Supplement

This supplement describes the application of the 3-stage approach to create a genetic risk score (GRS) for obesity. The supplement is organized into 3 sections: The first section describes the creation of the obesity GRS: Stage 1. Extraction; Stage 2. Clustering; and Stage 3. Selection. The second section describes analyses comparing the resulting GRS to GRSs created with the best-guess and top-hits approaches. The final section describes sensitivity analyses to test heterogeneity in GRS associations.

PART 1. CREATING THE OBESITY GRS

Stage 1. Extraction

For our 3-stage approach analyses, we considered GWAS of European-descent samples that targeted 4 phenotypes: obesity, weight, waist circumference, and body mass index (BMI) (hereafter "obesity-related phenotypes"). A search of the NGHRI GWAS Catalog using the HuGE Navigator (http://www.hugenavigator.org) identified 16 GWAS that met these inclusion criteria, 9 of which were published by December 31, 2008 (**Supplementary Table 1**).

In Stage 1 (Extraction), we compiled association results reported in the manuscripts and supplementary materials of the GWAS and extracted rs-numbers and p-values for SNPs associated with any of the 4 phenotypes in the discovery or combined discovery and replication samples at an alpha level of $1x10^{-5}$ (n=103 SNPs in the subset of 9 GWAS, n=519 SNPs in the full set of 16 GWAS, **Supplementary Table 2**). The significance level of $p<1x10^{-5}$ was the most generous threshold at which most GWAS published results and is the threshold used in the NHGRI GWAS Catalog (Hindorff et al. 2009). Associations were not extracted from replication samples because few GWAS reported novel associations identified in replication samples and some GWAS did not include replication samples or included replication samples of different ethnicity. Discovery sample risk SNPs that failed to replicate within an individual GWAS were included because replication was evaluated at the level of the GWAS publication rather than the specific test sample.

Stage 2. Clustering

In Stage 2 (Clustering), we grouped the extracted SNPs into "LD blocks." We defined LD blocks using data from the HapMap CEU sample (Phase 3), queried using Seattle SNPs' web-based Genome Variation Server (http://gvs.gs.washington.edu/GVS). For each SNP extracted in Stage 1 ("seeds"), we defined an LD block as the region containing all SNPs in LD with that seed at a threshold of $R^2 \geq 0.95$. Then, beginning

with the block closest to the start of each chromosome, we pruned blocks that did not contain a unique seed. This process yielded n=66 LD blocks from the subset of 9 GWAS published by December 31, 2008 and n=158 LD blocks from the full set of 16 GWAS.

Stage 3. Selection

In Stage 3 (Selection), we retained LD blocks that we classified as genome-wide significant or as replicated. Genome-wide significant LD blocks were those that contained ≥1 SNP associated with an obesity-related phenotype at $p<1x10^{-8}$. Replicated blocks were those that contained SNPs extracted from ≥2 GWAS. This process yielded n=37 LD blocks clustered around 11 loci on chromosomes 1-4,9,11,12,16,18, and 19 from the subset of 9 GWAS and n=69 LD blocks clustered around 32 loci on chromosomes 1-6,9,11-14,16,18, and 19 from the full set of 16 GWAS (**Supplementary Tables 3, 4**). Sensitivity analyses relaxing the LD threshold used to define LD blocks yielded fewer LD blocks (e.g., for the full set of 16 GWAS, n=58 at an R^2 threshold of 0.70), but did not alter the loci identified as genome-wide significant or replicated in the original analyses.

PART 2. COMPARING THE 3-STAGE APPROACH GRSS TO THE TOP-HITS AND BEST-GUESS GRSS

To construct and test our GRSs, we followed-up the LD blocks identified in our 3-stage approach analyses in the GWAS dataset from the Atherosclerosis Risk in Communities (ARIC) Study. This dataset is publicly available through the National Institutes of Health Database of Genotypes and Phenotypes (dbGaP) (http://www.ncbi.nlm.nih.gov/gap, phs000090.v1.p1) and is described in the Data section of the main text.

We selected SNPs in the ARIC database to include in our two GRSs as follows: We defined tag SNPs for each of the LD blocks as SNPs that were in LD with every seed contained in the block at $R^2 \geq 0.95$. We then matched 1 tag SNP per LD block with a SNP in the ARIC study genotype database that met the GENEVA ARIC Project Team's quality control criteria (GENEVA ARIC Project 2009). If no tag SNPs in an LD block could be matched in the ARIC database, we relaxed the LD threshold used to define a tag SNP until either a) the resulting set of tag SNPs overlapped with tag SNPs that we had already matched in the ARIC database, or b) a match with a new SNP in the ARIC database was achieved. These analyses yielded a set of n=28 SNPs from the subset of 9 GWAS and a set of n=57 SNPs from the full set of 16 GWAS.

To compute the 3-stage approach GRSs for each ARIC participant, we (1) identified the obesity-associated allele for each SNP from the GWAS where that SNP was reported; (2) calculated the mean number of risk alleles at each locus; and (3) summed these means across loci to produce the 3-stage approach genome-wide scores.

To compute the top-hits and best-guess approach GRSs, we selected SNPs from the ARIC database to match SNPs from 3 published GRSs (Li et al. 2010; Peterson et al. 2011; Speliotes et al. 2010) and the full set of obesity-associated SNPs listed in the NHGRI GWAS catalog for GWAS of European-descent samples. In cases where a specific SNP was not available in the ARIC database, we selected its closest LD proxy. We then summed obesity-associated alleles across each set of selected SNPs to create the comparison genome-wide scores.

To test if the 3-stage approach could construct a GRS that was at least as predictive of BMI and obesity as GRSs created with the top-hits and best-guess approaches, we compared effect sizes for different GRSs using the ARIC data. All GRSs were standardized to have mean=0 and standard deviation=1. To measure GRS effect sizes for BMI, we estimated Pearson correlations (r) from separate linear regressions of BMI on each of the GRSs. To measure GRS effect sizes for obesity, we estimated odds ratios (OR) from separate logistic regressions of obesity on each of the GRSs. Regression models were adjusted for age (linear and quadratic terms), gender, the age-gender interaction, and the ARIC Study Centers where data were collected (hereafter these statistical adjustments are described as "demographics and geography"). To test differences between GRS effect sizes, we conducted F-tests (for effect sizes estimated from linear regressions) and Wald tests (for effect sizes estimated from logistic regressions). For these tests, models including each of the GRSs being compared were jointly estimated using the seemingly unrelated regression method. Seemingly unrelated regression is a statistical approach for comparing coefficients from non-nested regression models (Baltagi 1980; Verzilli, Stallard, and Whittaker 2005). Effect sizes were similar for all GRSs. Statistical tests indicated that our 3-stage approach GRSs performed as well as or better than GRSs created using top-hits and best-guess approaches (**Supplementary Table 5**). Thus, the 3-stage approach produced a GRS that was at least as predictive as top-hits and best guess approach GRSs. We used the 3-stage approach GRS created from the full set of 16 GWAS (hereafter the "Obesity GRS") in subsequent analyses.

Refining the 3-Stage Approach GRS for Obesity. At 7 of the 32 loci identified in the 3-stage approach analyses of GWAS results (in or near the genes *TMEM18*, *ETV5*, *BDNF*, *MTCH2*, *FTO*, *MC4R*, and *KCTD15*), multiple LD blocks met selection criteria (genome-wide significance or replication). To

refine the 3-stage approach GRS, we asked whether the genotype for a single SNP could be used instead of the mean number of risk alleles at a locus. First, we identified the BMI-increasing allele for each SNP and calculated the linear association between the number of BMI-increasing alleles for that SNP and BMI measured at the first ARIC study visit. We next compared test-statistics and effect sizes between SNPs at each locus to identify the "lead-SNP", the SNP with the strongest association, and the worst-associated SNP. We then compared the effect size for the lead-SNP to the effect sizes for the worst-associated SNP and for the mean number of risk alleles across SNPs at the locus. These analyses asked 1) whether there was any difference in the signal from the different SNPs in a correlated set; and 2) whether a single SNP could provide an adequate summary of obesity-associated variation at the locus. Models were fitted using linear regression with statistical adjustment for demographics and geography. We compared effect sizes using the seemingly unrelated regression method (Baltagi 1980; Verzilli, Stallard, and Whittaker 2005). **Supplementary Table 6** shows results from this analysis. At all loci, the lead SNP, worst-associated SNP, and mean number of risk alleles performed similarly, with the exception of the *FTO* locus, at which the lead SNP rs9939609 performed slightly better than the worst-associated SNP rs1477196. Finally, we tested whether including multiple SNPs at a locus improved the prediction of BMI in a regression model. Analyses were conducted using the variable selection algorithm in the Stata program mfp (Royston and Ambler 1999). Details of this method are reported elsewhere (Royston and Sauerbrei 2003). Briefly, SNPs were added to a baseline model predicting BMI as a function of age, sex, and geography in order of decreasing statistical significance of the SNPs' bivariate association with BMI. SNPs were retained in the model if their inclusion resulted in a statistically significant ($p<0.05$) decrease in model deviance. Results showed that model fit was not improved by the inclusion of multiple SNPs at any locus. Therefore, we retained only the best-associated SNPs from each of the 7 loci, resulting in a 32-SNP GRS (**Supplementary Table 7**).

