Genome-Wide Association Study of Serum Fructosamine and Glycated Albumin in Adults Without Diagnosed Diabetes: Results From the Atherosclerosis Risk in Communities Study

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Fructosamine and glycated albumin are potentially useful alternatives to hemoglobin A_{1c} (HbA_{1c}) as diabetes biomarkers. The genetic determinants of fructosamine and glycated albumin, however, are unknown. We performed genome-wide association studies of fructosamine and glycated albumin among 2,104 black and 7,647 white participants without diabetes in the Atherosclerosis Risk in Communities (ARIC) Study and replicated findings in the Coronary Artery Risk Development in Young Adults (CARDIA) study. Among whites, rs34459162, a novel missense single nucleotide polymorphism (SNP) in *RCN3*, was associated with fructosamine ($P = 5.3 \times 10^{-9}$) and rs1260236, a known diabetes-related missense mutation in *GCKR*, was associated with percent glycated albumin ($P = 5.9 \times 10^{-9}$) and replicated in CARDIA. We also found two novel associations among blacks: an intergenic SNP, rs2438321, associated with fructosamine ($P = 6.2 \times 10^{-9}$), and an intronic variant in *PRKCA*, rs59443763, associated with percent glycated albumin ($P = 4.1 \times 10^{-9}$), but these results did not replicate. Few established fasting glucose or HbA_{1c} SNPs were also associated with fructosamine or glycated albumin. Overall, we found genetic variants associated with the glycemic information captured by fructosamine and glycated albumin as well as with their nonglycemic component. This highlights the importance of examining the genetics of hyperglycemia biomarkers to understand the information they capture, including potential glucose-independent factors.

Diabetes is defined by elevated blood glucose levels (hyperglycemia). Hemoglobin A_{1c} (HbA_{1c}) is formed as glucose binds to hemoglobin molecules within erythrocytes and is the standard clinical measure of chronic hyperglycemia used to diagnose and monitor diabetes (1). However, factors related to the nonglycemic portion of HbA_{1c} such as erythrocyte turnover and hemoglobin characteristics can affect HbA_{1c} values (2).

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There is growing interest in fructosamine and glycated albumin, additional biomarkers of hyperglycemia that demonstrate associations with diabetes risk and complications similar to HbA_{1c} (3–14). Fructosamine measures total serum protein bound to glucose. Glycated albumin is expressed as a percentage of serum albumin, the most abundant serum protein. Both biomarkers reflect glucose exposure over a shorter period of time (2–4 weeks) than HbA_{1c} (2–3 months) (15). Fructosamine may be used to monitor glycemic control in clinical situations where HbA_{1c} is problematic, such as in the setting of anemia or hemoglobinopathies (2). While glycated albumin is not frequently used in the U.S., it is widely used in Japan and other countries as a complement to HbA_{1c} to monitor short-term glycemic control (16).

The genetics of HbA_{1c} and glucose have been well studied; however, genetic factors that influence fructosamine and glycated albumin are uncharacterized. Of the known genome-wide association study (GWAS) variants associated with fasting glucose and HbA_{1c} in European ancestry cohorts, few loci are associated with both (17). Many HbA_{1c} variants are in genes related to hematological factors rather than glucose metabolism (18–20), while fasting glucose variants are in genes involved in glucose metabolism (although these variants are not all associated with diabetes) (21–23). This lack of overlap suggests that some underlying genetic variants are specific to particular biomarkers of hyperglycemia rather than to type 2 diabetes. Understanding the genetic determinants of fructosamine and glycated albumin should help in the interpretation of these tests and possibly extend our understanding of the pathophysiology of glucose metabolism. In particular, comparing the genetic overlap between different measures of glycemia may provide insight into the contributions of glycemic versus nonglycemic gene variants, i.e., to what extent genetic factors operate via pathways directly relevant to diabetes pathophysiology ("glycemic") or operate via glycemic-independent pathways that do not influence glucose metabolism or diabetes risk ("nonglycemic," such as the hematological variants associated with HbA_{1c}). If nonglycemic genetic variants strongly impact fructosamine and glycated albumin, this may need to be taken into account in the interpretation of these biomarkers as measures of hyperglycemia.

We conducted GWAS of fructosamine and glycated albumin in blacks and whites in the Atherosclerosis Risk in Communities (ARIC) Study. We also compared previously identified genetic determinants for HbA_{1c} and fasting glucose with fructosamine and glycated albumin to identify common genetic factors related to glucose metabolism and those that may be distinct to fructosamine and glycated albumin.

