SUPPLEMENTARY DATA

Shah H, Gao H, Morieri ML, et al. Genetic predictors of cardiovascular mortality during intensive glycemic control in type 2 diabetes.

Supplementary Material S1.

1. Genotyping for Genome-wide Association and Quality Control

Genome-wide genotyping of ACCORD DNA samples was performed independently in two centers using different vendor platforms and chips: 6,112 DNA samples, including HapMap Control samples, were genotyped at the University of Virginia (UVA), Center for Public Health Genomics Laboratory between August 2102 and January 2013 on Illumina HumanOmniExpressExome-8 (v1.0) chips containing 951,117 SNPs (ACCORD UVA Set); and 8,628 samples, including HapMap Control samples, were genotyped at the University of North Carolina, Chapel Hill (UNC) Functional Genomics Core during spring/summer 2013 on Affymetrix Axiom Biobank1 chips containing 628,679 probes (ACCORD UNC Set). The samples genotyped at UNC were samples for which consent had been provided for genetic studies by ACCORD investigators. The samples genotyped at the UVA Laboratory were the subset of the ACCORD UNC Set, for which consent had been provided for studies by both ACCORD and external investigators. The criteria for an ACCORD investigator were defined during the Trial. The genotyping and laboratory quality control (QC) at the two genotyping centers was performed according to standard Illumina Infinium (UVA) and Affymetrix Axiom (UNC) protocols. The complete sample quality control steps are listed in Table S1, together with incremental samples dropped at each successive QC step. The SNP QC steps are listed in Table S2.

For the ACCORD UVA Set, an exact test was used to check for Hardy-Weinberg Equilibrium (HWE) on a homogeneous self-reported white racial subset of ACCORD participants who did not report any racial or ethnic group membership other than white in the original ACCORD study (N=4,348).[1] The HWE test was applied to identify SNPs that may have poor genotyping quality. The SNP was dropped if the p-value from the HWE test was <0.0001 which may be indicative of poor genotyping quality. For X chromosome SNPs the HWE test was run on just the white female subset of samples but again filtered at p<0.0001. Cryptic sample duplicates and relatedness was checked using the program KING, which is used to infer the presence of unreported kinship (family relatedness) or unexpected duplication by testing all pairs of samples in the genotyping data set, based on the overall similarity of sample genotypes across all genome-wide genotyped SNPs for each pair (Chen Lab, Center for Public Health Genomics, University of Virginia).[2] KING identified 57 cryptic (unexpected) duplicate or related pairs within the ACCORD UVA Set: 4 were duplicates, 7 were parent-offspring, and 46 were full sibling pairs. There was one family cluster of size 3, resulting in 56 samples dropped. The member of the pair kept was preferentially the one with: 1) primary ACCORD trial CVD endpoint event; 2) ACCORD expanded CVD or microvascular event; 3) higher genotyping call rate. There were an estimated 11 second degree related pairs (half-siblings or avuncular relatedness) that were retained plus other more distantly related pairs such as first cousins.

For the ACCORD UNC set, pre-genotyping QC removed 3 samples for genotyping failure, 12 samples for low signal quality and 87 samples for low call rates. The remaining 8,526 samples were genotyped as a single batch. Post-genotyping QC removed 12 samples for misclassified sex. Removal of 274 duplicates (3 per plate, 270 intentional and 4 unintentional) and 180 HapMap samples (2 per plate) gave a final dataset consisting of 8,060 samples. A total of 628,679 probes were genotyped. All 223 mitochondria and Y chromosome probes were removed before computing Affymetrix probe metrics, which included call rate, Fisher's linear discriminant, heterozygous cluster strength offset and homozygote ratio offset. A total of 36,483 probes failed at least one metric and were removed. Intra and inter-plate duplicate ACCORD samples were used to compute probe concordance while 30 family trios of CEU HapMap samples were used to compute Mendelian trio errors. A total of 7,491 probes with either <95% concordance or >1 Mendelian error were removed, resulting in a final dataset consisting of 584,482 probes. HWE was checked using Pearson's chi-squared test. However, deviation from HWE was not used to remove probes from the dataset but was used to flag probes for further analysis if found to have a significant association. Cryptic relatedness was not used to remove samples for the overall dataset with the intention of potentially retaining a few samples when analyzing subsets of the data - KING was part of the UNC analysis pipeline rather than the QC pipeline.

SUPPLEMENTARY DATA

2. Post-Genotyping Merge and QC

The two genetic datasets were merged into a single dataset using the merge mode 1 (consensus genotype calls) option of PLINK v1.07 (Purcell Lab, Center for Human Genetic Research, Massachusetts General Hospital, and the Broad Institute of Harvard and MIT)[3], an open-source software for managing and analyzing genome-wide data. After the intra-laboratory QC, this merge resulted in a dataset with 8,084 samples and 1,283,000 total SNPs. The consensus genotype was set to missing if the two genotypes for the same sample for the same SNP were different between the datasets; if one set contained the genotype, but in the other set it was missing (because either the sample or the SNP had not been genotyped, or the SNP had been dropped for quality reasons), the consensus genotype was set to the value in the one dataset where it was present. There were 220,185 SNPs in common between the data sets, which were largely localized to exome regions of genes since both source SNP panels contained a significant whole exome component to their coverage.

The merging of the data sets was useful to detect less robust SNPs in each data set as non-concordant genotypes for the same SNP typed in the same subset of individuals on different platforms, and to rescue samples that might have been dropped from one data set as a result of sample-based QC but which passed QC in the other data set. Any sample that was in both datasets was assigned to the UVA set. Any sample in the UVA Set that was dropped by UVA QC but was in the UNC Set (but with different, smaller number of SNP markers) was considered part of UNC Set after merge and vice versa, resulting in two non-overlapping sets: 5,971 UVA Set (Any investigator set, ANYSET) and 2,113 UNC Set (ACCORD investigator set, ACCSET) samples. The bulk of the 2,113 samples in the ACCSET derive ACCORD samples that were not in the original UVA set, again because of the limitations of the ACCORD Trial consent. We also resolved the strand issues for 1,304 ambiguous SNPs (C/G or A/T) that were detected by poor homozygote concordance rates, adding back 1,053 that had been dropped but for which the strand was resolvable.

A further round of SNP QC was performed. A SNP was dropped if:
1.) The SNP Call Rate (genotype missing rate) was less than 95%.
2.) HWE exact test run on the white subset of ACCORD gave $p<0.0001$ (as in sub-section [1]).
3.) The SNP was apparently tri-allelic when comparing the consensus merge set alleles to those in 1000 genomes public data.

Table S3 summarizes the post-merge, post-QC data set. After rerunning KING using 264,697 autosomal SNPs in the merged data, we found 38 residual first degree relative pairs: 4 parent-offspring and 34 full sibling pairs, with one sibship of size 3 within the sibling pairs. Due to the timing of the merge, and the primary genome-wide association analyses, and the slightly differing approaches to QC at the two genotyping centers, these 38 pairs were discovered during the primary genome-wide association analysis reported in this paper. Nine (9) pairs were found within the ACCSET while 29 had one relative in the ANYSET and the other in the ACCSET. For the genome-wide screening datasets, we dropped one member of each relative pair, preferentially retaining the member with a cardiovascular event.

3. Residual Genotyping Biases between the Post-Merge UVA and UNC Set

The merge of the data sets using PLINK consensus mode updated discordant common genotypes to missing and attenuated some of the genotyping bias, but to gauge the magnitude of any remaining genotyping bias between the data sets at common SNPs, the merged data set was visualized using principal component analysis (PCA). There were 560,314 common autosomal SNPs which were filtered by minimum minor allele frequency (MAF) and then pruned to a low inter-SNP linkage disequilibrium (LD) set. Linkage disequilibrium (r^2) was calculated for all pairs of SNPs separated by less than 500kb in the ACCORD homogeneous white subset of participants, and a low LD SNP set created by greedy selection of SNPs walking along the physical autosomal genome. This procedure resulted in a PCA SNP set of 172,811 (MAF >0.01) and 129,348 (MAF >0.05). As shown in Figure S4, the UVA and UNC sample sets were not systematically biased in their distribution for PC1, 2, 3, 4. These components show the typical trans-continental patterns of ancestry and indicate that the major

components of variation in the data set are *not* UVA versus UNC Set biases. PC5 is the component that distinguishes the UVA versus UNC Set and summarizes residual biases attributable to the different genotyping platforms, but also more subtle genetic consent biases in the ascertainment of the samples of the two sets. Stratified analysis of the two sets followed by meta-analysis meant that PC5 was not needed as a confounder adjustment in the individual set models.

Figure S5 shows the same data with the 26 populations of the 1000 Genomes Phase 3 release (release date 2013/05/02) projected onto the major axes of variation in ACCORD (PC1-3). These data confirm the diversity in the self-reported ACCORD Trial race and ethnicity using the genetic data. The ACCORD genetics set is racially and ethnically non-homogeneous with admixtures of European, African, Asian, and Amerindian ancestry.

4. Pre-Imputation QC and 1000 Genomes Imputation Algorithm

Prior to imputation, duplicate SNPs by name (for example rs number) and by genome location/allele pair were identified and the SNP with the higher genotyping call rate retained. Also, all insertion-deletion (indel) allele pair SNPs were dropped prior to imputation due to non-1000 Genomes consistent indel coding in Illumina and Affymetrix annotation files.

The post-merge ANYSET and ACCSET were separately imputed because of the very different SNP content of the two sets. SHAPEIT v2.r790 (Zagury Lab, Conservatoire National des Artes et Metiers, Paris; Marchini Lab, Department of Statistics, University of Oxford) was used to phase the sets separately with parameter settings --burn 10 –prune 10 –main 50 –states 200.[4] Impute version 2.3.1 (Marchini Lab, Department of Statistics, University of Oxford) was then used to impute against the full 1000 Genomes Phase 3 (Oct 2014) panel for autosomes and Phase 1 Integrated version 3 panel for the X chromosome since the corresponding later panel had not been formatted for the X chromosome.[5] Impute was run with parameter settings -buffer 300 -Ne 20000 -k 120 -k_hap 700, restricting the imputation to SNPs with an overall 1000 Genomes minor allele frequency of >0.002 to reduce the imputation burden for very rare alleles that may be monomorphic in Europeans. After discarding imputed SNPs with an information content <0.3, the total imputed SNPs were 25,017,489 in the ANYSET, and 25,012,865 in the ACCSET.