PART 3. SENSITIVITY ANALYSES TO TEST HETEROGENEITY IN GRS ASSOCIATIONS

We tested the linearity of GRS-BMI associations using quadratic and cubic specifications of the GRS in linear regression models. Coefficients for the higher order (i.e. squared and cubic) GRS terms were not statistically significant ($p>0.10$ for all), indicating that the GRS-BMI association was approximately linear. We tested the measurement specificity of GRS-BMI associations by comparing GRS effect sizes for BMI to GRS effect sizes for weight and for waist circumference using the seemingly unrelated regression method (Baltagi 1980). GRS coefficients were similar across all three models

(p>0.10 for tests of differences), indicating that the GRS predicted not just BMI, but related measures of body size and adiposity. We tested the whether GRS-BMI associations were different for men and women or for older as compared to younger individuals using product terms in linear regression models. Coefficients for product terms were not statistically significant (p>0.10 for all), indicating that GRS-BMI associations were similar for men and women and across early to late mid-life. Finally, we tested whether GRS-BMI associations differed across the 4 in-person assessments in the ARIC Study using the seemingly unrelated regression method. GRS effect sizes were similar across all 4 assessments (p>0.10 for all comparisons), indicating that GRS-BMI associations were consistent across measurement intervals.

Supplementary Table 1. Genome Wide Association Studies Included In 3-Stage Approach Analyses. GWAS information comes from the NHGRI GWAS Catalog (www.genome.gov). Risk SNPs were defined as any SNP associated with an obesity-related phenotype (BMI, weight, waist circumference, categorical obesity) at $p<10^{-5}$ in the discovery or combined discovery and replication samples of the GWAS. *Italicized counts include imputed genotypes; **Lindgren et al. also investigated associations with waist circumference, and these are the association tests included in the SNP selection analysis; ***Scherag et al. also investigated associations with BMI and both phenotypes were included in the SNP selection analysis. Citations for the GWAS are included as (Cotsapas et al. 2009; Fox et al. 2007; Frayling et al. 2007; Heard-Costa et al. 2009; Herbert et al. 2006; Hinney et al. 2007; Johansson et al. 2010; Lindgren et al. 2009; Liu et al. 2010; Liu et al. 2008; Loos et al. 2008; Meyre et al. 2009; Scherag et al. 2010; Scuteri et al. 2007; Speliotes et al. 2010; Thorleifsson et al. 2009; Willer et al. 2009).

	GWAS Chip Manufacturer	SNPs Genotyped*	SNPs in GWAS Catalog		Risk SNPs Included in Analyses
			SNPs	Phenotypes	
Herbert et al. 2006	Affymetrix	86,604	0	Obesity	0
Frayling et al. 2007	Affymetrix	490,032	1	BMI	1
Scuteri et al. 2007	Affymetrix	362,129	1	BMI, Weight	12
Fox et al. 2007	Affymetrix	70,897	5	BMI, Waist Circumference	12
Hinney et al. 2007	Affymetrix	440,794	1	Obesity (early onset extreme)	15
Liu et al. 2008	Affymetrix	379,319	0	Obesity	3
Loos et al. 2008	Affymetrix	344,883	2	BMI	10
Thorleifsson et al. 2009	Illumina	305,846	18	BMI, Weight	47
Willer et al. 2009	Affymetrix & Illumina	*2,399,588*	11	BMI	24
Meyre et al. 2009	Illumina	308,846	5	Obesity	32
Cotsapas et al. 2009	Illumina	457,251	13	Obesity (extreme)	15
Lindgren et al. 2009	Affymetrix & Illumina	2,573,738	NA	Adiposity**	10
Heard-Costa et al. 2009	Affymetrix & Illumina	512,349	7	Waist Circumference	320
Johansson et al. 2009	Illumina	318,237	17	BMI, Weight	26
Liu et al. 2010	Illumina	*559,712*	2	BMI	3
Scherag et al. 2010	Affymetrix & Illumina	*1,596,878*	2	Obesity (extreme)***	13
Speliotes et al. 2010	Affymetrix, Illumina, Perlegen	*~2.8 million*	38	BMI	42

Supplementary Table 2. Risk SNPs and Source Publications: All SNPs reported as associated with Obesity, BMI, Weight, or Waist Circumference at $p<1x10^{-5}$ in Discovery or Combined Discovery and Replication Samples

Risk SNP	Trait	Publication
rs9939609	BMI	Frayling et al. 2007 Science
rs1121980	BMI	
rs6602024	BMI	
rs7193144	BMI	
rs8050136	BMI	
rs9926289	BMI	
rs9930506	BMI	Scuteri et al. 2007
rs9939609	BMI	
rs9939973	BMI	
rs9940128	BMI	
*rs4512445**	Waist Circumference	
rs7193144	Waist Circumference	
rs8050136	Waist Circumference	
rs1106683	BMI	
rs1106684	BMI	
rs1333026	BMI	
rs10488165	Waist Circumference	
rs10504576	Waist Circumference	
rs1875517	Waist Circumference	Fox et al. 2007
rs2206682	Waist Circumference	
rs2223662	Waist Circumference	
rs4469448	Waist Circumference	
rs4471028	Waist Circumference	
rs6996971	Waist Circumference	
rs953536	Waist Circumference	
rs10008032	Extreme Obesity	
rs1121980	Extreme Obesity	
rs16998603	Extreme Obesity	
rs2172478	Extreme Obesity	
rs2969001	Extreme Obesity	
rs3783950	Extreme Obesity	
rs41492957	Extreme Obesity	
rs6076920	Extreme Obesity	Hinney et al. 2007
rs619819	Extreme Obesity	
rs7193144	Extreme Obesity	
rs8050136	Extreme Obesity	
rs9276431	Extreme Obesity	
rs9939609	Extreme Obesity	
rs9939973	Extreme Obesity	
rs9940128	Extreme Obesity	

Supplementary Table 2 Continued

Risk SNP	Trait	Publication
rs16986921	BMI	
rs6013029	BMI	
rs6020712	BMI	Liu et al. 2008
rs10498767	BMI	
rs1121980	BMI	
rs17700633	BMI	
rs17782313	BMI	
rs2572106	BMI	Loos et al. 2008
rs2679120	BMI	
rs4623795	BMI	
rs7212681	BMI	
rs7336049	BMI	
rs748192	BMI	
rs10501087	BMI	
rs10783050	BMI	
rs10913469	BMI	
rs12970134	BMI	
rs1776012	BMI	
rs2568958	BMI	
rs2867125	BMI	
rs29941	BMI	
rs3101336	BMI	
rs3751812	BMI	
rs4074134	BMI	
rs467650	BMI	
rs4788102	BMI	
rs4854344	BMI	
rs4923461	BMI	
rs6265	BMI	
rs6499640	BMI	
rs7138803	BMI	
rs7190492	BMI	
rs7336332	BMI	
rs7481311	BMI	
rs7498665	BMI	
rs7561317	BMI	Thorleifsson et al. 2009
rs7647305	BMI	
rs7647305	BMI	
rs8044769	BMI	
rs8049439	BMI	
rs8050136	BMI	
rs836964	BMI	
rs867559	BMI	
rs925946	BMI	
rs9424977	BMI	
rs1047440	Weight	
rs1077393	Weight	
rs10835211	Weight	
rs1350341	Weight	
rs1350341	Weight	
rs17069257	Weight	
rs1973993	Weight	
rs2115172	Weight	
rs2260000	Weight	
rs2260000	Weight	
rs2844479	Weight	
rs2844479	Weight	
rs3766431	Weight	
rs633265	Weight	
rs6477693	Weight	

