before weights were applied). The kernel density plot shows the distribution of the weighted genetic risk score.
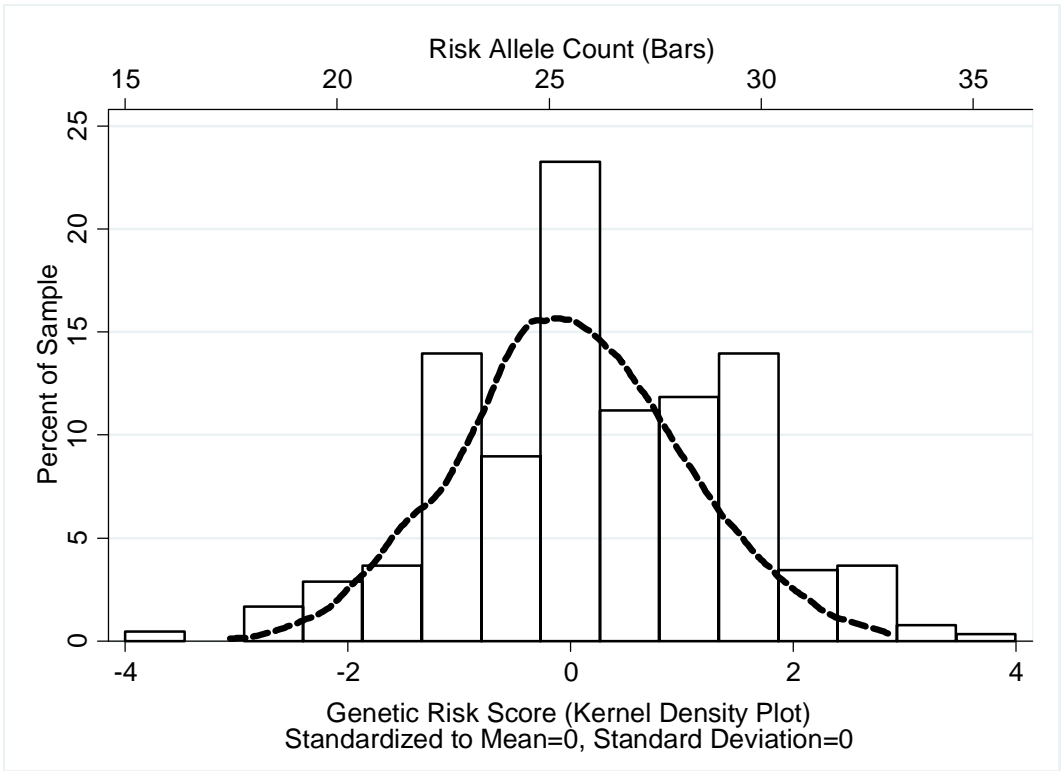
eReferences

1. International HapMap Project. International HapMap Project Genotype Data, Release 1. 3rd ed. 2010.

2. Speliotes EK, Willer CJ, Berndt SI, et al; MAGIC; Procardis Association. Association analyses of 249,796 individuals reveal 18 new loci associated with body mass index. *Nat Genet.* 2010;42(11):937-948.

3. Thorleifsson G, Walters GB, Gudbjartsson DF, et al. Genome-wide association yields new sequence variants at seven loci that associate with measures of obesity. *Nat Genet.* 2009;41(1):18-24.

4. Peterson RE, Maes HH, Holmans P, et al. Genetic risk sum score comprised of common polygenic variation is associated with body mass index. *Hum Genet.* 2011;129(2):221-230.

5. Li S, Zhao JH, Luan J, et al. Cumulative effects and predictive value of common obesity-susceptibility variants identified by genome-wide association studies. *Am J Clin Nutr.* 2010(1);91:184-190.

6. Mackinnon DP, Dwyer JH. Estimating mediated effects in prevention studies. *Eval Rev.* 1993;17:144-158.