SUPPLEMENTARY DATA

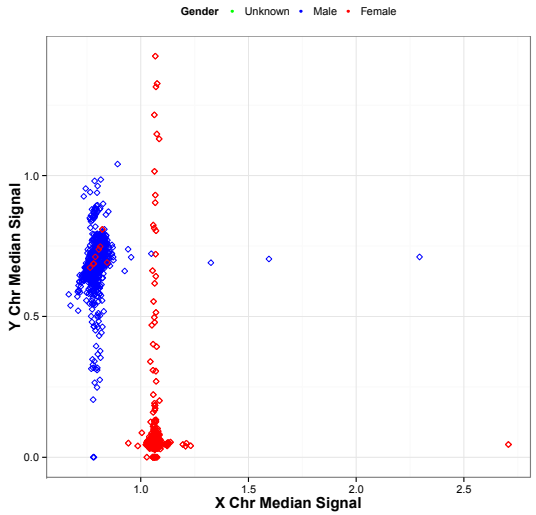
References

1. Wigginton JE, Cutler DJ, Abecasis GR. A note on exact tests of Hardy-Weinberg equilibrium. Am J Hum Genet 2005 May;76(5):887-93.
2. Manichaikul A, Mychaleckyj JC, Rich SS, Daly K, Sale M, Chen WM. Robust relationship inference in genome-wide association studies. Bioinformatics 2010 Nov;26(22):2867-73.
3. Purcell S, Neale B, Todd-Brown K, Thomas L, Ferreira MAR, Bender D, Maller J, Sklar P, de Bakker PIW, Daly MJ & Sham PC. PLINK: a toolset for whole-genome association and population-based linkage analysis. Am J Hum Genet 2007; 81(3):559-75 [URL: http://pngu.mgh.harvard.edu/purcell/plink/]
4. Delaneau O, Zagury JF, and Marchini J. Improved whole chromosome phasing for disease and population genetic studies. Nat Methods 2013; 10(1):5-6. doi: 10.1038/nmeth.2307
5. Howie BN, Donnelly P, and Marchini J. A flexible and accurate genotype imputation method for the next generation of genome-wide association studies. PLoS Genetics 2009; 5(6): e1000529.

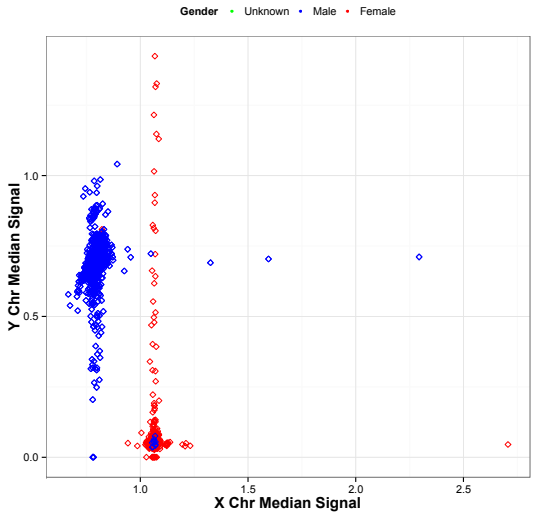
SUPPLEMENTARY DATA

Supplementary Figure S1. **Misclassification of DNA sample sex versus gender in the ACCORD trial database for the UVA genotyped samples**. These panels plot the median signal (sum of alleles) for SNPs annotated on the X and Y chromosomes. These effectively plot the copy number of X versus Y but do not require a genotype call and hence are robust to genotype calling errors. In Panel A, 8 misclassified females cluster with the males and in Panel B, 10 misclassified males cluster with females.

Panel A.

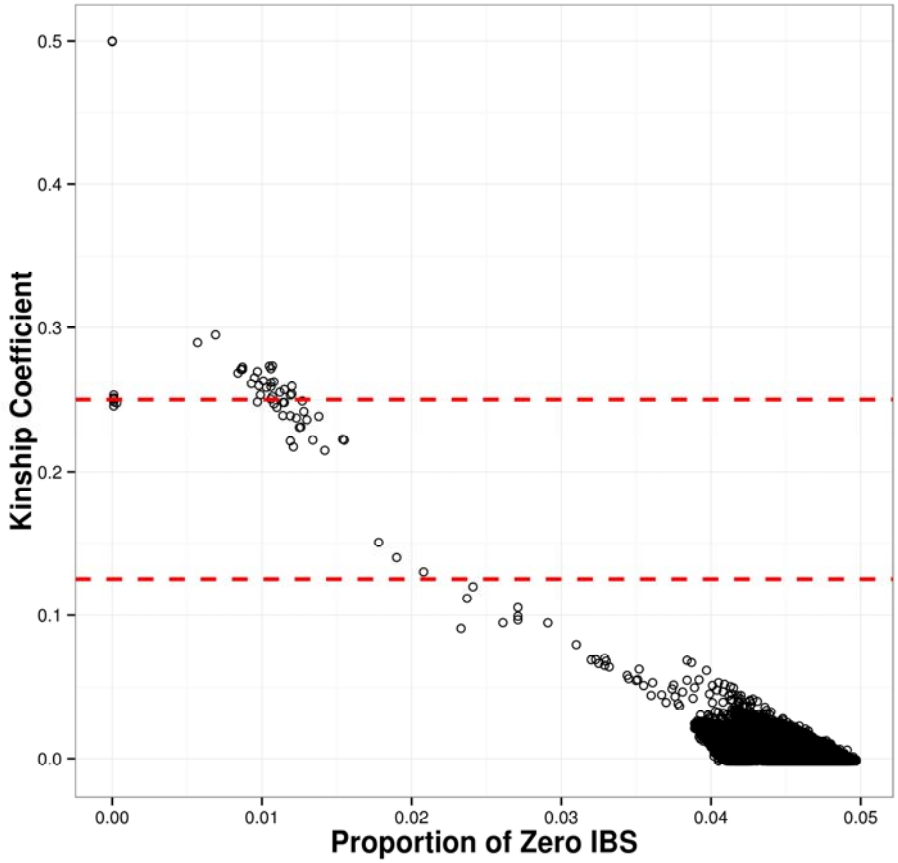


Panel B.



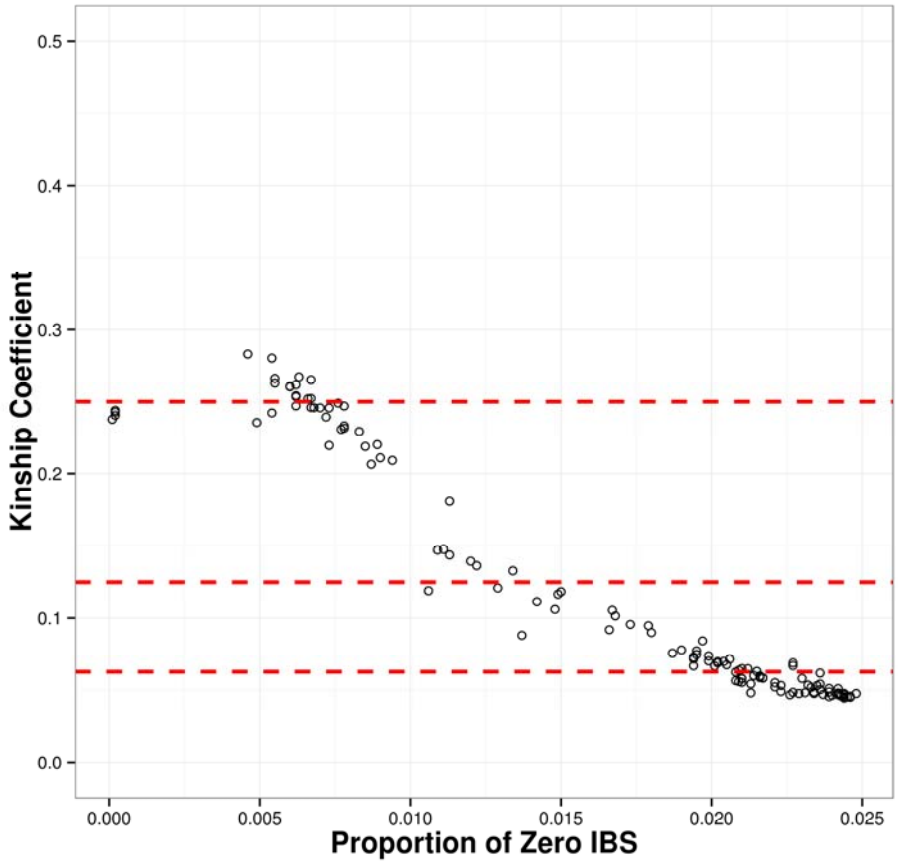
SUPPLEMENTARY DATA

Supplementary Figure S2. Cryptic relatedness in the UVA Set revealed by KING analysis. Each glyph on the figure represents one sample pair and shows the kinship coefficient of the pair plotted against the proportion of IBS=0 SNPs found for the pair. The relationship parameter values were estimated using KING. Pairs with Kinship > 0 only shown for clarity. The 57 cryptic pairs are easily seen in clusters at: kinship =0.5 (duplicates); kinship = 0.25 and Pr(IBS=0) ~ 0 (parent-offspring); kinship ~0.25 and Pr(IBS=) > 0 and <0.015) full siblings.