Supplementary Table 2 Continued

Risk SNP	Trait	Publication
rs10769908	BMI	
rs10769908	BMI	
rs10838738	BMI	
rs10838738	BMI	
rs10938397	BMI	
rs10938397	BMI	
rs11084753	BMI	
rs11084753	BMI	
rs11084753	BMI	
rs11773921	BMI	
rs12324805	BMI	
rs1421085	BMI	
rs1439845	BMI	
rs17700144	BMI	
rs17782313	BMI	
rs17782313	BMI	
rs2145270	BMI	Willer et al. 2009
rs2145270	BMI	
rs2245715	BMI	
rs2815752	BMI	
rs2815752	BMI	
rs2815752	BMI	
rs4752856	BMI	
rs6548238	BMI	
rs6548238	BMI	
rs6548238	BMI	
rs6907460	BMI	
rs7181095	BMI	
rs7498665	BMI	
rs7498665	BMI	
rs752238	BMI	
rs9931989	BMI	
rs9939609	BMI	
rs9939609	BMI	
rs10508503	Obesity	
rs11071927	Obesity	
rs11956401	Obesity	
rs12588659	Obesity	
rs12633433	Obesity	
rs1326986	Obesity	
rs1343772	Obesity	
rs1380100	Obesity	
rs1396618	Obesity	
rs1421085	Obesity	
rs1424233	Obesity	
rs16829231	Obesity	
rs17782313	Obesity	
rs1805081	Obesity	
rs1858367	Obesity	
rs2011946	Obesity	
rs2158044	Obesity	Meyere et al. 2009
rs2908338	Obesity	
rs3026762	Obesity	
rs3102841	Obesity	
rs413693	Obesity	
rs4712652	Obesity	
rs4786847	Obesity	
rs6463923	Obesity	
rs646839	Obesity	
rs6580742	Obesity	
rs6796959	Obesity	
rs7506051	Obesity	
rs7717673	Obesity	
rs908078	Obesity	
rs9275582	Obesity	
rs987052	Obesity	

Supplementary Table 2 Continued

Risk SNP	Trait	Publication
rs10433903	Extreme Obesity	
rs10999409	Extreme Obesity	
rs12295638	Extreme Obesity	
rs12492816	Extreme Obesity	
rs12635698	Extreme Obesity	
rs1435703	Extreme Obesity	
rs2274459	Extreme Obesity	
rs374748	Extreme Obesity	Cotsapas et al. 2009
rs6110577	Extreme Obesity	
rs6726292	Extreme Obesity	
rs7474896	Extreme Obesity	
rs7603514	Extreme Obesity	
rs9366829	Extreme Obesity	
rs9941349	Extreme Obesity	
rs999943	Extreme Obesity	
rs10085177	Waist Circumference	
rs11970116	Waist Circumference	
rs13116494	Waist Circumference	
rs2245667	Waist Circumference	
rs4737325	Waist Circumference	Lindgren et al. 2009
rs6429082	Waist Circumference	
rs7194591	Waist Circumference	
rs7826222	Waist Circumference	
rs7970350	Waist Circumference	
rs987237	Waist Circumference	
rs10096750	BMI	
rs10145154	BMI	
rs10146997	BMI	
rs10150332	BMI	
rs10173167	BMI	
rs10188334	BMI	
rs10189761	BMI	
rs10190052	BMI	
rs10193244	BMI	
rs10511835	BMI	
rs10813208	BMI	
rs10852521	BMI	
rs10871777	BMI	
rs10875982	BMI	
rs10969478	BMI	
rs11075985	BMI	
rs11075987	BMI	
rs11075989	BMI	
rs11075990	BMI	
rs11127483	BMI	
rs11127484	BMI	
rs11127485	BMI	Heard-Costa et al. 2009
rs11127491	BMI	
rs11152213	BMI	
rs11169176	BMI	
rs1121980	BMI	
rs11520442	BMI	
rs11642841	BMI	
rs11660783	BMI	
rs11662368	BMI	
rs11663816	BMI	
rs11664883	BMI	
rs11665563	BMI	
rs12002080	BMI	
rs12149832	BMI	
rs12446228	BMI	
rs12623218	BMI	
rs12714414	BMI	
rs12714415	BMI	
rs12954782	BMI	
rs12955983	BMI	
rs12957347	BMI	
rs12960928	BMI	
rs12964203	BMI	

Supplementary Table 2 Continued

Risk SNP	Trait	Publication
rs12966550	BMI	
rs12967135	BMI	
rs12969709	BMI	
rs12970134	BMI	
rs12992154	BMI	
rs12995480	BMI	
rs13007080	BMI	
rs13007086	BMI	
rs13012571	BMI	
rs13021737	BMI	
rs1320330	BMI	
rs1320331	BMI	
rs1320336	BMI	
rs1320337	BMI	
rs1320338	BMI	
rs13386517	BMI	
rs13386627	BMI	
rs13386964	BMI	
rs13388043	BMI	
rs13393304	BMI	
rs13396935	BMI	
rs13397165	BMI	
rs13401686	BMI	
rs13415094	BMI	
rs1350341	BMI	
rs1421085	BMI	
rs1456404	BMI	
rs1457489	BMI	
rs1477196	BMI	
rs1539952	BMI	
rs1553754	BMI	
rs1555967	BMI	
rs1558902	BMI	
rs1619975	BMI	
rs1673518	BMI	Heard-Costa et al. 2009
rs17109256	BMI	
rs17175643	BMI	
rs17201502	BMI	
rs17299673	BMI	
rs17700144	BMI	
rs17782313	BMI	
rs17817288	BMI	
rs17817449	BMI	
rs17817964	BMI	
rs1861866	BMI	
rs1861867	BMI	
rs1942860	BMI	
rs1942863	BMI	
rs1942866	BMI	
rs2051311	BMI	
rs2051312	BMI	
rs2058908	BMI	
rs2168708	BMI	
rs2168711	BMI	
rs2206277	BMI	
rs2288278	BMI	
rs2331841	BMI	
rs2397026	BMI	
rs2860323	BMI	
rs2867108	BMI	
rs2867109	BMI	
rs2867110	BMI	
rs2867112	BMI	
rs2867113	BMI	
rs2867122	BMI	
rs2867123	BMI	
rs2867125	BMI	
rs2867131	BMI	
rs2903492	BMI	

Supplementary Table 2 Continued

Risk SNP	Trait	Publication
rs2947411	BMI	
rs297924	BMI	
rs34341	BMI	
rs3751812	BMI	
rs3751813	BMI	
rs3928247	BMI	
rs4045166	BMI	
rs4299252	BMI	
rs4423631	BMI	
rs4438957	BMI	
rs4452188	BMI	
rs4613321	BMI	
rs4615388	BMI	
rs4620360	BMI	
rs474112	BMI	
rs475134	BMI	
rs476828	BMI	
rs4783819	BMI	
rs4784323	BMI	
rs4793927	BMI	
rs4854344	BMI	
rs4854348	BMI	
rs4854349	BMI	
rs487720	BMI	
rs489693	BMI	
rs492443	BMI	
rs497353	BMI	
rs5017300	BMI	
rs5017303	BMI	
rs521663	BMI	
rs523288	BMI	
rs536783	BMI	
rs538656	BMI	
rs545708	BMI	
rs559623	BMI	Heard-Costa et al. 2009
rs562622	BMI	
rs563726	BMI	
rs565239	BMI	
rs565970	BMI	
rs571312	BMI	
rs574988	BMI	
rs589850	BMI	
rs590215	BMI	
rs591166	BMI	
rs611428	BMI	
rs633265	BMI	
rs649721	BMI	
rs6499640	BMI	
rs6548237	BMI	
rs6567155	BMI	
rs6567160	BMI	
rs6567161	BMI	
rs663129	BMI	
rs666181	BMI	
rs6711012	BMI	
rs6719518	BMI	
rs6719980	BMI	
rs6725549	BMI	
rs6728726	BMI	
rs6731348	BMI	
rs6731688	BMI	
rs6732471	BMI	
rs6734363	BMI	
rs6742576	BMI	
rs6743060	BMI	
rs6744646	BMI	
rs6744653	BMI	
rs6745266	BMI	
rs6752470	BMI	

Supplementary Table 2 Continued

Risk SNP	Trait	Publication
rs6755502	BMI	
rs681630	BMI	
rs682614	BMI	
rs683430	BMI	
rs7022642	BMI	
rs7132908	BMI	
rs7138803	BMI	
rs7144011	BMI	
rs7185735	BMI	
rs7190492	BMI	
rs7193144	BMI	
rs7201850	BMI	
rs7202116	BMI	
rs7203521	BMI	
rs7205986	BMI	
rs7206010	BMI	
rs7206790	BMI	
rs7240566	BMI	
rs7338657	BMI	
rs7561317	BMI	
rs7567570	BMI	
rs7570198	BMI	
rs7571957	BMI	
rs7574359	BMI	
rs7576624	BMI	
rs7576635	BMI	
rs7585056	BMI	
rs7587786	BMI	
rs7604609	BMI	
rs7608050	BMI	
rs7715806	BMI	
rs7831920	BMI	
rs8043757	BMI	Heard-Costa et al.
rs8044769	BMI	2009
rs8047395	BMI	
rs8050136	BMI	
rs8051591	BMI	
rs8055197	BMI	
rs8057044	BMI	
rs8083289	BMI	
rs8086627	BMI	
rs8089364	BMI	
rs8091524	BMI	
rs8095404	BMI	
rs921971	BMI	
rs939582	BMI	
rs939583	BMI	
rs953442	BMI	
rs975918	BMI	
rs981106	BMI	
rs981113	BMI	
rs987237	BMI	
rs9922047	BMI	
rs9922619	BMI	
rs9922708	BMI	
rs9923147	BMI	
rs9923233	BMI	
rs9923544	BMI	
rs9928094	BMI	
rs9930333	BMI	
rs9930501	BMI	
rs9930506	BMI	
rs9931494	BMI	
rs9932754	BMI	
rs9935401	BMI	
rs9936385	BMI	
rs9937053	BMI	