RESEARCH DESIGN AND METHODS

Study Population

The ARIC Study is an ongoing prospective cohort of 15,792 participants initiated in 1987 (24). Participants were middle-aged adults recruited from four U.S. communities (Jackson, Mississippi; Forsyth County, North Carolina; Washington County, Maryland; and suburban Minneapolis, Minnesota). All study participants provided written informed consent, and study protocols were approved by the relevant institutional review boards.

In the current study, we included 9,751 participants (7,647 whites and 2,104 blacks) who attended visit 2 (1990–1992), consented for use of DNA, did not have diagnosed diabetes (self-reported diagnosis or use of diabetes medications), had valid data on fructosamine and glycated albumin, and had genotyping data meeting quality control criteria (Supplementary Fig. 1). Individuals with diagnosed diabetes were excluded to avoid potential bias caused by altered glucose levels as a result of diabetes treatment.

Genotyping

ARIC Study participants were genotyped using the Affymetrix 6.0 array and imputed separately by race using IMPUTE2 (25) with the 1000 Genomes Project phase 1 (March 2012) reference panel. Quality control excluded individuals based on single nucleotide polymorphism (SNP) mismatch, high discordance with previous TaqMan assay genotypes, genetic outlier status, and relatedness. SNPs with IMPUTE info score <0.8 or minor allele frequency (MAF) <0.05 were excluded. Only autosomal variants (on chromosomes 1–22) were considered. Principal components analysis was used to estimate population substructure with EIGENSTRAT (26).

Glycemic Markers

Fructosamine (Roche Diagnostics, Indianapolis, IN) and glycated albumin and serum albumin (GA-L; Asahi Kasei Pharma Corporation, Tokyo, Japan) were measured in 2012–2013 using a Roche Modular P800 system from serum collected at visit 2 and stored at −70°C (3). Percent glycated albumin was calculated per the manufacturer's protocol: [(glycated albumin concentration in g/dL/serum albumin concentration in g/dL)*100/1.14] + 2.9. We also examined total glycated albumin (g/dL) as well as serum albumin (g/dL) to help distinguish genetic factors specific to serum protein concentration versus hyperglycemia.

Serum glucose was measured on the Roche Hitachi 911 analyzer using the hexokinase method (Roche Diagnostics), and HbA_{1c} was measured from whole blood stored at −70°C using high-performance liquid chromatography, standardized to the assay used in the Diabetes Control and Complications Trial (DCCT) (27).

Statistical Analysis

GWAS in blacks and whites were conducted using SNPTEST v2 (28) for all glycemic biomarkers using imputed allele dosage and controlling for age, sex, field center, and the first 10 principal components under an additive genetic model. Fructosamine and glycated albumin (both percent (%) and total [g/dL]) were transformed

on the natural log scale; therefore, the effect sizes are the change in the natural log of the biomarker per each additional risk allele. Exponentiating the effect sizes thus corresponds to the percent higher or lower biomarker levels per additional risk allele. Fasting glucose and HbA_{1c} were not transformed. To identify additional independent SNPs associated with the traits, we performed conditional analyses for genome-wide significant findings. Using fructosamine, percent glycated albumin, and total glycated albumin as the dependent variable and the index SNP (SNP with the lowest *P* value in a region showing a genome-wide significant association) as a covariate, we evaluated the association between other SNPs with a MAF ≥1% within 250 kB of the index SNP or between recombination hotspots surrounding the index SNP. To estimate percentage of variance explained by each SNP, we used the equation $R_i^2 = b_i^2 \times var(SNP_i)/var(y)$ where b_i = the effect size of the association between the SNP_i and the phenotype y, $var(SNP_i)$ is $2 \times MAF_{SNPi} \times (1\text{-}MAF_{SNPi})$ and var(y) is the variance in the phenotype (29,30). We meta-analyzed across ancestries using a random-effects model by GWAMA (31).

In sensitivity analyses, we performed GWAS excluding case subjects with undiagnosed diabetes (participants with fasting glucose ≥126 mg/dL or nonfasting glucose >200 mg/dL). To further evaluate the genetic variants pertaining to serum protein levels rather than hyperglycemia, we evaluated the top fructosamine and glycated albumin SNPs for association with total glycated albumin and with serum albumin (transformed on the natural log scale). To determine the extent to which glycemic biomarkers shared genetics, we used the program LDSC, which calculated genetic correlations between the biomarkers from ARIC summary statistics by taking advantage of the LD structure (variants in LD with more SNPs are more likely to have larger effect sizes, which extends to the product of correlated traits). We used precomputed LD scores from 1000 Genomes European data (32). Genetic correlations are not bounded to [–1,1], and estimates outside of this range indicate strong genetic correlations.