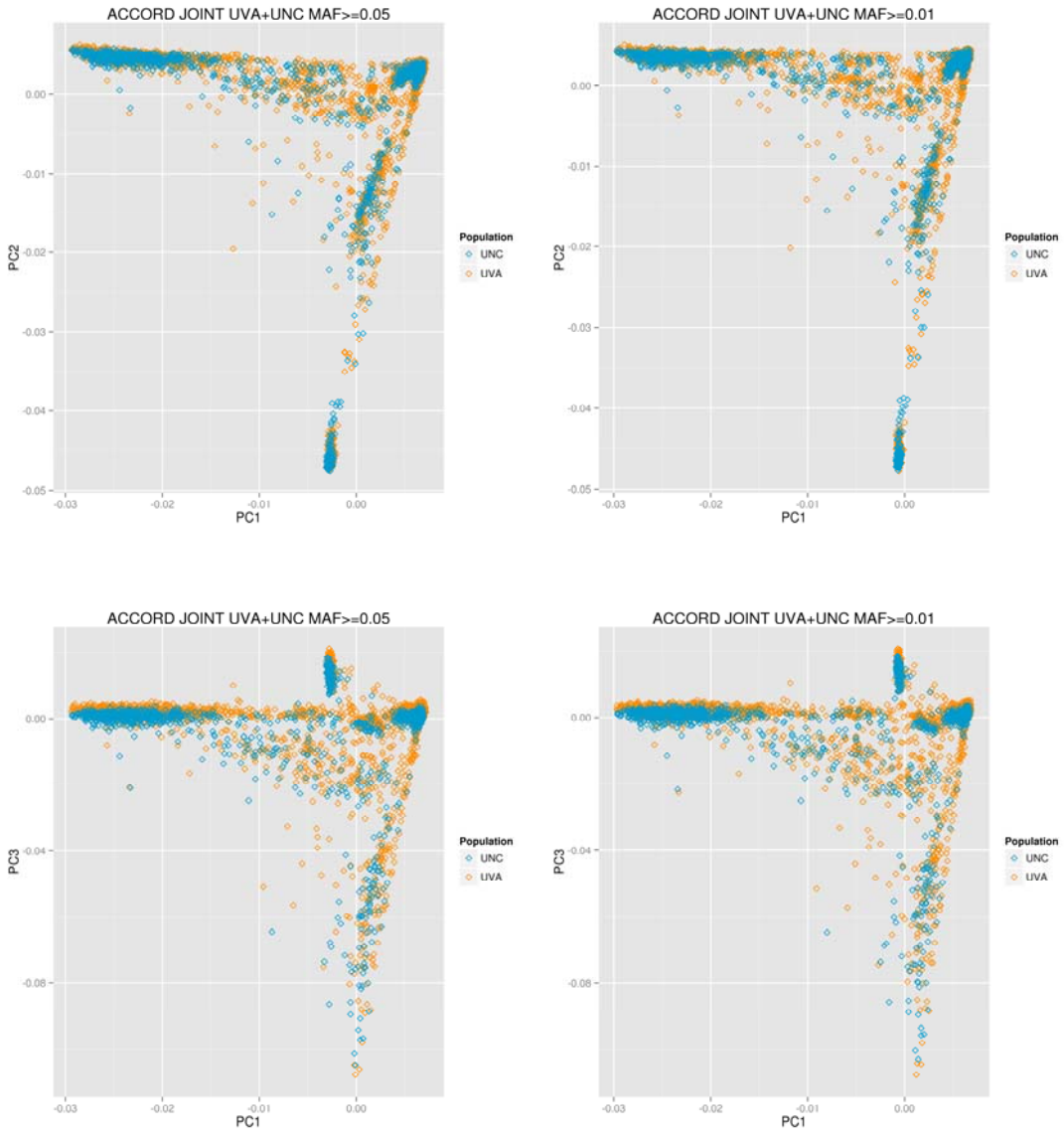
SUPPLEMENTARY DATA

Supplementary Figure S3. Residual Relatedness post UVA and UNC merge. A similar figure to Figure S2 showing the residual relatedness after merging the UVA and UNC genetic data sets and re-running KING on the combined autosomal data. No duplicates are seen in this plot but parent-offspring pairs at kinship ~ 0.25, Pr(IBS=0) ~ 0, and full sibling pairs at kinship ~ 0.25, Pr(IBS=) > 0.0025 and <0.010).

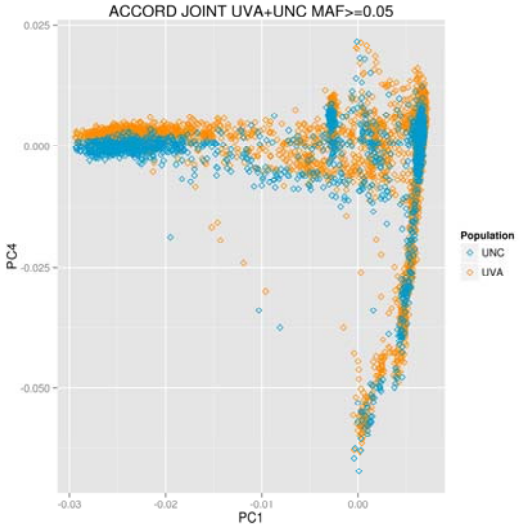


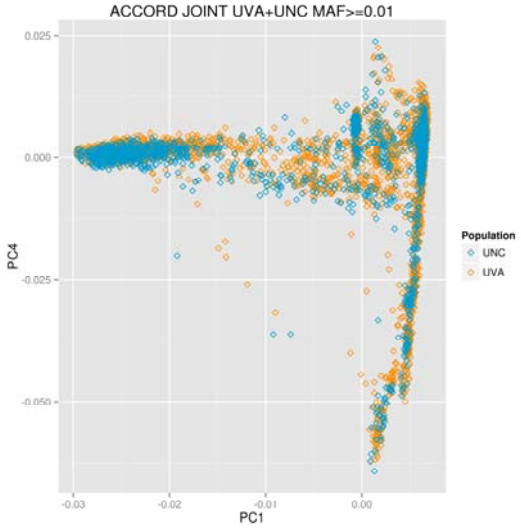
SUPPLEMENTARY DATA

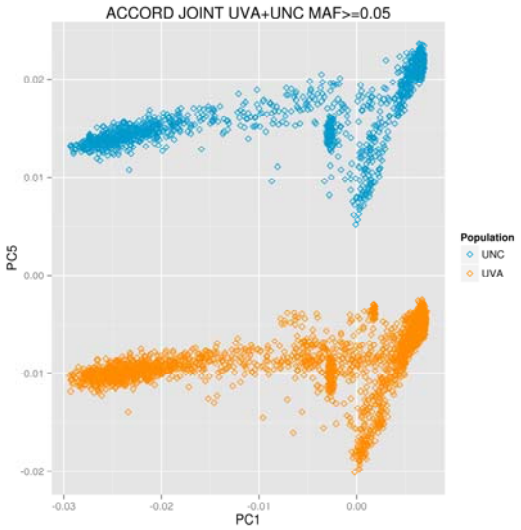
Supplementary Figure S4. Principal Component Analysis plots for the UVA + UNC merged (joint) genotyped data. The x-axis is Principal Component 1 (PC1) in all plots, while the y-axes are PC2, PC3, PC4 and PC5, respectively from top to bottom of the four plot rows. The left column analyses used SNPs with Minor Allele Frequency (MAF) ≥ 0.05 and the right column analyses used SNPs with MAF ≥ 0.01. Each blue diamond marks a position of a UVA genotyped ACCORD sample in the PC axis plots, while each orange diamond represents one from the UNC genotyped set. The principal components axes are new variables derived from the genotype data and are useful in revealing hidden population structure in the genetic data, particularly race and ancestry groups, but also systematic biases. For example, PC5 here clearly separates UVA (Illumina) and UNC (Affymetrix) data sets. PC1 explains the greatest amount of variation in the genetic data, PC2 the second greatest, and so on.