Supplementary Table 2 Continued

Risk SNP	Trait	Publication
rs993887	BMI	
rs9939609	BMI	
rs9939973	BMI	
rs9940128	BMI	
rs9940646	BMI	
rs9941349	BMI	
rs10059683	Waist Circumference	
rs10066756	Waist Circumference	
rs10068332	Waist Circumference	
rs10146690	Waist Circumference	
rs10150482	Waist Circumference	
rs10869557	Waist Circumference	
rs10869558	Waist Circumference	
rs10869559	Waist Circumference	
rs11778132	Waist Circumference	
rs11780082	Waist Circumference	
rs11857639	Waist Circumference	
rs11990688	Waist Circumference	
rs12271537	Waist Circumference	
rs12274672	Waist Circumference	
rs12475139	Waist Circumference	
rs12792768	Waist Circumference	
rs13404551	Waist Circumference	
rs1447905	Waist Circumference	
rs1521252	Waist Circumference	
rs16930931	Waist Circumference	
rs17008958	Waist Circumference	
rs17061143	Waist Circumference	
rs17109221	Waist Circumference	
rs17476669	Waist Circumference	
rs17537900	Waist Circumference	
rs17836088	Waist Circumference	
rs2164210	Waist Circumference	
rs2236783	Waist Circumference	
rs2322659	Waist Circumference	Heard-Costa et al.
rs2322660	Waist Circumference	2009
rs2365642	Waist Circumference	
rs2370982	Waist Circumference	
rs303211	Waist Circumference	
rs309134	Waist Circumference	
rs309137	Waist Circumference	
rs309160	Waist Circumference	
rs309168	Waist Circumference	
rs4098360	Waist Circumference	
rs4420638	Waist Circumference	
rs4701252	Waist Circumference	
rs4758213	Waist Circumference	
rs4758215	Waist Circumference	
rs507824	Waist Circumference	
rs569406	Waist Circumference	
rs6499641	Waist Circumference	
rs6714750	Waist Circumference	
rs6716536	Waist Circumference	
rs6754311	Waist Circumference	
rs6817633	Waist Circumference	
rs6837818	Waist Circumference	
rs6870971	Waist Circumference	
rs687670	Waist Circumference	
rs693895	Waist Circumference	
rs6998794	Waist Circumference	
rs7110070	Waist Circumference	
rs7156625	Waist Circumference	
rs745500	Waist Circumference	
rs748841	Waist Circumference	
rs7579771	Waist Circumference	
rs7824886	Waist Circumference	
rs7932813	Waist Circumference	
rs8059991	Waist Circumference	
rs892715	Waist Circumference	
rs9598518	Waist Circumference	
rs9790104	Waist Circumference	

Supplementary Table 2 Continued

Risk SNP	Trait	Publication
rs1024889	BMI	Johansson et al. 2009
rs1152846	BMI	
rs12517906	BMI	
rs1458095	BMI	
rs1878047	BMI	
rs1927702	BMI	
rs2383393	BMI	
rs3803915	BMI	
rs3803915	BMI	
rs3934834	BMI	
rs4085400	BMI	
rs824931	BMI	
rs875283	BMI	
rs10844154	Weight	
rs10972341	Weight	
rs10972350	Weight	
rs1152846	Weight	
rs12517906	Weight	
rs1570885	Weight	
rs1816002	Weight	
rs1840440	Weight	
rs2765086	Weight	
rs4879869	Weight	
rs7209395	Weight	
rs7919006	Weight	
rs965178	Weight	
rs2275215	BMI	Liu et al. 2010
rs10458787	BMI	
rs11127485	BMI	Scherag et al. 2010
rs1558902	BMI	
rs9935401	BMI	
rs10926984	Obesity	
rs12145833	Obesity	
rs2783963	Obesity	
rs11127485	Obesity	
rs17150703	Obesity	
rs13278851	Obesity	
rs516175	Obesity	
rs1558902	Obesity	
rs9935401	Obesity	
rs17700144**	Obesity	

Supplementary Table 2 Continued

Risk SNP	Trait	Publication
rs1558902	BMI	Speliotes et al. 2010
rs2860323	BMI	
rs6567160	BMI	
rs10938397	BMI	
rs10767664	BMI	
rs543874	BMI	
rs2815752	BMI	
rs10182181	BMI	
rs12444979	BMI	
rs7498665	BMI	
rs987237	BMI	
rs2241423	BMI	
rs9816226	BMI	
rs7138803	BMI	
rs2287019	BMI	
rs1514177	BMI	
rs13107325	BMI	
rs2112347	BMI	
rs10968576	BMI	
rs3817334	BMI	
rs3810291	BMI	
rs887912	BMI	
rs10150332	BMI	
rs7640855	BMI	
rs11847697	BMI	
rs2890652	BMI	
rs11165643	BMI	
rs4771122	BMI	
rs4836133	BMI	
rs4929949	BMI	
rs29938	BMI	
rs9296115	BMI	
rs2922763	BMI	
rs2444217	BMI	
rs867559	BMI	
rs3764400	BMI	
rs255414	BMI	
rs6955651	BMI	
rs17016663	BMI	
rs6477694	BMI	
rs2652594	BMI	
rs2035935	BMI	

Supplementary Table 2 Footnote: *Reported as "SNP_A-2284869" and crosswalked to rs ID using the Affy 6.0 SNP name to rs ID crosswalk file "GenomeWideSNP_6.na30.annot.csv"; **The GWAS catalog reports rs10871777 (in LD with rs17700144 at R^2=0.85) as the obesity-associated SNP near the gene MC4R in Scherag et al. SNPs are reported only once per GWAS. Associations are reported for BMI where present and for other phenotypes where BMI was not investigated or the SNP was not associated with BMI at $p<1 \times 10^{-5}$

Supplementary Table 3. Replicated and/or Genome-Wide Significant LD Blocks Identified in 3-Stage Approach Analyses. LD blocks were defined from LD analyses of risk SNPs (genotype-phenotype association at $p<1x10^{-5}$) using data from the HapMap version 3 CEU sample accessed via Seattle SNPs's Genome Variation Server and an LD threshold of $R^2 \geq 0.95$. Replication was evaluated as the number of GWAS reporting any SNP in the block as a risk SNP. Genes were evaluated within 100kb in either direction from an LD block's outermost SNPs.

Chromsome	Identified LD Blocks	Replicated LD Blocks	Mean Number of Replications (All Blocks)	Genes
1	4	3	2.0	*NEGR1, TNNI3K, PTB2, SEC16B*
2	6	2	2.0	*LRP1B, TMEM18*
3	3	0	1.0	*CADM2, ETV5/DGKG*
4	2	1	1.5	*GNPDA2, SLC39A8*
5	2	0	1.0	*POC5, ZNF608*
6	1	1	3.0	*TFAP2B*
9	2	1	1.5	*LING02/LRRN6C, LMX1B*
11	7	0	1.0	*RPL27A, BDNF, MTCH2*
12	1	1	3.0	*BDCDIN3D/FAIM2/NCKAP5L*
13	1	0	3.0	*MTIF3, GRF3A*
14	2	1	1.5	*PRKD1, NRXN3*
15	1	0	1.0	*MAP2K5*
16	26	14	3.0	*GRP5B, ATXN2L/TUFM/SH2B1, FTO*
18	7	7	2.6	*MC4R*
19	4	1	1.3	*KCTD15, ZC3H4, QPCTL, TMEM160*

Supplementary Table 4. Characteristics of Replicated and/or Genome-Wide Significant LD Blocks