Replication

Significant associations between genetic variants and fructosamine and percent glycated albumin in ARIC were evaluated for replication in the Coronary Artery Risk Development in Young Adults (CARDIA) cohort, a prospective cohort study initiated in 1985 to evaluate risk factors for heart disease among unrelated young adults (33).

Serum specimens from 2005 to 2006 were stored at –70°C and used to analyze glycated albumin and fructosamine in 2014 using a Roche COBAS 6000 chemistry analyzer (Roche Diagnostics). Glycated albumin and fructosamine were measured using the same assays used in ARIC (glycated albumin by Lucica GA-L from Asahi Kasei Pharma Corporation and fructosamine via Roche Diagnostics).

Genotyping was performed using the Affymetrix 6.0 array. Standard quality control metrics were applied, and imputation to HapMap Phase II, Build 36, Release 22 was done using MACH (34). Genetic, covariate, fructosamine, and glycated albumin data were available on 1,304 whites and 608 blacks. Individuals with diabetes (current use of glucose-lowering medications or fasting glucose ≥126 mg/dL) were excluded from analysis. Linear regression analyses stratified by race were done for the association between significant ARIC SNPs and natural log–transformed fructosamine and percent glycated albumin adjusted for age, sex, field center, and the first three principal components.

Statistical analysis was done using SAS v9.4 (SAS Institute, Cary, NC) (data manipulation) and ProbABELv0.2 (35). If the ARIC SNP was not available in the CARDIA data set, we determined whether proxy SNPs in linkage disequilibrium (LD) with the ARIC SNP ($r^2 > 0.7$ from 1000 Genomes phase 3v5 European population, GRCh37 assembly using Single Nucleotide Polymorphisms Annotator (SNiPA) [36]) were available and, if so, analyzed the associations with the proxy SNP. We considered a Bonferroni-corrected one-sided *P* value threshold of <0.05 (0.1/2 SNPs per race) for replication significance. We meta-analyzed ARIC and CARDIA results using fixed-effects inverse variance weighted model by METAL (37).

Candidate SNP Analysis

We additionally evaluated previously identified fasting glucose (n = 41) and HbA_{1c} (n = 46) candidate SNPs from the National Human Genome Research Institute (NHGRI)-EBI Catalog of published GWAS using the search terms "fasting glucose" and "HbA1c" (http://www.ebi.ac.uk/gwas/ as of 14 December 2017) for association with fructosamine and percent glycated albumin in ARIC. SNPs were included if they were discovered in European ancestry cohorts, were genome-wide significant ($P < 5 \times 10^{-8}$), and were not in LD with each other ($r^2 < 0.2$, using SNiPA) (36). For the candidate SNP analyses, we used a study-wide significance threshold: two traits (fructosamine and glycated albumin), two races (black and white), and the number of candidate SNPs for each trait: $P < 4.6 \times 10^{-4}$ (0.05/(2*2*27)) for fasting glucose and $P < 2.6 \times 10^{-4}$ (0.05/(2*2*49)) for HbA_{1c}.

We additionally performed analyses controlling for known fasting glucose and HbA_{1c} SNPs with $P < 0.05$ in ARIC, compiled into scores calculated as the sum of the number of risk alleles, weighted by the effect size in ARIC among whites.

Comparison of Variance Explained

To compare the influence of glycemic and nonglycemic genetic variants on fructosamine and glycated albumin to that of HbA_{1c}, we calculated the percent phenotypic variance explained by the SNPs in our study to those from published results of HbA_{1c}. In addition, we calculated variance explained by known fasting glucose and albumin SNPs (identified by the same criteria used for fasting glucose and HbA_{1c}). Percent variance explained was calculated using the equation described above.

RESULTS

Overall, 7,647 whites and 2,104 blacks from ARIC and 1,304 whites and 608 blacks from CARDIA were included in this study (Supplementary Table 1). Mean age in ARIC (56–57 years) was higher than in CARDIA (45–46 years). The cohorts had similar distribution of sex. CARDIA had a greater percentage of black participants and lower mean values for each measure of glycemia as compared with ARIC.