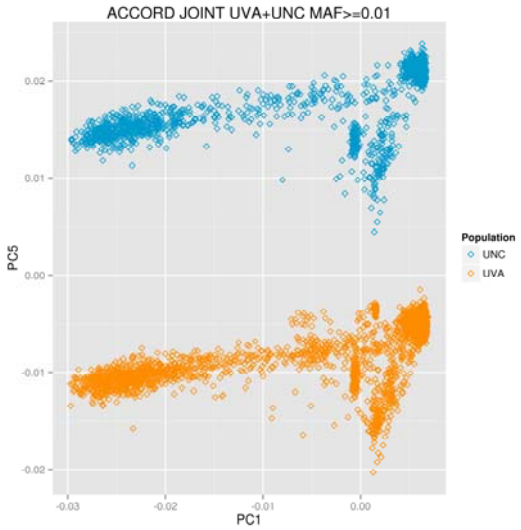


SUPPLEMENTARY DATA



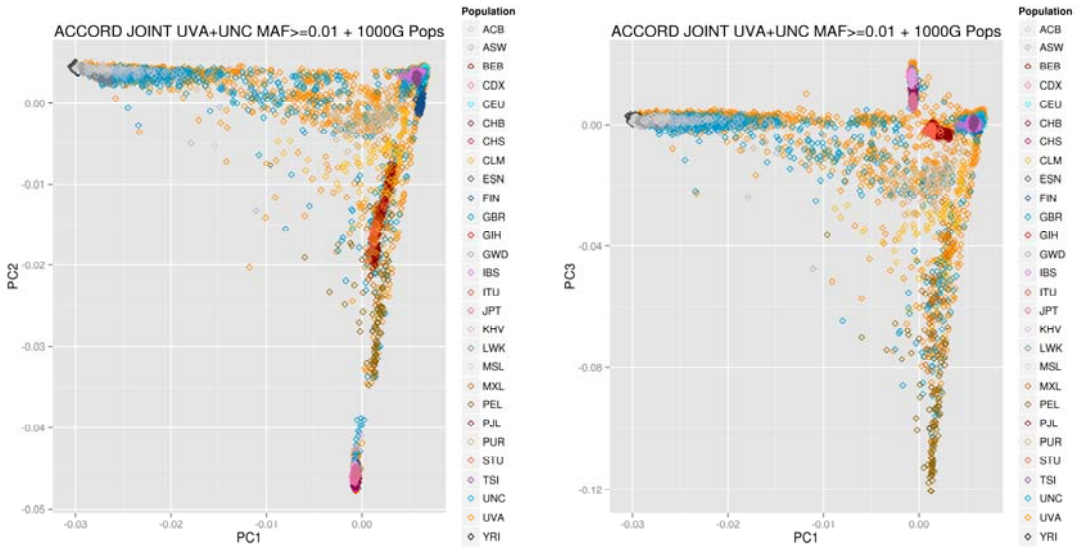






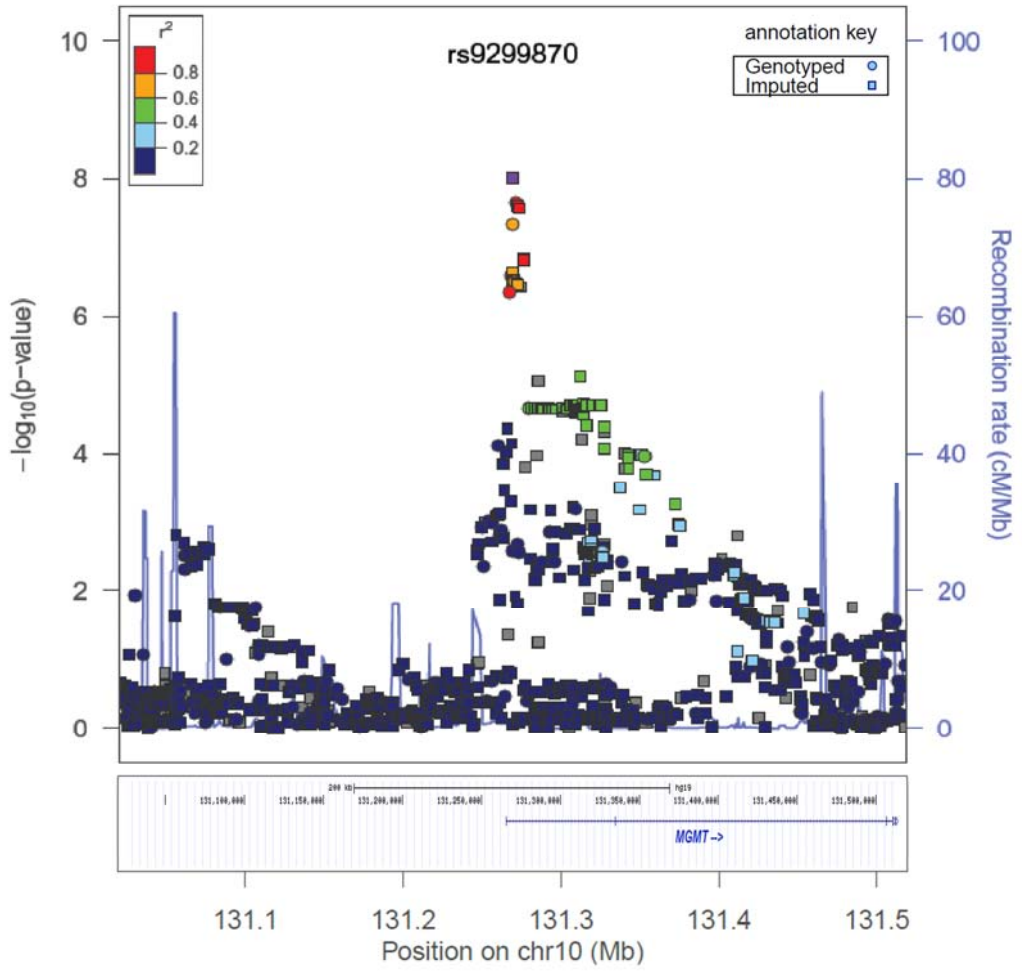
SUPPLEMENTARY DATA

Supplementary Figure S5. Principal Component Analysis for UNC+UVA joint data and 1000 Genomes. These plots are analogous to Figure S4 and show the same ACCORD UVA and UNC Sets colored with the same blue and orange diamonds, together with samples of the 26 Phase 3 1000 Genomes populations (release date 2013/05/02) projected onto the ACCORD sample axes. The color-coded 1000 Genomes samples are of different race/ethnic ancestries and hence the smearing of the ACCORD UVA and UNC samples across a wide range of PC1, PC2, and PC3 values indicates that the ACCORD samples are from different admixtures of European, African, Hispanic, and Asian race/ethnicity. European samples cluster at approximate coordinates PC1 ~ -0.007, PC2 ~ 0 to -0.005; African at approximately PC1 ~ -0.03; Asian at PC2 ~ -0.045; and Hispanic at PC3 ~ -0.12 to ~ -0.01.



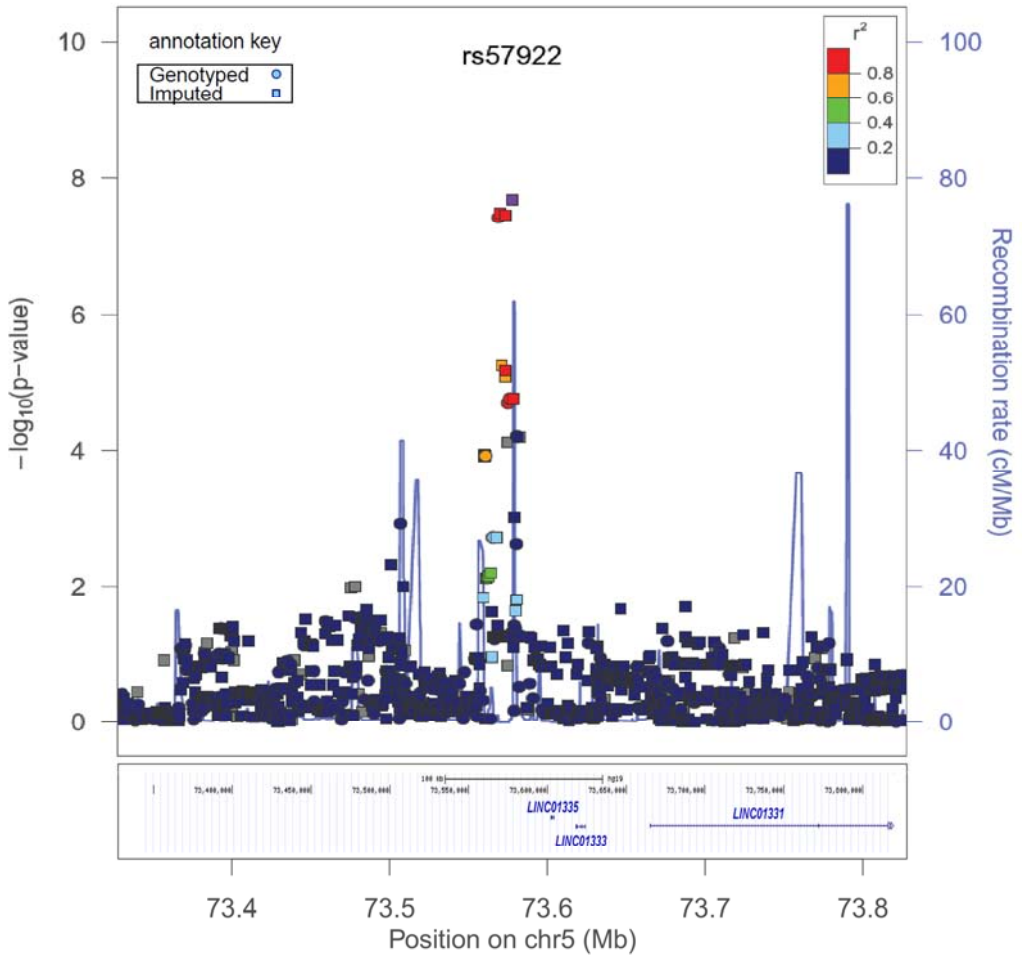
SUPPLEMENTARY DATA

Supplementary Figure S6. 500kbp Regional plot of locus 10q26.3. Each data point on the regional association plot represents a single nucleotide polymorphism (SNP). Variants displayed are within 250kbp upstream and downstream of the lead SNP (rs9299870). The x-axis shows the chromosomal positions of SNPs as per NCBI Build 37, and the y-axis shows their –log10 p values for association with cardiovascular mortality in the ACCORD intensive arm. Variants in strong linkage disequilibrium (based on 1000 Genomes Project) with the leading SNP (in purple) are marked in red (r^2>0.8). The blue peaks in the plot represent recombination hotspots. The bottom panel depicts UCSC genes within the region, with exons as tick marks and arrows showing direction of transcription. As shown here, the index SNP lies within the intron 1 of MGMT (O-6-methylguanine-DNA methyltransferase) gene. Plots were generated using LocusZoom v1.1 (Abecasis Lab, University of Michigan School of Public Health).



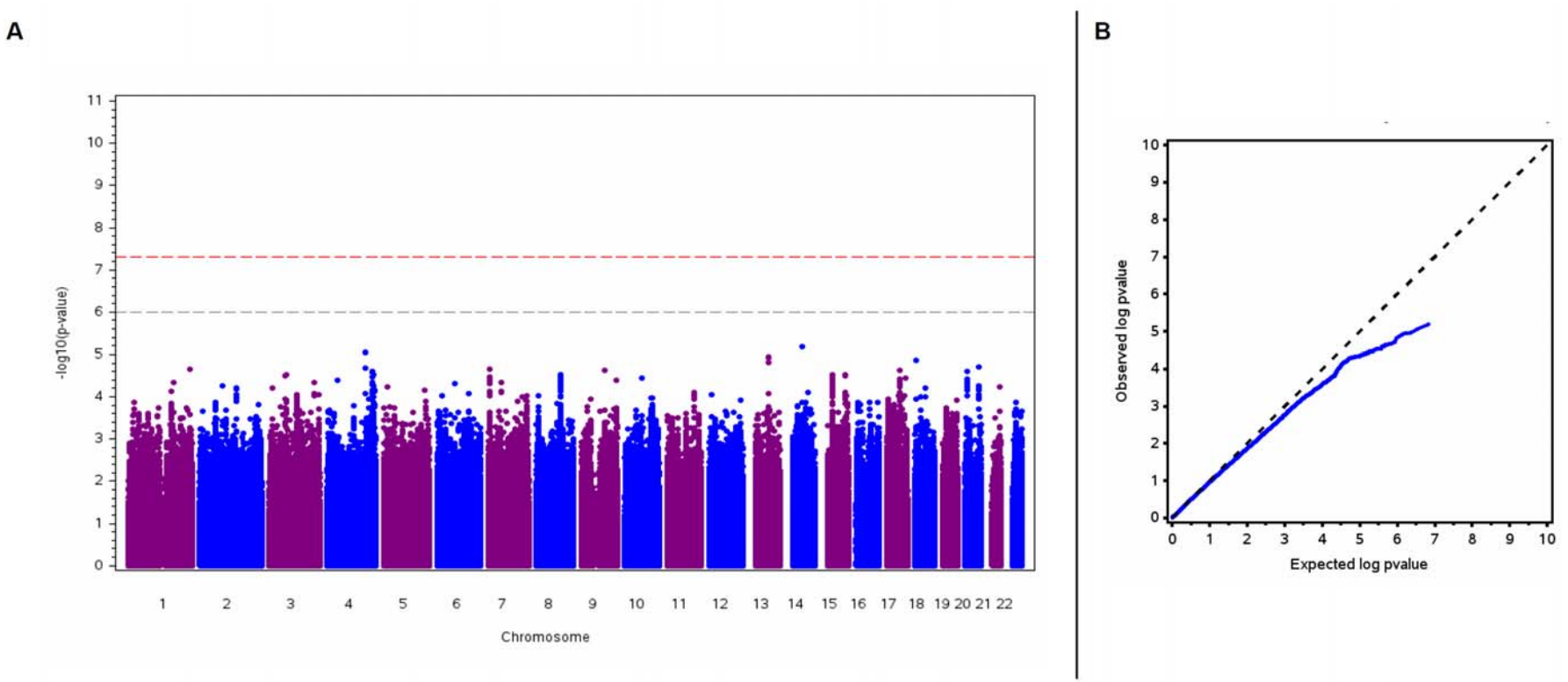
SUPPLEMENTARY DATA

Supplementary Figure S7. 500kbp Regional plot of locus 5q13.3. Each data point on the regional association plot represents a single nucleotide polymorphism (SNP). Variants displayed are within 250kbp upstream and downstream of the 2nd lead SNP (rs57922). The x-axis shows the chromosomal positions of SNPs as per NCBI Build 37, and the y-axis shows their –log10 p values for association with cardiovascular mortality in the ACCORD intensive arm. Variants in strong linkage disequilibrium (based on 1000 Genomes Project) with the leading SNP are marked in red (r2>0.8). The blue peaks in the plot represent recombination hotspots. The bottom panel depicts UCSC genes within the region, with exons as tick marks and arrows showing direction of transcription. As shown here, the index SNP lies proximal to a cluster of long intergenic non-coding RNAs. Plots were generated using LocusZoom v1.1 (Abecasis Lab, University of Michigan School of Public Health).