			LD Block		GWAS Publication															
Chrom-osome	Chromosomal Space Covered by All Risk SNPs in the LD Block (NCBI Build 36)	Nearby Genes	Seed SNPs (risk SNPs in LD with all risk SNPs in block at $R^2 \geq 0.95$) // Proxy SNPs (risk SNPs in LD with any seed SNP at R2≥0.95)	Any SNP in Block Genome-Wide Significant	[1]	[2]	[3]	[4]	[5]	[6]	[7]	[8]	[9]	[10]	[11]	[12]	[13]	[14]	[15]	[16]
1	72,523,773 - 72,585,028	NEGR1	rs2568958, rs2815752, rs3101336	Yes							X	X								X
	74,763,990	TNNI3K	rs1514177	Yes																X
	96,696,685 - 96,716,582	*PTBP2*	rs11165643 // rs1973993	Yes							X									X
	176,156,103 - 176,180,142	SEC16B	rs10913469, rs543874	Yes							X									X
2	604,168 - 643,874	TMEM18	See footnote	Yes							X					X			X	X
	604,210 - 643,874	TMEM18		Yes							X					X			X	X
	624,905	TMEM18	rs6548238	Yes								X								
	25,003,800		rs10182181	Yes																X
	59,156,381		rs887912	Yes																X
	142,676,401	LRP1B	rs2890652	Yes																X
3	85,956,854	CADM2	rs7640855	Yes																X
	187,316,984	ETV5/DGKG	rs7647305	Yes							X									
	187,317,193	ETV5/DGKG	rs9816226	Yes																X
4	44,877,284		rs10938397	Yes								X								X
	103,407,732	SLC39A8	rs13107325	Yes																X
5	75,050,998	POC5	rs2112347	Yes																X
	124,360,002		rs4836133	Yes																X
6	50,906,485 - 50,911,009	TFAP2B	rs2206277, rs987237	Yes											X	X				X
9	28,404,339	LING02	rs10968576	Yes																X
	128,505,146	LMX1B	rs867559	$p<1x10^{-6}$							X									X
11	8,561,169	STK33	rs4929949	Yes																X
	27,603,861 - 27,626,684	BDNF	rs10501087, rs4074134, rs4923461	Yes							X									
	27,636,492	BDNF	rs6265	Yes							X									
	27,682,562	BDNF	rs10767664	Yes																X
	27,623,778 - 27,623,778	BDNF	rs925946	Yes							X									
	47,604,618 - 47,619,625	MTCH2	rs10838738, rs4752856	Yes								X								
	47,607,569	MTCH2	rs3817334	Yes																X
12	48,533,735	BDCDIN3D, FAIM2, NCKAP5L	rs7138803	Yes							X					X				X
13	26,918,180	MTIF3, *GRF3A*	rs4771122	Yes																X
14	29,584,863		rs11847697	Yes																X
	78,961,635 - 79,014,915	NRXN3	rs10145154, rs10150332, rs17109256, rs7144011 // rs10146997, rs10150482, rs17109221, rs17836088, rs7156625	Yes												X				X
15	65,873,892	MAP2K5	rs2241423	Yes																X

Supplementary Table 4 Continued

			LD Block		GWAS Publication															
Chrom-osome	Chromosomal Space Covered by All Risk SNPs in the LD Block (NCBI Build 36)	Genes Overlapping LD Block/ 10kb of SNP*	Seed SNPs (risk SNPs in LD with all risk SNPs in block at R^2≥0.95) // Proxy SNPs (risk SNPs in LD with any seed SNP at R2≥0.95)	Any SNP in Block Genome-Wide Significant	[1]	[2]	[3]	[4]	[5]	[6]	[7]	[8]	[9]	[10]	[11]	[12]	[13]	[14]	[15]	[16]
	19,841,101	GPRC5B	rs12444979	Yes																X
	28,745,016 - 28,790,742	ATXN2L, TUFM, SH2B1	rs4788102, rs7498665, rs8049439	Yes							X	X								X
	52,312,678 - 52,327,178	FTO	rs6499640, rs7203521, rs7206010	Yes							X					X				
	52,355,409	FTO	rs7206790	Yes												X				
	52,356,024 - 52,361,841	FTO	rs8047395 //rs1861866, rs8055197	Yes												X				
	52,356,024 - 52,363,781	FTO	rs1861866, rs8055197 // rs10852521, rs8047395, rs9922047	Yes												X				
	52,360,657 - 52,372,662	FTO	rs10852521, rs9922047 // rs11075987, rs1861866, rs8055197	Yes												X				
	52,362,466 - 52,372,662	FTO	rs11075987 // rs10852521, rs9922047	Yes												X				
	52,365,265	FTO	rs17817288	Yes												X				
	52,370,115	FTO	rs8057044	Yes												X				
	52,396,636	FTO	rs8044769	Yes							X					X				
	52,357,008 - 52,366,748	FTO	rs11075985, rs9940646 // rs1121980, rs9923147, rs9923544, rs9928094, rs9930333, rs9937053, rs9939973, rs9940128	Yes		X		X		X						X				
	52,357,008 - 52,384,680	FTO	rs1121980, rs9923147, rs9923544, rs9928094, rs9930333, rs9937053, rs9939973, rs9940128 // rs11075985, rs1421085, rs1558902, rs7201850, rs9931494, rs9940646, rs9941349	Yes		X		X		X		X	X	X		X			X	X
	52,357,008 - 52,385,567	FTO	rs1421085, rs1558902 // rs17817964, rs7185735, rs7193144, rs7202116, rs9937053	Yes		X		X				X	X			X			X	X
16	52,357,008 - 52,389,272	FTO	rs7201850, rs9931494, rs9941349 // rs1121980, rs9922619, rs9922708, rs9923147, rs9923544, rs9928094, rs9930333, rs9930501, rs9930506, rs9932754, rs9937053, rs9939973, rs9940128	Yes		X		X		X				X		X				
	52,358,455 - 52,400,409	FTO	rs17817964, rs7185735 // rs11075989, rs11075990, rs12149832, rs1421085, rs1558902, rs17817449, rs3751812, rs7193144, rs7202116, rs8043757, rs8050136, rs8051591, rs9923233, rs9935401, rs9939609	Yes	X	X		X			X	X	X			X			X	X
	52,361,075 - 52,400,409	FTO	rs7193144, rs7202116 // rs11075989, rs11075990, rs12149832, rs1558902, rs17817449, rs17817964, rs3751812, rs7185735, rs8043757, rs8050136, rs8051591, rs9923233, rs9935401, rs9939609	Yes	X	X		X			X	X				X			X	X
	52,368,187 - 52,385,567	FTO	rs11075989, rs11075990, rs17817449, rs3751812, rs8043757, rs8050136, rs8051591, rs9923233, rs9935401, rs9939609 // rs17817964, rs7185735, rs7193144, rs7202116, rs9936385	Yes	X	X		X			X	X				X			X	
	52,368,187 - 52,400,409	FTO	rs12149832 // rs17817964, rs7185735, rs7193144, rs7202116	Yes		X		X								X				
	52,376,670 - 52,377,378	FTO	rs9936385 // rs11075989, rs9923233	Yes												X				
	52,379,363 - 52,389,272	FTO	rs9922619, rs9922708, rs9930501, rs9932754 // rs7201850, rs9930506, rs9931494, rs9941349	Yes		X								X		X				
	52,382,989 - 52,389,272	FTO	rs9930506 // rs9922619, rs9922708, rs9930501, rs9931494, rs9932754, rs9941349	Yes		X								X		X				
	52,406,062	FTO	rs1861867	Yes												X				
	52,357,888 - 52,386,253	FTO	rs12446228, rs1477196, rs4783819, rs7190492	Yes							X					X				
	52,376,209	FTO	rs3751813	Yes												X				
	52,402,988	FTO	rs11642841	Yes												X				