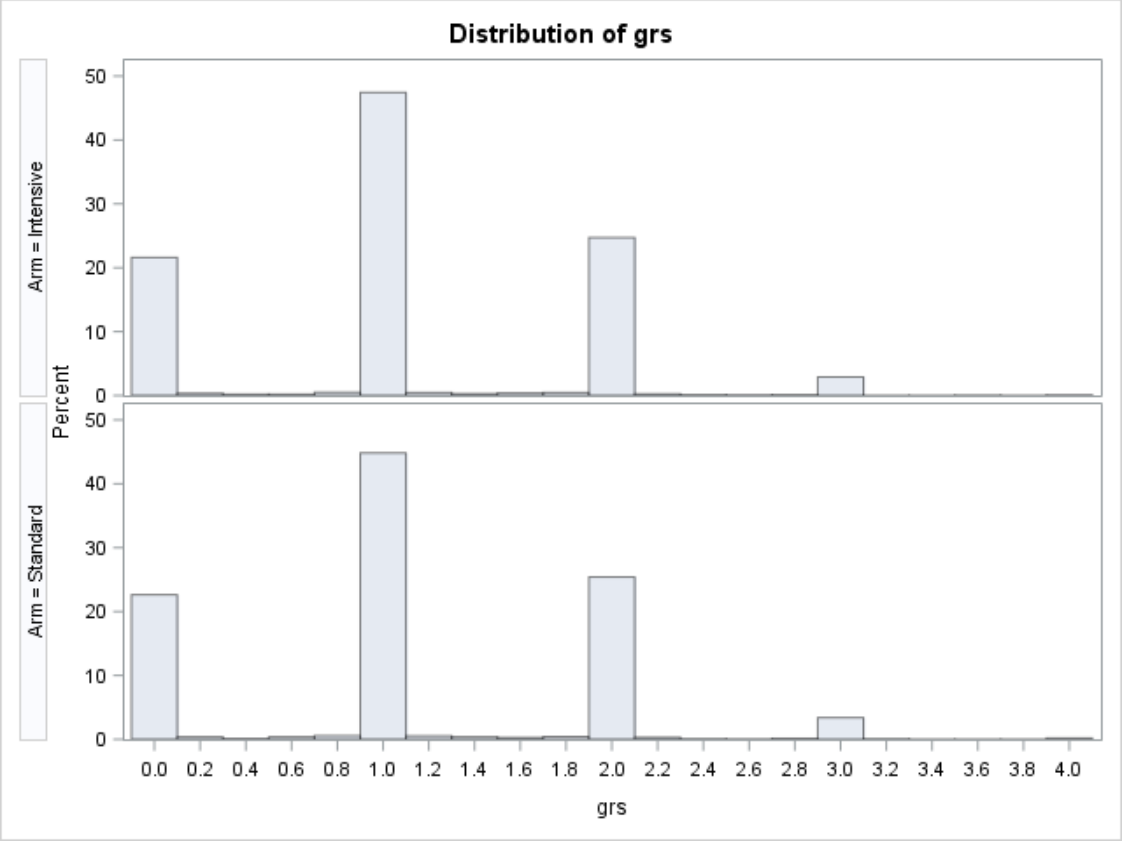
SUPPLEMENTARY DATA

Supplementary Figure S8. Genome-wide screen for gene x treatment interaction. Panel A shows the genomic distribution of p-values (Manhattan plot) for SNP x glycemic treatment interaction at 6.8 million common polymorphic loci in 5,360 self-reported Whites from the ACCORD cohort in a cox proportional hazards model for cardiovascular mortality. P-values are plotted as $-\log_{10}$ values to facilitate visualization. Each dot represents a polymorphism. The red dashed reference line corresponds to the genome-wide significance threshold ($p=5x10^{-8}$) whereas the grey dashed line corresponds to the notable significance level ($p=1x10^{-6}$). Panel B shows the relationship between observed and expected p-values (quantile-quantile, or Q-Q plot) in the genome-wide analysis. The dotted line corresponds to the null hypothesis.



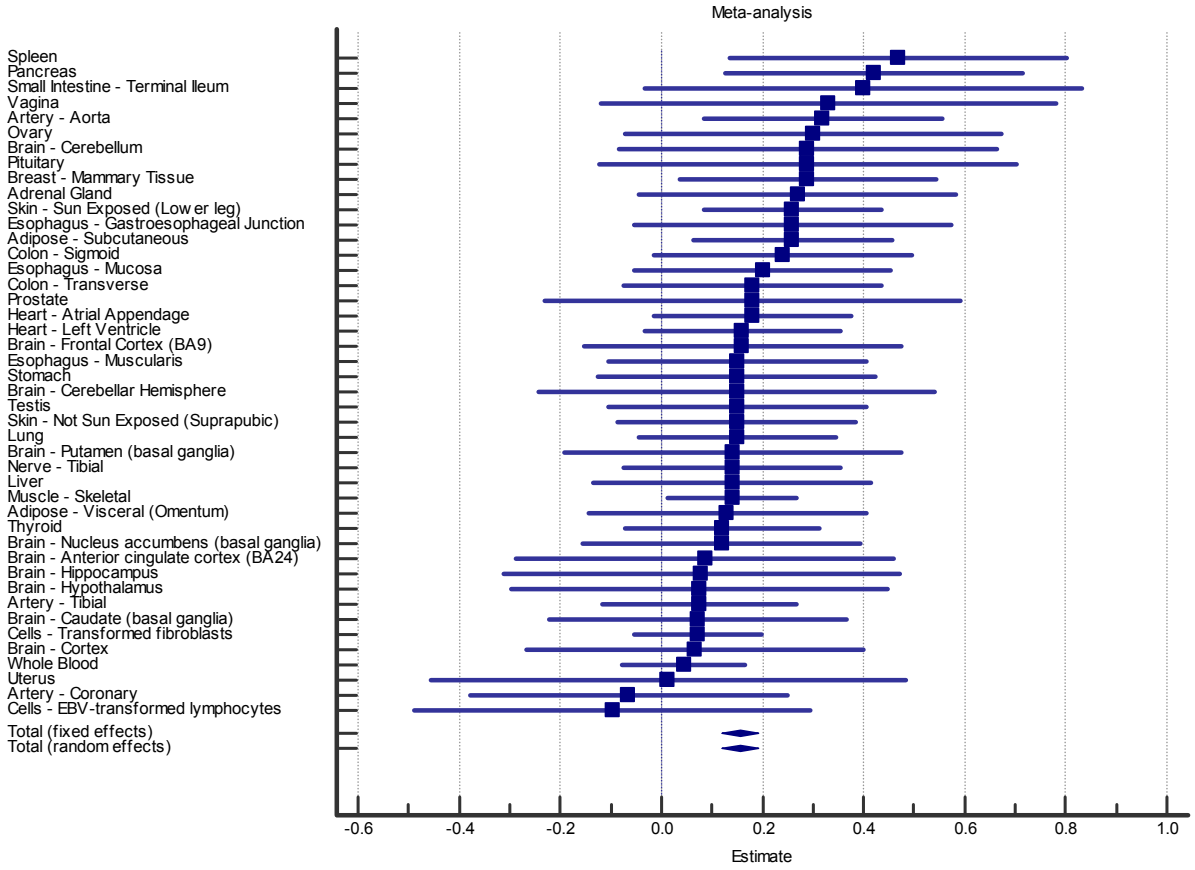
SUPPLEMENTARY DATA

Supplementary Figure S9. Distribution of the Genetic risk score (GRS) within ACCORD intensive and standard treatment arms. The GRS is a continuous variable, obtained by adding the risk allele dosages of the top two genome-wide significant variants, rs57922 and rs9299870.



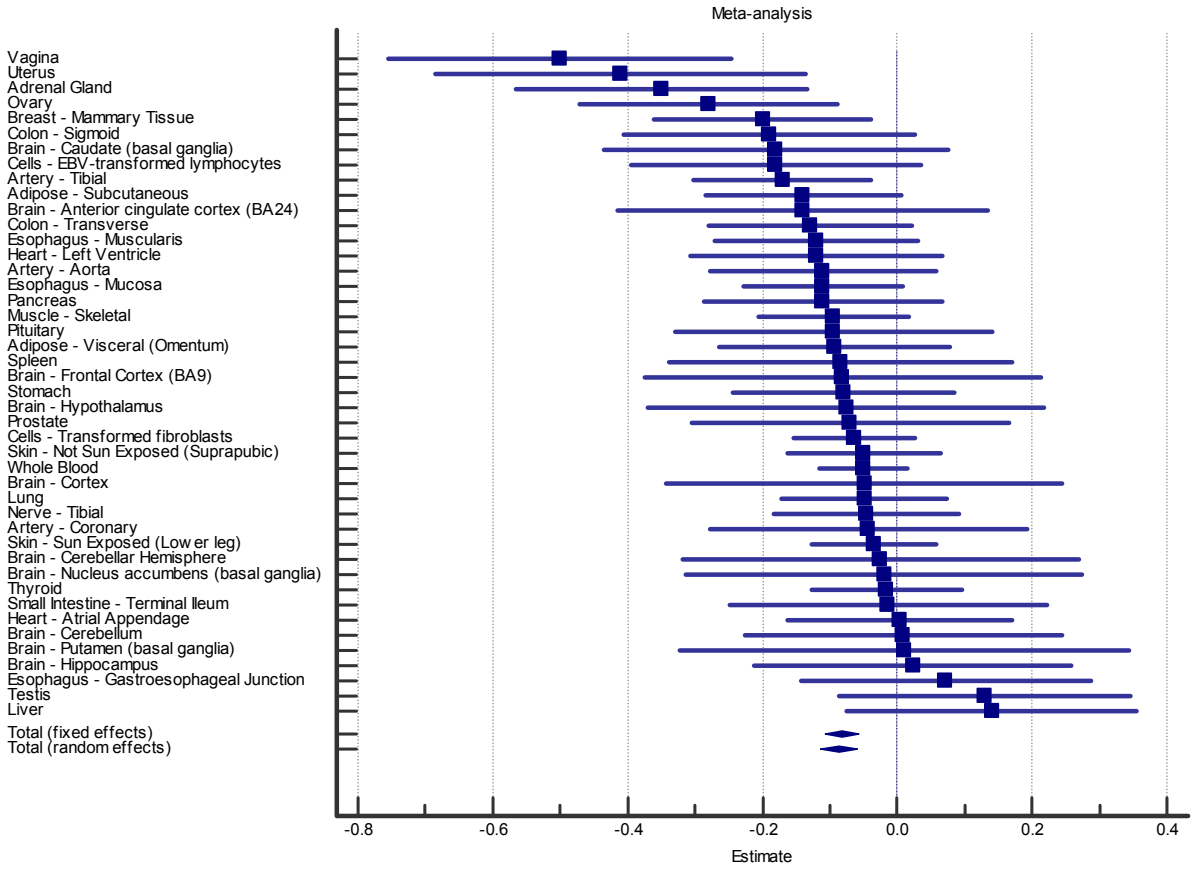
SUPPLEMENTARY DATA

Supplementary Figure S10. Association between rs9299870 and tissue-specific *MGMT* (O-6-methylguanine-DNA methyltransferase) expression. The tissues include those with more than 70 samples with matched gene expression and genotype data in the Genotype Tissue Expression (GTex) database (http://www.gtexportal.org/home/). The Estimate corresponds to the effect size, defined as the slope "beta" of the linear regression and is computed as the effect of the minor allele (G) relative to the reference allele (C). The meta-analysis (with generic inverse variance method) yielded to a total effect (fixed effect) = 0.157 ± 0.019 P = 3.6×10^{-17} (Test for heterogeneity P=0.97; I^2 0%). Meta-analysis and graphs produced by MedCalc Software version 16.4.1.