Supplementary Table 4 Continued

	LD Block				GWAS Publication														
Chrom-osome	Chromosomal Space Covered by All Risk SNPs in the LD Block (NCBI Build 36)	Genes Overlapping LD Block/ 10kb of SNP*	Seed SNPs (risk SNPs in LD with all risk SNPs in block at R^2≥0.95) // Proxy SNPs (risk SNPs in LD with any seed SNP at R2≥0.95)	Any SNP in Block Genome-Wide Significant	[1]	[2]	[3]	[4]	[5]	[6]	[7]	[8]	[9]	[10]	[11]	[12]	[13]	[14]	[15]	[16]
18	55,962,962	*MC4R*	rs17700144	$p<1x10^{-6}$								X				X			X	
	55,980,115 - 56,003,928	*MC4R*	rs10871777, rs11152213, rs12967135, rs17782313, rs2168711, rs476828, rs523288, rs538656, rs571312, rs6567160, rs663129	Yes						X		X	X			X				X
	55,964,628 - 56,003,732	*MC4R*	rs1350341, rs1619975, rs1673518, rs2051311, rs2051312, rs2331841, rs474112, rs475134, rs487720, rs536783, rs545708, rs559623, rs562622, rs565239, rs565970, rs574988, rs589850, rs591166, rs611428, rs649721, rs6567161, rs666181, rs681630, rs682614, rs683430, rs975918, rs993887 // rs521663, rs633265	$p<1x10^{-6}$								X				X				
	56,009,782 - 56,048,783	*MC4R*	rs12960928 // rs11663816, rs11664883, rs11665563, rs12954782, rs12969709, rs12970134, rs1457489, rs17175643, rs492443, rs8083289, rs8089364, rs921971	Yes								X				X				
	56,009,782 - 56,062,310	*MC4R*	rs921971 // rs11663816, rs11664883, rs11665563, rs12954782, rs12955983, rs12960928, rs12964203, rs12966550, rs12969709, rs12970134, rs1457489, rs17175643, rs2168708, rs492443, rs8083289, rs8089364	Yes								X				X				
	56,009,809 - 56,047,722	*MC4R*	rs12955983 // rs11663816, rs11664883, rs11665563, rs12954782, rs12969709, rs12970134, rs1457489, rs17175643, rs8083289, rs8089364, rs921971	Yes								X				X				
	56,009,809 - 56,062,310	*MC4R*	rs11663816, rs11664883, rs11665563, rs12954782, rs12964203, rs12966550, rs12969709, rs12970134, rs1457489, rs17175643, rs2168708, rs8083289, rs8089364 // rs12955983, rs12960928, rs921971	Yes								X				X				
19	39,001,372 - 39,003,321	KCTD15	rs29938, rs29941	Yes								X								X
	39,013,977	*KCTD15*	rs11084753	Yes									X							
	52,260,843	ZC3H4, TMEM160	rs3810291	Yes																X
	50,894,012	QPCTL	rs2287019	Yes																X

Supplementary Table 4 Footnote: GWAS are numbered as follows: [1] Frayling et al. 2007, *Science*; [2] Scuteri et al. 2007, *PLoS Genetics*; [3] Fox et al. 2007, *BMC Medical Genetics*; [4] Hinney et al. 2007, *PLoS One*; [5] Liu et al. 2008, *Human Molecular Genetics*; [6] Loos et al. 2008, *Nature Genetics*; [7] Thorleifsson et al. 2009, *Nature Genetics*; [8] Willer et al. 2009, *Nature Genetics*; [9] Meyere et al. 2009 *Nature Genetics*; [10] Cotsapas et al. 2009, *Human Molecular Genetics*; [11] Lindgren et al. 2009 *PLoS Genetics*; [12] Heard-Costa et al. 2009, *PLoS Genetics*; [13] Johansson et al. 2009, *Obesity*; [14] Liu et al. 2010, *Twin Research and Human Genetics*; [15] Shcerag et al. 2010, *PLoS Genetics*; Speliotes et al. 2010, *Nature Genetics*. LD Blocks were defined using an R^2 threshold of 0.95. Genes are reported within 100 kb of any seed SNP. Italicized genes fall outside the 100kb range, but contain SNPs in LD with a block seed. GWAS are indicated as replicating a block if they reported a SNP in LD at R^2≥0.95 with a block seed or proxy as associated with an obesity-related phenotype at $p<1x10^{-5}$ in either their discovery or combined discovery and replication samples.

Block 2.2: (**seeds**) rs10173167, rs10188334, rs10189761, rs10190052, rs10193244, rs11127484, rs11127485, rs11127491, rs12714414, rs12714415, rs12992154, rs12995480, rs13007080, rs13007086, rs13012571, rs13021737, rs1320331, rs1320336, rs1320337, rs1320338, rs13386517, rs13386627, rs13386964, rs13388043, rs13393304, rs13396935, rs13397165, rs13401686, rs13415094, rs2860323, rs2867108, rs2867109, rs2867110, rs2867112, rs2867113, rs2867122, rs2867125, rs2903492, rs2947411, rs4423631, rs4452188, rs4613321, rs4854344, rs4854348, rs4854349, rs5017300, rs5017303, rs6711012, rs6719518, rs6719980, rs6725549, rs6728726, rs6731348, rs6731688,

rs6732471, rs6734363, rs6743060, rs6744646, rs6744653, rs6752470, rs6755502, rs7561317, rs7567570, rs7570198, rs7571957, rs7574359, rs7576624, rs7576635, rs7585056, rs7604609, rs7608050, rs939582, rs939583

Block 2.3: (**seeds**) rs2867123, (**proxies**) rs10173167, rs10188334, rs10189761, rs10190052, rs10193244, rs11127484, rs11127485, rs11127491, rs12714414, rs12714415, rs12992154, rs12995480, rs13007080, rs13007086, rs13012571, rs13021737, rs1320331, rs1320336, rs1320337, rs1320338, rs13386517, rs13386627, rs13386964, rs13388043, rs13393304, rs13396935, rs13397165, rs13401686, rs13415094, rs2860323, rs2867108, rs2867109, rs2867110, rs2867112, rs2867113, rs2867122, rs2867123, rs2867125, rs2903492, rs4423631, rs4452188, rs4613321, rs4854344, rs4854348, rs4854349, rs5017300, rs5017303, rs6711012, rs6719518, rs6719980, rs6725549, rs6728726, rs6731348, rs6731688, rs6732471, rs6734363, rs6743060, rs6744646, rs6744653, rs6752470, rs6755502, rs7561317, rs7567570, rs7570198, rs7571957, rs7574359, rs7576624, rs7576635, rs7585056, rs7604609, rs7608050, rs939582, rs939583

Supplementary Table 5. Effect Sizes for Genetic Risk Scores Created Using the 3-Stage Approach and the Best-Guess and Top-Hits Approaches. To measure BMI effect sizes for the GRSs, we estimated Pearson correlations (r) from separate linear regressions of BMI on each of the GRSs. To measure obesity effect sizes for the GRSs, we estimated odds ratios (OR) from separate logistic regressions of obesity on each of the GRSs. Regression models were adjusted for age (linear and quadratic terms), gender, the age-gender interaction, and the ARIC Study Centers where data were collected. In Panel A, the Best-Guess GRS was based on the GRS published by Li and colleagues (Li et al. 2010) and the Top-Hits GRS was based on the GRS published by Peterson and colleagues (Peterson et al. 2011). In Panel B, the Best Guess GRS was based on the full set of obesity- and BMI-associated SNPs listed in the NHGRI GWAS Catalog and the Top-Hits GRS was based on the GRS published by Speliotes and colleagues (Speliotes et al. 2010). ***p<0.001. Comparison of effect sizes using the seemingly unrelated regression method (Baltagi 1980) indicated that effect sizes for the 3 GRSs in Panel A were not statistically different from one another (p-value for difference >0.10 for all), but that among the GRSs in Panel B, the 3-stage approach performed better than the Best-Guess and Top-Hits GRSs (p<0.05 for all). However, our sample had only 40% power to detect effect size differences of r=0.01 / OR=1.01, so this result should be interpreted with caution.

		Effect Sizes	
		BMI	Obesity
Approach to GRS Construction	SNPs	Pearson Correlation (r)	Odds Ratio [95% CI]
Panel A. GRSs Constructed from Results of 9 GWAS Published by December 31, 2008			
3-Stage	28	0.08***	1.08 [1.06-1.10]
Best-Guess	12	0.08***	1.08 [1.06-1.11]
Top-Hits	59	0.06***	1.07 [1.04-1.09]
Panel B. GRSs Constructed from Results of the Full Set of 16 GWAS			
3-Stage	57	0.11***	1.12 [1.10-1.15]
Best-Guess	97	0.10***	1.11 [1.09-1.13]
Top-Hits	32	0.10***	1.10 [1.08-1.12]

Supplementary Table 6. Analysis of Loci with Multiple Tag SNPs. * "Lead SNP" is underlined; "Worst-associated SNP" is italicized; Test statistics and effect sizes were estimated in linear regression models of BMI adjusted for demographics and geography. "Lead SNPs" and "Worst-associated SNPs" were determined from the test statistics for the individual SNPs. Effect sizes were compared using the seemingly unrelated regressions method (Baltagi 1980).

Locus	ARIC SNPs Tagging LD Blocks in Genic Region	Minimum R^2 Among Tag SNPs	Effect Size (Pearson's r) p-value for comparison with lead SNP Lead SNP	Worst-Associated SNP	Mean Number of BMI-Increasing Alleles
Chr 2 *TMEM18*	*rs10189761* , rs2867123, rs4854345	0.94	0.027	0.023 p=0.276	0.025 p=0.371
Chr 3 ETV5/DGKG	rs12516728, *rs9863591*	0.85	0.007	<0.001 p=0.721	0.018 p=0.427
Chr 11 BDNF	rs10501087, *rs7103411* , rs6265, rs11030108	0.86	0.027	0.022 p=0.124	0.026 p=0.485
Chr 11 MTCH	rs12419692, *rs3817334*	0.77	0.020	0.019 p=0.871	0.020 p=0.878
Chr 16 FTO	*rs1477196* , rs17817288, rs1121980, rs9922047, rs9939973, rs9940128, rs9941349, rs7193144, rs7203521, rs9939609, rs8050136, rs9930506	0.40	0.072	0.034 p<0.001	0.068 p=0.104
Chr 18 MC4R	*rs476828* , rs1673518, rs17782313, rs11663816, rs11665563, rs12969709, rs12970134	0.25	0.026	0.019 p=0.158	0.025 p=0.062
Chr 19 KCDT15	*rs29942* , rs11084753	0.58	0.010	0.009 p=0.879	0.009 p=0.913

Supplementary Table 7. SNPs Included in the Obesity Genetic Risk Score.