SUPPLEMENTARY DATA

Supplementary Figure S11. Association between rs57922 and tissue-specific *NSA2* (Nop-7 associated 2) expression. The tissues include those with more than 70 samples with matched gene expression and genotype data in the Genotype Tissue Expression (GTex) database (http://www.gtexportal.org/home/). The Estimate corresponds to the effect size, defined as the slope "beta" of the linear regression and is computed as the effect of the minor allele (T) relative to the reference allele (C). The meta-analysis (with generic inverse variance method) yielded to a total effect (fixed effect) = -0.082 ± 0.012 P = 1.8×10^{-11} (Test for heterogeneity P=0.17; I^2 17%); Meta-analysis and graphs produced by MedCalc Software version 16.4.1.



SUPPLEMENTARY DATA

Supplementary Table S1. Sample Genotyping Quality Control (QC)

QC Step*	Number removed	Number remaining
UVA Genotyping Laboratory		
Total DNA Samples Genotyped		6,112
HapMap Control Samples	23	6,089
Genotyping Failure	13	6,076
Known Duplicates	3	6,073
Inappropriate Sample	1	6,072
Sample Call Rate < 95% or 40% < Sample Heterozygosity < 17%	27	6,045
Misclassified sex	18	6,027
Cryptic duplicate or 1st degree relative pairs	56	5,971
ACCORD Total Remaining		**5,971**
UNC Genotyping Laboratory		
Total DNA Samples Genotyped		8,628
HapMap Control Samples	180	8,448
Genotyping Failure	3	8,445
Known Duplicates	270	8,175
Affymetrix dish-QC <0.82	12	8,163
Sample Call Rate < 97%	87	8,076
Misclassified sex	12	8,064
Unintentional duplicates[#]	4	8,060
ACCORD Total Remaining		**8,060**

*This table depicts the quality control steps for the 6,112 samples genotyped at the UVA genotyping laboratory and the 8,628 genotyped at UNC genotyping laboratory. The QC Step Number lists the incremental additional number of samples removed at that step, not the total number of samples that failed each separate QC criterion.
[#]Unintentional duplicates were identified by having the same sample identification numbers.

SUPPLEMENTARY DATA

Supplementary Table S2. SNP Genotyping Quality Control (QC)

QC Step*	Number removed	Number remaining
UVA Genotyping Laboratory: Illumina HumanOmniExpressExome-8		
Total SNPs on chip		951,117
SNP Failed: Call Rate = 0%	719	
SNP Call Rate < 95%	3,689	
HWE $p<10^{-4}$ in ACCORD white race group	4,736	
Total Unique SNPs	8,335	942,782
Total SNPs Remaining		**942,782**
UNC Genotyping Laboratory: Affymetrix Axiom Biobank1		
Total SNPs (Probes) on chip		628,679
Affymetrix Quality Control**	36,483	
Concordance/Mendelian Trio	7,491	
Mitochondria or Y chromosome	223	
Total Unique SNPs	44,197	584,482
Total SNPs Remaining		**584,482**

* This table shows SNP quality control steps for the 6,112 samples genotyped at the UVA genotyping laboratory and the 8,628 genotyped at UNC genotyping laboratory. ** Standard Affymetrix QC thresholds for retaining SNPs included SNP call rate ≥ 0.97, Fisher's linear discriminant ≥ 3.6 (for > 1 cluster), heterozygous cluster strength offset ≥ -0.1 (for > 1 cluster), and homozygote ratio offset ≥ 0.3 (for 3 clusters) or > -0.9 (for < 3 clusters).

SUPPLEMENTARY DATA

Supplementary Table S3. Summary of the post-QC merged data, ANYSET and ACCSET

	ANYSET	ACCSET
Number of Samples	5,971	2,113
Total Initial SNPs in merge set	1,283,000	1,283,000
Ambiguous strand resolved SNPs added back	1,053	0
SNPs dropped: Call Rate <95% OR HWE $p<10^{-4}$ in ACCORD white race group	20,468	710,808*
Remaining SNPs	1,263,585	572,192
Overall Genotyping Rate	99.4%	99.7%

*The large number of SNPs dropped post-merge in the ACCSET of samples is expected since most of the samples were only typed on ~500K SNPs and many of the SNPs will have come into the data set from the denser Illumina panel used for the original ANYSET.

SUPPLEMENTARY DATA

Supplementary Table S4. Baseline characteristics of ACCORD full, genotyped and non-genotyped cohorts

Characteristic	Whole dataset (N=10,251)	Genotyped dataset (N=8,084)**	Non-Genotyped dataset (N=2,167)
Demographics			
Female sex, No. (%)	3,952 (38.6)	3,198 (39.6)	754 (34.8)*
Age, mean (SD), y	62.5 (6.7)	62.4 (6.6)	62.7 (7.3)
Whites, No. (%)	6,525 (63.6)	5,311 (65.7)	1,214 (56.0)*
Education, No. (%)			
Less than high school	1,521 (14.8)	1,137 (14.1)	384 (17.7)*
High-school graduate	2,704 (26.4)	2,109 (26.1)	595 (27.5)
Some college	3,357 (32.8)	2,663 (32.9)	694 (32.0)
College degree or higher	2,662 (26.0)	2,169 (26.8)	493 (22.8)*
Baseline Cardiovascular risk factors			
Diabetes duration, median (IQR), y	10.0 (5.0-15.0)	10.0 (5.0-15.0)	9.0 (5.0-15.0)
Previous cardiovascular event, No. (%)	3,609 (35.2)	2,751 (34.0)	858 (39.6)*
Current Smoker, No. (%)	1,237 (12.1)	958 (11.9)	279 (12.9)
Glycated Hemoglobin, %			
Mean (SD)	8.3 (1.0)	8.3 (1.0)	8.3 (1.0)
Median (IQR)	8.1 (7.6-8.9)	8.1 (7.6-8.9)	8.1 (7.5-8.8)
Fasting serum glucose, mean (SD), mg/dl	174.4 (53.4)	175.3 (53.3)	171.0 (53.5)
Body Mass Index, mean (SD), kg/m^2	32.2 (5.4)	32.3 (5.4)	31.9 (5.4)*
Waist circumference, mean (SD), cm	106.7 (13.6)	106.8 (13.7)	106.4 (13.4)
Blood Pressure, mean (SD), mm Hg			
Systolic	136.3 (16.9)	136.2 (17.1)	136.4 (16.1)
Diastolic	74.8 (10.5)	74.9 (10.7)	74.6 (10.0)
Potassium, mean (SD), mEq/L	0.02 (0.15)	0.03 (0.16)	0.02 (0.14)
Serum creatinine, mean (SD), mg/dl	0.91 (0.23)	0.91 (0.22)	0.93 (0.24)*
Lipids, mean (SD),mg/dl			
Total cholesterol	183 .2 (41.2)	183.7 (41.3)	181.2 (40.8)*
Low-density lipoprotein	104.8 (33.6)	104.9 (33.5)	104.7 (33.7)
High-density lipoprotein			
Women	47.0 (12.4)	47.0 (12.5)	47.0 (11.9)
Men	38.6 (9.5)	38.6 (9.5)	38.7 (9.5)
Triglyceride	188.5 (138.6)	191.1 (144.7)	178.6 (111.9)*
Characteristic	**Whole dataset (N=10,251)**	**Genotyped dataset (N=8,084)****	**Non-Genotyped dataset (N=2,167)**
Medications, No. (%)			
Insulin	3,582 (34.9)	2,891 (35.8)	691 (31.9)*
Any biguanide	6,554 (63.9)	5,146 (63.7)	1,408 (65.0)
Any sulfonylurea	5,474 (53.4)	4,256 (52.7)	1,218 (56.2)*
Any thiazolidinedione	2,258 (22.0)	1,797 (22.2)	461 (21.3)
Any antihypertensive agent	8,785 (85.7)	6,850 (84.7)	1,935 (89.3)*
Angiotensin-converting-enzyme inhibitor	5,568 (54.3)	4,269 (52.8)	1,299 (59.9)*
Aspirin	5,579 (54.4)	4,450 (55.1)	1,129 (52.1)*
Beta-blocker	3,079 (30.0)	2,425 (30.0)	654 (30.2)
Any thiazide diuretic	2,830 (27.6)	2,239 (27.7)	591 (27.3)
Statin	6,500 (63.4)	5,048 (62.4)	1,452 (67.0)*
Main Glycemia Trial, No. (%)	10,251 (100)	8,084 (100)	2,167 (100)
Standard	5,123 (50.0)	4,040 (50.0)	1,083 (50.0)
Intensive	5,128 (50.0)	4,044 (50.0)	1,084 (50.0)
Blood Pressure Trial, No. (%)	4,733 (46.2)	3,670 (45.4)	1,063 (49.1)*

SUPPLEMENTARY DATA

Standard	2,371 (23.1)	1,852 (22.9)	519 (24.0)
Intensive	2,362 (23.0)	1,818 (22.5)	544 (25.1)
Lipid Trial, No. (%)	5,518 (53.8)	4,414 (54.6)	1,104 (51.0)*
Statin + Placebo	2,753 (26.9)	2,165 (26.8)	588 (27.1)*
Statin + Fibrate	2,765 (27.0)	2,249 (27.8)	516 (23.8)*

SI conversion factors: To convert HbA1c to proportion of total hemoglobin, multiply values by 0.01; to convert fasting serum glucose to mmol/L, multiply values by 0.0555; to convert serum potassium to mmol/L, multiply values by 1; to convert serum creatinine to mmol/L, multiply values by 76.25; to convert cholesterol to mmol/L, multiply values by 0.0259; to convert triglycerides to mmol/L, multiply values by 0.0113.

*Significant differences ($p<0.05$) among genotyped and non-genotyped groups at baseline.
**This includes the combined genotyped ANYSET and ACCSET post quality control measures described in Supplemental Methods

SUPPLEMENTARY DATA

Supplementary Table S5. Baseline characteristics of intensive and standard arm participants in the ACCORD white GWAS subset [N=5,360]

Characteristic	Intensive arm (N=2,667)	Standard arm (N=2,693)
Demographics		
Female sex, No. (%)	927 (34.8)	961 (35.7)
Age, mean (SD), y	62.7 (6.5)	62.7 (6.5)
Education, No. (%)		
Less than high school	275 (10.3)	243 (9.0)
High-school graduate	687 (25.8)	708 (26.3)
Some college	958 (35.9)	924 (34.3)
College degree or higher	744 (27.9)	818 (30.4)*
Baseline Cardiovascular risk factors		
Diabetes duration, median (IQR), y	9.0 (5.0-15.0)	9.0 (5.0-15.0)
Previous cardiovascular event, No. (%)	953 (35.7)	952 (35.4)
Current Smoker, No. (%)	313 (11.8)	290 (10.8)
Glycated Hemoglobin, %		
Mean (SD)	8.2 (1.0)	8.2 (0.9)
Median (IQR)	8.0 (7.6-8.7)	8.0 (7.6-8.7)
Fasting serum glucose, mean (SD), mg/dl	179.1 (51.1)	178.0 (50.7)
Body Mass Index, mean (SD), kg/m^2	33.0 (5.2)	33.0 (5.2)
Waist circumference, mean (SD), cm	109.4 (13.0)	109.2 (12.9)
Blood Pressure, mean (SD), mm Hg		
Systolic	135.2 (17.0)	135.6 (17.2)
Diastolic	74.2 (10.6)	74.3 (10.7)
Potassium, mean (SD), mEq/L	0.02 (0.14)	0.03 (0.18)
Serum creatinine, mean (SD), mg/dl	0.9 (0.2)	0.9 (0.2)
Lipids, mean (SD),mg/dl		
Total cholesterol	183.6 (42.3)	183.2 (41.1)
Low-density lipoprotein	103.1 (33.0)	103.0 (32.8)
High-density lipoprotein		
Women	45.3 (12.1)	45.2 (10.9)
Men	37.5 (9.1)	37.9 (9.1)
Triglyceride	210.1 (162.6)	206.5 (148.1)
Characteristic	**Intensive arm (N=2,667)**	**Standard arm (N=2,693)**
Medications, No. (%)		
Insulin	940 (35.3)	967 (35.9)
Any biguanide	1686 (63.2)	1751 (65.0)
Any sulfonylurea	1400 (52.5)	1409 (52.3)
Any thiazolidinedione	635 (23.8)	638 (23.7)
Any antihypertensive agent	2202 (82.6)	2309 (85.7)*
Angiotensin-converting-enzyme inhibitor	1418 (53.2)	1469 (54.6)
Aspirin	1546 (58.0)	1550 (57.6)
Beta-blocker	795 (29.8)	858 (31.9)
Any thiazide diuretic	677 (25.4)	719 (26.7)
Statin	1692 (63.4)	1733 (64.4)
Blood Pressure Trial, No. (%)	1144 (42.9)	1151 (42.7)
Standard	556 (20.8)	588 (21.8)
Intensive	588 (22.0)	563 (20.9)
Lipid Trial, No. (%)	1523 (57.1)	1542 (57.3)
Statin + Placebo	747 (28.0)	749 (27.8)
Statin + Fibrate	776 (29.1)	793 (29.4)

SUPPLEMENTARY DATA

SI conversion factors: To convert HbA1c to proportion of total hemoglobin, multiply values by 0.01; to convert fasting serum glucose to mmol/L, multiply values by 0.0555; to convert serum potassium to mmol/L, multiply values by 1; to convert serum creatinine to mmol/L, multiply values by 76.25; to convert cholesterol to mmol/L, multiply values by 0.0259; to convert triglycerides to mmol/L, multiply values by 0.0113.

*Significant differences ($p<0.05$) among intensive and standard groups at baseline.

SUPPLEMENTARY DATA

Supplementary Table S6. Top loci ($p<1x10^{-5}$) for progression to cardiovascular mortality in the intensive arm, effects within the ANYSET and ACCSET

Closest Gene[a]	SNP[b]	Position[c]	MAF[d]		ANYSET [N=2146]				ACCSET [N=528]				Meta-analysis of ACCSet and ANYSet [N=2674]				
				Ref/Non-ref Alleles	*Info*[e]	*Effect*[f]	*SE*[g]	*P*	*Info*	*Effect*	*SE*	*P*	*Effect*	*SE*	*P*	*Direction*	*P-value for heterogeneity*
MGMT	rs9299870	10:131269309	0.08	G/C	0.98	1.38	0.23	1.12E-09	0.95	-0.87	1.05	0.407	1.28	0.22	9.77E-09	+-	0.04
LINC01333	rs57922	5:73577939	0.48	T/C	0.99	0.96	0.19	3.31E-07	0.98	1.02	0.42	0.016	0.97	0.17	2.04E-08	++	0.91
MASP2	rs373946618	1:11088774	0.08	G/T	0.71	1.18	0.28	2.95E-05	0.72	2.47	0.66	2.00E-04	1.39	0.26	1.15E-07	++	0.07
AX748080	rs79525442	11:43990932	0.06	T/A	0.97	1.08	0.23	3.47E-06	0.95	1.18	0.55	0.031	1.09	0.21	3.63E-07	++	0.86
CCNJL	rs6878970	5:159771753	0.06	T/C	0.97	1.14	0.24	2.09E-06	0.90	1.05	0.59	0.072	1.13	0.22	4.68E-07	++	0.89
ANKFN1	rs116899003	17:54448567	0.05	G/C	0.99	1.11	0.22	8.32E-07	0.98	0.37	0.79	0.631	1.05	0.22	1.35E-06	++	0.37
GALNT18	rs1487122	11:11472617	0.06	T/C	1.00	1.11	0.25	5.75E-06	0.82	0.95	0.64	0.135	1.09	0.23	2.19E-06	++	0.81
LINC01102	rs200457531	2:104694510	0.21	C/G	0.87	0.72	0.19	1.10E-04	0.81	1.45	0.47	0.002	0.82	0.17	2.63E-06	++	0.15
KIF2B	rs79761505	17:51588871	0.06	C/T	0.96	0.94	0.22	3.09E-05	0.91	1.27	0.57	0.026	0.98	0.21	3.09E-06	++	0.58
PCGEM1	rs200184681	2:194259469	0.05	T/TATAA	0.77	1.28	0.26	1.26E-06	0.74	0.06	0.94	0.955	1.19	0.26	3.31E-06	++	0.21
RASAL2	rs2209169	1:178601492	0.42	T/C	1.00	0.74	0.17	2.00E-05	0.95	0.74	0.40	0.068	0.74	0.16	4.07E-06	++	1.00
TMEM189	rs55757919	20:48748548	0.21	T/C	1.00	0.78	0.18	1.20E-05	0.97	0.63	0.43	0.145	0.76	0.17	4.79E-06	++	0.75
ACTL7B	rs142631117	9:111614117	0.07	C/CT	0.96	0.89	0.23	7.76E-05	0.96	1.40	0.57	0.013	0.97	0.21	5.13E-06	++	0.40
IKZF2	rs56175857	2:213929465	0.10	T/TCTAA	0.92	0.93	0.22	2.34E-05	0.85	1.06	0.60	0.078	0.95	0.21	5.25E-06	++	0.84
MIR548I1	rs140432795	3:125518739	0.05	A/G	0.83	1.24	0.28	7.59E-06	0.78	0.83	0.73	0.257	1.19	0.26	5.25E-06	++	0.59
MIR_584	rs72947763	6:115041783	0.06	A/G	0.89	1.10	0.27	3.80E-05	0.88	1.08	0.56	0.054	1.10	0.24	6.17E-06	++	0.97
SETBP1	rs56161428	18:42524278	0.06	A/G	0.91	1.05	0.23	6.03E-06	0.88	0.58	0.81	0.479	1.02	0.22	6.31E-06	++	0.58
LOC155060	rs6974847	7:148998960	0.25	G/A	1.00	0.73	0.18	3.55E-05	0.96	0.75	0.41	0.066	0.74	0.16	6.92E-06	++	0.96
SLC25A26	rs78974441	3:66343805	0.09	T/A	0.99	0.95	0.24	7.08E-05	0.96	1.06	0.51	0.035	0.97	0.22	7.94E-06	++	0.83
CNPY1	rs55907517	7:155302020	0.07	C/T	1.00	0.80	0.26	1.74E-03	0.88	1.78	0.49	3.00E-04	1.02	0.23	8.32E-06	++	0.08
PER4	rs111891616	7:9437462	0.08	T/C	0.85	0.86	0.25	4.30E-04	0.83	1.44	0.49	0.003	0.98	0.22	8.51E-06	++	0.29
ERMAP	rs12406643	1:43311563	0.18	G/A	1.00	0.88	0.18	6.31E-07	0.95	-0.83	0.65	0.204	0.76	0.17	9.12E-06	+-	0.01
SUMO1P1	rs62206653	20:52538079	0.06	T/C	0.86	1.13	0.25	7.94E-06	0.87	-21.40	36.34	0.55	1.13	0.26	9.33E-06	+-	0.54
PFKP	rs58751041	10:3007494	0.16	T/C	0.85	0.78	0.19	5.62E-05	0.79	0.82	0.43	0.059	0.78	0.18	9.77E-06	++	0.93

[a]Closest gene within 500kbp of the SNP. [b]Single nucleotide polymorphism, one representative per locus. [c]Position is chromosome:bp. Position according to NCBI Assembly build GRCh37/hg19. [d]MAF is the Minor allele frequency. This is the average of the minor allele frequencies of the ANYSET and ACCSET. [e]Info is an IMPUTE V2 variable for quality of imputation. Values Closer to 1 means excellent imputation quality of the variant; [f]Effect is the beta estimate for marginal association of the SNP with time to cardiac mortality in the intensive arm; [g]SE=Standard error.

SUPPLEMENTARY DATA

Supplementary Table S7. Top loci ($p<1x10^{-5}$) for progression to cardiovascular mortality in the intensive arm, further adjusted analyses.