								White Participants, n=8,210-8,8,286				Black Participants, n=2,402-2,442			
Chr	Nearby Gene	Tag SNP	GWAS Replications	BMI-Increasing Allele in GWAS	Test Alelle	Other Allele	Effect-Size Weight	Test Allele Frequency	Per Allele Change in BMI	p-value	Direction of Association Inconsistent with GWAS	Test Allele Frequency	Per Allele Change in BMI	p-value	Direction of Association Inconsistent with GWAS
1	NEGR1	rs2815752	3	Major	G	A	0.13	38%	-0.259	0.001		45%	-0.071	0.673	
	TNNI3K	rs1514175	1	Minor	A	G	0.07	43%	-0.001	0.985		68%	-0.091	0.608	X
	PTBP2	rs1555543	2	Major	A	C	0.06	42%	-0.128	0.086		57%	-0.031	0.855	
	SEC16B	rs543874	2	Minor	G	A	0.22	20%	0.341	0.000		25%	0.335	0.095	
2	FANCL	rs759250	1	Minor	A	G	0.10	29%	0.036	0.656		8%	-0.242	0.475	X
	LRP1B	rs2121279	1	Minor	T	C	0.08	14%	0.234	0.032		3%	-0.253	0.651	X
	TMEM18	rs2867123	5	Major	G	C	0.30	17%	-0.237	0.018		12%	0.022	0.935	X
	RBJ	rs10182181	1	Minor	G	A	0.14	46%	0.117	0.117		84%	0.758	0.001	
3	CADM2	rs12714640	1	Minor	A	C	0.10	19%	0.278	0.003		6%	0.006	0.987	
	ETV5/DGKG	rs1516728	2	Major	T	A	0.11	23%	-0.060	0.489		52%	-0.098	0.565	
4	GNPDA2	rs12641981	2	Minor	T	C	0.18	43%	0.088	0.238		23%	0.103	0.602	
	SLC39A8	rs13114738	1	Minor	T	C	0.13	8%	0.506	4.15E-04		1%	-1.583	0.008	X
5	POC5 FLJ35779	rs10057967	1	Major	C	T	0.10	37%	-0.227	0.003		49%	0.128	0.435	X
	ZNF608	rs6864049	1	Minor	G	A	0.07	46%	-0.189	0.012	X	19%	-0.463	0.033	X
6	TFAP2B	rs734597	3	Minor	A	G	0.13	17%	0.382	1.21E-04		9%	0.030	0.920	
9	LING02 LRRN6C	rs1412235	1	Minor	C	G	0.11	31%	0.003	0.970		16%	0.365	0.111	
	LMX1B	rs867559	2	Minor	G	A	0.24	20%	0.088	0.339		32%	0.025	0.889	
11	RPL27A	rs2028882	1	Major	C	A	0.06	50%	-0.065	0.375		66%	0.116	0.515	X
	BDNF	rs10501087	2	Major	C	T	0.18	21%	-0.223	0.013		7%	-0.521	0.181	
	MTCH2	rs12419692	2	Minor	A	C	0.05	36%	0.146	0.059		9%	0.012	0.968	
12	BDCDIN3D, FAIM2	rs7138803	3	Minor	A	G	0.12	38%	0.164	0.033		17%	0.100	0.650	
13	MTIF3, GRF3A	rs1475219	1	Minor	C	T	0.09	21%	0.262	0.004		22%	-0.099	0.632	X
14	PRKD1	rs1440983	1	Minor	A	G	0.15	5%	0.266	0.129		23%	0.156	0.449	
	NRXN3	rs7144011	2	Minor	T	G	0.13	22%	0.165	0.064		24%	0.164	0.428	
15	MAP2K5	rs28670272	1	Major	G	A	0.13	23%	-0.212	0.014		41%	0.005	0.977	X
16	GPR5B	rs11639988	1	Major	G	A	0.17	15%	0.006	0.952	X	24%	-0.262	0.194	
	ATXN2L, TUFM, SH2B1	rs12443881	3	Minor	T	C	0.15	39%	-0.005	0.948	X	9%	-0.607	0.030	X
	FTO	rs9939609	11	Minor	A	T	0.38	41%	0.496	8.19E-11		48%	0.129	0.443	
18	MC4R	rs12970134	6	Minor	A	G	0.21	26%	0.209	0.012		13%	0.057	0.822	
19	KCTD15	rs11084753	3	Major	A	G	0.04	33%	-0.071	0.371		36%	0.197	0.270	X
	QPCTL	rs11083779	1	Major	C	T	0.07	4%	-0.227	0.196		11%	-0.267	0.294	
	ZC3H4 TMEM160	rs7250850	1	Major	G	C	0.09	29%	-0.174	0.032		80%	-0.343	0.124	

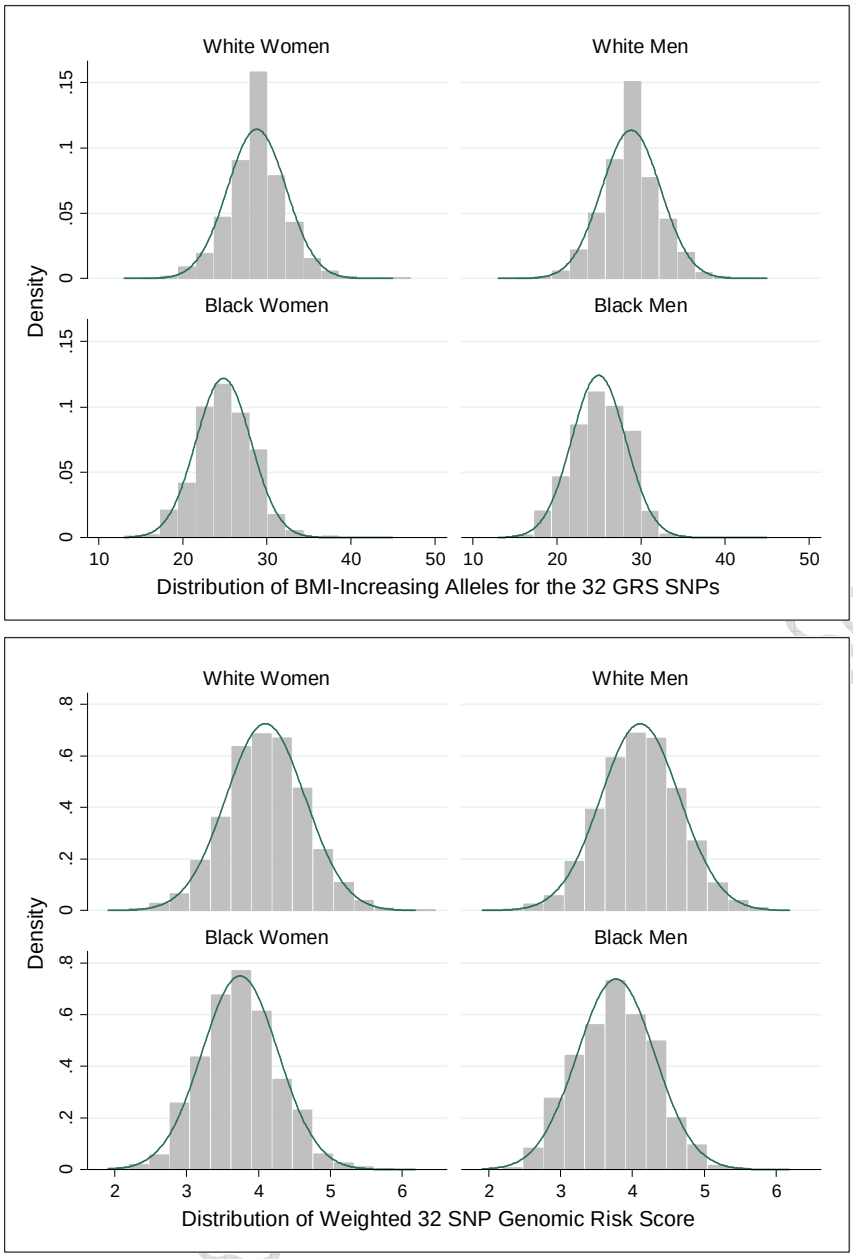
Supplementary Table 7 Footnote: GWAS replications include GWAS reporting any SNP in any LD block tagged by the SNP as obesity-associated at $p<1x10^{-5}$ in the discovery or combined discovery and replication samples. Test allele and other allele are reported from the positive strand. Effect-size weights were obtained from (Speliotes et al. 2010) for all SNPs with the exception of rs867559, for which the effect size weight was obtained from (Thorleifsson et al. 2009). Allele frequencies and per-allele effects are reported based on all participants in the analysis sample. Per-allele effects were estimated from linear regressions of BMI on SNP genotype (number of minor alleles), adjusted for demographics and geography. P-values are reported based on heteroskedasticity robust standard errors.