Closest Gene[a]	SNP[b]	Position[c]	MAF[d]	Primary Analysis[e] with baseline CVD[f] adjustment		Primary Analysis with baseline CVD, age and sex adjustments	
				Hazard Ratio (95% CI)	*P value*	*Hazard Ratio (95% CI)*	*P value*
MGMT	rs9299870	10:131269309	0.08	3.52 (2.29-5.41)	9.40E-09	3.63 (2.36-5.59)	4.99E-09
LINC01333	rs57922	5:73577939	0.48	2.69 (1.91-3.79)	1.38E-08	2.63 (1.86-3.70)	3.52E-08
MASP2	rs373946618	1:11088774	0.08	4.36 (2.58-7.36)	3.62E-08	4.60 (2.69-7.87)	2.36E-08
AX748080	rs79525442	11:43990932	0.06	2.82 (1.86-4.27)	1.08E-06	2.79 (1.83-4.25)	1.92E-06
CCNJL	rs6878970	5:159771753	0.06	2.69 (1.74-4.16)	8.15E-06	2.71 (1.75-4.19)	8.06E-06
ANKFN1	rs116899003	17:54448567	0.05	2.78 (1.81-4.27)	2.78E-06	2.72 (1.77-4.18)	5.44E-06
GALNT18	rs1487122	11:11472617	0.06	3.00 (1.90-4.74)	2.71E-06	2.95 (1.86-4.70)	4.88E-06
LINC01102	rs200457531	2:104694510	0.21	2.25 (1.60-3.16)	3.44E-06	2.18 (1.55-3.07)	7.40E-06
KIF2B	rs79761505	17:51588871	0.06	2.51 (1.66-3.80)	1.32E-05	2.66 (1.74-4.08)	6.74E-06
PCGEM1	rs200184681	2:194259469	0.05	3.26 (2.02-5.27)	1.39E-06	3.23 (1.99-5.25)	1.98E-06
RASAL2	rs2209169	1:178601492	0.42	2.05 (1.51-2.78)	4.74E-06	2.02 (1.48-2.75)	9.09E-06
TMEM189	rs55757919	20:48748548	0.21	2.05 (1.48-2.84)	1.71E-05	2.05 (1.48-2.86)	2.01E-05
ACTL7B	rs142631117	9:111614117	0.07	2.35 (1.56-3.55)	4.21E-05	2.26 (1.51-3.38)	7.11E-05
IKZF2	rs56175857	2:213929465	0.10	2.56 (1.70-3.85)	7.03E-06	2.66 (1.76-4.00)	2.95E-06
MIR548I1	rs140432795	3:125518739	0.05	2.97 (1.76-4.99)	4.21E-05	3.09 (1.83-5.21)	2.34E-05
MIR_584	rs72947763	6:115041783	0.06	3.15 (1.96-5.06)	2.15E-06	3.22 (1.99-5.20)	1.77E-06
SETBP1	rs56161428	18:42524278	0.07	2.58 (1.67-3.98)	1.91E-05	2.61 (1.68-4.05)	1.99E-05
LOC155060	rs6974847	7:148998960	0.25	2.04 (1.48-2.81)	1.17E-05	2.09 (1.51-2.88)	7.62E-06
SLC25A26	rs78974441	3:66343805	0.09	2.66 (1.74-4.05)	5.70E-06	2.72 (1.78-4.15)	3.53E-06
CNPY1	rs55907517	7:155302020	0.07	2.89 (1.83-4.56)	5.01E-06	2.94 (1.86-4.64)	3.73E-06
PER4	rs111891616	7:9437462	0.08	2.61 (1.70-4.01)	1.05E-05	2.65 (1.72-4.07)	8.59E-06
ERMAP	rs12406643	1:43311563	0.18	2.05 (1.47-2.85)	2.09E-05	2.06 (1.48-2.88)	2.09E-05
SUMO1P1	rs62206653	20:52538079	0.06	3.00 (1.83-4.91)	1.37E-05	3.07 (1.85-5.09)	1.45E-05
PFKP	rs58751041	10:3007494	0.16	2.06 (1.46-2.91)	3.94E-05	2.02 (1.43-2.85)	6.93E-05

SUPPLEMENTARY DATA

[a]Closest gene within 500kbp of the SNP.
[b]Single nucleotide polymorphism, one representative per locus.
[c]Position is chromosome:bp. Position according to NCBI Assembly build GRCh37/hg19.
[d]MAF=Minor allele frequency. This is the average of the minor allele frequencies for subjects of the ANYset and ACCSet.
[e]Primary Analysis includes adjustment for assignment to blood-pressure and lipid sub-trials, interventions within these sub-trials, the seven clinical center networks, and the first three principal components (PC1-PC3), as shown in main results Table 1.
[f]CVD=Cardiovascular Disease.

SUPPLEMENTARY DATA

Supplementary Table S8. Baseline characteristics of participants among genetic risk score (GRS) strata in the ACCORD white GWAS subset [N=5,360]**

Characteristic	GRS=0 (N=1,212)	GRS=1 (N=2,558)	GRS≥2 (N=1,590)
Demographics			
Female sex, No. (%)	419 (34.6)	908 (35.5)	561 (35.3)
Age, mean (SD), y	62.8 (6.3)	62.6 (6.6)	63.0 (6.4)
Education, No. (%)			
Less than high school	113 (9.3)	247 (9.7)	158 (9.9)
High-school graduate	324 (26.7)	650 (25.4)	421 (26.5)
Some college	390 (32.2)*	929 (36.3)	563 (35.4)
College degree or higher	385 (31.8)*	731 (28.6)	446 (28.1)
Baseline Cardiovascular risk factors			
Diabetes duration, median (IQR), y	10.0 (5.0-15.0)	9.0 (5.0-15.0)	9.0 (5.0-15.0)
Previous cardiovascular event, No. (%)	426 (35.2)	915 (35.8)	564 (35.5)
Current Smoker, No. (%)	144 (11.9)	281 (11.0)	178 (11.2)
Glycated Hemoglobin, %			
Mean (SD)	8.2 (1.0)	8.2 (0.9)	8.2 (0.9)
Median (IQR)	8.0 (7.5-8.7)	8.0 (7.5-8.7)	8.1 (7.6-8.8)
Fasting serum glucose, mean (SD), mg/dl	178.7 (50.0)	178.0 (51.5)	179.1 (50.7)
Body Mass Index, mean (SD), kg/m^2	33.0 (5.2)	33.0 (5.3)	32.9 (5.2)
Waist circumference, mean (SD), cm	109.4 (13.0)	109.4 (13.1)	109.2 (12.8)
Blood Pressure, mean (SD), mm Hg			
Systolic	135.0 (16.5)	135.6 (17.1)	135.5 (17.5)
Diastolic	74.0 (10.2)	74.5 (10.9)	74.2 (10.6)
Potassium, mean (SD), mEq/L	0.03 (0.16)	0.03 (0.16)	0.03 (0.17)
Serum creatinine, mean (SD), mg/dl	0.90 (0.22)	0.90 (0.22)	0.90 (0.22)
Lipids, mean (SD),mg/dl			
Total cholesterol	185.6 (42.9)	181.7 (39.7)*	184.4 (43.9)
Low-density lipoprotein	104.7 (34.3)	102.6 (32.2)	102.6 (33.0)
High-density lipoprotein			
Women	45.2 (12.2)	45.5 (11.1)	44.8 (11.6)
Men	38.3 (9.8)	37.6 (8.9)	37.3 (9.0)
Triglyceride	208.9 (143.1)*	201.2 (135.5)*	219.4 (190.4)
Characteristic	**GRS=0 (N=1,212)**	**GRS=1 (N=2,558)**	**GRS≥2 (N=1,590)**
Medications, No. (%)			
Insulin	411 (33.9)	935 (36.6)	561 (35.3)
Any biguanide	743 (61.3)*	1,675 (65.5)	1,019 (64.1)
Any sulfonylurea	634 (52.3)	1,331 (52.0)	844 (53.1)
Any thiazolidinedione	311 (25.7)*	616 (24.1)*	346 (21.8)
Any antihypertensive agent	1,022 (84.3)*	2,186 (85.5)*	1,303 (82.0)
Angiotensin-converting-enzyme inhibitor	662 (54.6)	1,408 (55.0)	817 (51.4)
Aspirin	705 (58.2)	1,497 (58.5)	894 (56.2)
Beta-blocker	367 (30.3)	795 (31.1)	491 (30.9)
Any thiazide diuretic	338 (27.9)	660 (25.8)	398 (25.0)
Statin	771 (63.6)	1,665 (65.1)	989 (62.2)
Main Glycemia Trial, No. (%)	1,212 (100)	2,558 (100)	1,590 (100)
Standard	622 (51.3)	1,256 (49.1)	815 (51.3)
Intensive	590 (48.7)	1,302 (50.9)	775 (48.7)
Blood Pressure Trial, No. (%)	530 (43.7)	1,083 (42.3)	682 (42.9)
Standard	245 (20.2)	546 (21.3)	353 (22.2)
Intensive	285 (23.5)	537 (21.0)	329 (20.7)

SUPPLEMENTARY DATA

Lipid Trial, No. (%)	682 (56.3)	1,475 (57.7)	908 (57.1)
Statin + Placebo	337 (27.8)	715 (28.0)	444 (27.9)
Statin + Fibrate	345 (28.5)	760 (29.7)	464 (29.2)

SI conversion factors: To convert HbA1c to proportion of total hemoglobin, multiply values by 0.01; to convert fasting serum glucose to mmol/L, multiply values by 0.0555; to convert serum potassium to mmol/L, multiply values by 1; to convert serum creatinine to mmol/L, multiply values by 76.25; to convert cholesterol to mmol/L, multiply values by 0.0259; to convert triglycerides to mmol/L, multiply values by 0.0113.

*Significant difference ($p<0.05$) in baseline characteristic when compared to that in GRS≥2.
**Genetic risk score formed by adding the minor allele dosages of the two top variants, rs9299870 and rs57922

SUPPLEMENTARY DATA

Supplementary Table S9. Characteristics of subjects in the Joslin Kidney Study for Type 2 diabetes

	Mean glycemic control during Joslin visits		
	HbA1c<7.5% [N=108]	**HbA1c≥7.5% [N=314]**	**P-value**
Females, No. (%)	39 (36.1)	144 (45.9)	0.08
Age at study entry[a], mean (SD), y	57.3 (9.9)	57.7 (9.6)	0.71
Age at diabetes diagnosis, mean (SD), y	44.6 (9.5)	43.3 (8.8)	0.20
Diabetes duration at baseline, median (IQR), y	10.5 (5.5 – 20.0)	14.0 (8.0 – 20.0)	0.06
Body mass index at baseline, mean (SD), kg/m^2	28.5 (5.6)	30.1 (6.6)	0.02
HbA1c at baseline, mean (SD), %	6.8 (0.9)	8.9 (1.3)	<0.0001
HbA1c during Joslin visits[b], mean (SD), %	6.9 (0.5)	8.8 (0.9)	<0.0001
Number of HbA1c measurements during Joslin visits, median (IQR)	25 (12-37)	23 (12-37)	0.83
Time Range of HbA1c measurements at Joslin, median (IQR) , y	10.9 (6.0-18.0)	10.1 (6.3-15.9)	0.18
Chronic kidney disease at baseline, No. (%)	16 (15.4)	59 (19.1)	0.40
Albuminuria at baseline, No. (%)			0.007
Normoalbuminuria	69 (63.9)	146 (46.5)	
Microalbuminuria	20 (18.5)	96 (30.6)	
Macroalbuminuria	19 (17.6)	72 (22.9)	
Glucose-lowering therapy at baseline, No. (%)			<0.0001
Diet only	20 (18.5)	11 (3.5)	
Oral agents	40 (37.0)	79 (25.2)	
Insulin with/without oral agents	48 (44.4)	224 (71.3)	
Follow-up, mean (SD), y	13.8 (5.9)	12.4 (5.7)	0.03
Deaths as of 2011, No. (%)			
Total	43 (39.8)	177 (56.4)	<0.0001
Cardiovascular	18 (16.7)	106 (33.8)	0.0008

SI conversion factors: To convert HbA1c to proportion of total hemoglobin, multiply values by 0.01;
[a]Recruitment for Joslin Kidney Study in Type 2 diabetes occurred between 1993 and 1996.
[b]HbA1c measurements extracted from Joslin electronic medical records between 1990 and 2011 for subjects of the Joslin Kidney Study in Type 2 diabetes cohort.