Supplementary Table 8. Educational Attainment of White and African American ARIC Participants. Educational attainment was ascertained via self-report at the first ARIC visit. Distributions of BMI-increasing alleles for the 32 obesity GRS SNPs were comparable across educational strata in African Americans and whites (p>0.10 for all comparisons).

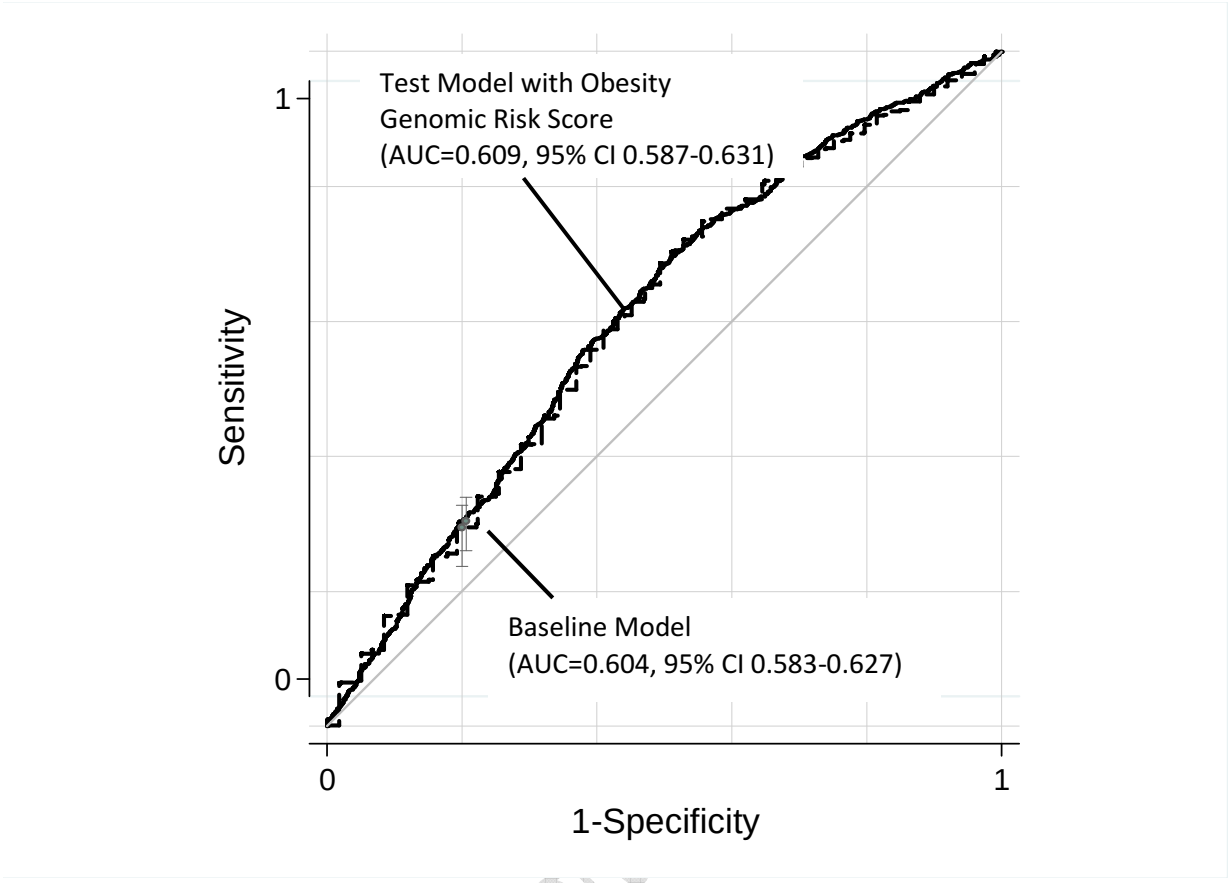
Highest Level of Schooling	Percent of Visit 1 Sample	
None/ Grade School	5%	19%
Some High School	11%	21%
High School Graduate	36%	22%
Vocational School	9%	7%
College	30%	18%
Graduate/ Professional School	9%	14%

Supplementary Table 9. Predictiveness of Model-Based Risk Scores With and Without The Obesity Genetic Risk Score. (m1-5) denote separate models used to estimate risk scores for BMI and obesity. Risk scores were predicted values from linear regression of BMI and predicted probabilities from probit regressions of obesity. The first model, m1, includes measures of age, sex, and ARIC Study Center where data were collected. The regression model was specified to include linear and quadratic terms for age and a product term modeling interaction between age and sex. The simple genetic risk assessment (SNPs in *FTO* and downstream of *MC4R*) is a component of the weighted obesity genomic risk score. Thus, model m3 contains all of the information in model m2 as well as information from the remaining 30 SNPs included in the GRS. The 5 categories of socioeconomic status were modeled as dichotomous variables and were allowed to vary by sex in their relationship with obesity and BMI. Values of R^2 were estimated using linear regression models adjusted for demographic and geographic information. Percentile-based confidence intervals were generated using the bootstrap method. AUCs and percentile-based confidence intervals were estimated from ROC curves constructed for predicted values generated using a probit regression model and were adjusted for the ARIC Study Center where data were collected using Pepe's method (Janes and Pepe 2009; Pepe, Longton, and Janes 2009). IDIs and test statistics were estimated only for comparisons of models m3 and m2 and models m5 and m4 using Pencina's Method (Pencina et al. 2008). IDIs for comparisons of models m2 and m3 with model m1 are identical to those reported for the respective obesity risk measures in Table 4 of the article.

		White ARIC Participants (n=8,286)			Black ARIC Participants (n=2,442)		
Model	Model Components	R^2 (95% CI)	AUC (95% CI)	IDI (p-value)	R^2 (95% CI)	AUC (95% CI)	IDI (p-value)
(m1)	Demographic & Geographic Information	3.20%	0.526		5.17%	0.604	
(m2)	m1 + Simple Genetic Risk Assessment	3.88%	0.550		5.35%	0.607	
(m3)	m1 + Weighted GRS	4.88%	0.574		5.52%	0.609	
	Change in predictiveness with addition of the weighted GRS	1.00% (0.006-0.014)	0.024 (0.012-0.036)	0.006 (7.81E-13)	0.17% (-0.001-0.005)	0.002 (-0.005-0.009)	0.001 (0.055)
(m4)	m1 + Socioeconomic Status	4.70%	0.550		7.70%	0.643	
(m5)	m4 + Weighted GRS	6.20%	0.586		7.92%	0.645	
	Change in predictiveness with addition of the weighted GRS	1.50% (0.010-0.020)	0.036 (0.023-0.050)	0.010 (5.46E-19)	0.22% (-0.001-0.006)	0.002 (-0.003-0.008)	0.002 (0.012)



Supplementary Figure 1. Distributions of BMI Increasing Alleles for the 32 GRS SNPs and the Weighted Obesity Genomic Risk Score Among White and African American ARIC Participants. Variance of the obesity genomic risk scores (GRS) was similar among women and men within ethnicity ($p>0.15$ for both samples), but was greater among whites as compared to African Americans ($p<0.001$) according to Brown and Forsythe's (Brown and Forsythe 1974) test for equality of variances.



Supplementary Figure 2. Receiver Operating Characteristic Curves for Obesity Among African American ARIC Participants (n=2,442). Baseline Model = gender, age (quadratic), gender x age interaction, ARIC study center; Test Model = baseline model + weighted obesity genomic risk score. ROC Curves were constructed using predicted values from probit regressions of obesity (BMI≥30) on the model terms. Delta AUC (AUC_{Test}-$AUC_{Baseline}$) = 0.005, 95% CI -0.005-0.015, p=0.30. Delta Partial AUC at 80% specificity=0, 95% CI -0.004-0.004, p=0.97. AUCs, partial AUCs, and delta AUCs were estimated using Pepe's method (Janes and Pepe 2009; Pepe, Longton, and Janes 2009).

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