We identified four genome-wide significant loci in ARIC, two associated with fructosamine and two with percent glycated albumin. Three of these variants, rs34459162 intronic to *RCN3*, rs2438321 (intergenic), and rs59443763 intronic to *PRKCA* have not previously been reported to be associated with any glycemic traits in humans (Table 1). None of the analyses showed evidence for inflation (Supplementary Figs. 2–7).

Among whites, rs34459162 (MAF = 0.08), a missense SNP in *RCN3* on chromosome 19, was significantly associated with 1.8% lower fructosamine per minor allele ($P = 5.3 \times 10^{-9}$, variance explained = 0.6%) (Table 1 and Figs. 1 and 2). This SNP was also associated with total glycated albumin ($P = 3.8 \times 10^{-8}$) (Table 2). The association with percent glycated albumin approached genome-wide significance ($P = 7.3 \times 10^{-8}$), but this SNP was not associated with fasting glucose or HbA_{1c} (Table 2). A proxy for rs34459162 (rs8105626, in $r^2 = 1$ rs34459162) was not associated in CARDIA for association with fructosamine ($P = 0.09$), although the effect sizes were identical and meta-analysis across the cohorts was significant ($P = 4.9 \times 10^{-9}$) (Table 1). Conditional analysis in ARIC showed that the additional 63 significant SNPs in the region became nonsignificant after conditioning on rs34459162. In blacks, rs34459162 did not meet the info score >0.8 threshold and thus was not analyzed (Table 2).

Among whites, rs1260326 (also known as rs343480), a known missense mutation in *GCKR* on chromosome 2 (MAF = 0.41), was significantly associated with 1.1% lower levels of percent glycated albumin per minor allele ($P = 5.3 \times 10^{-9}$, variance explained = 0.3%) (Supplementary Figs. 8 and 9) (Table 1). The association with percent glycated albumin was also significant in CARDIA ($P = 0.04$), with similar percent difference (0.8% lower per minor allele) and genome-wide significant meta-analysis results (2.3×10^{-8}) (Table 1). The conditional analysis did not reveal additional independent signals in this region. This SNP was not associated with any biomarker among blacks (MAF = 0.14) (Table 2 and Supplementary Table 2), but power was limited, and the meta-analysis across ancestries was not significant (Table 1 and Supplementary Fig. 10).

Among blacks, rs2438321 on chromosome 11 (MAF = 0.11) was associated with 3.5% higher levels of fructosamine per minor allele at a genome-wide significant level ($P = 6.2 \times 10^{-9}$, variance explained = 1.8%) (Table 1 and Supplementary Figs. 11 and 12) and approached significance with percent glycated albumin ($P = 6.4 \times 10^{-5}$) and

Table 1—Genome-wide significant loci for fructosamine and percent glycated albumin

SNP	Chr	Closest gene	A1/A2†	Outcome	Race	ARIC*					CARDIA*					ARIC+CARDIA*				ARIC White+Black*		
						A1 freq	β (SE)‡	% diff§	*P* value	% variance explained	A1 freq	β (SE)‡	% diff§	*P* value	% variance explained	β (SE)‡	% diff§	*P* value	% variance explained	β (SE)‡	% diff§	*P* value
rs34459162‖	19	*RCN3*	C/T	Fructosamine (μmol/L)	White	0.08	−0.02 (0.003)	−2%	5.3E-9	0.6%	0.09	−0.02 (0.014)	−2%	0.09	0.09	−0.02 (0.003)	−2%	4.9E-9	–	–	–	–
					Black	0.11	0.03 (0.006)	3%	6.2E-9	1.8%	0.06	0.006 (0.011)	0.6%	0.57	0.09	0.03 (0.005)	3%	2.9E-8	0.02 (0.02)	2%	0.37	0.09
rs1260326	2	*GCKR*	T/C	Percent glycated albumin (%)	White	0.41	−0.01 (0.002)	−1%	5.9E-9	0.3%	0.43	−0.01 (0.004)	−1%	0.04	0.04	−0.01 (0.002)	−1%	2.3E-8	−0.007 (0.005)	−0.7%	0.14	0.04
					Black	0.06	0.05 (0.009)	5%	4.1E-9	2.0%	–	–	–	–	–	–	–	–	–	–	–	–
rs2438321‖	11	*CNTN5*	G/A	Fructosamine (μmol/L)	White	0.11	0.03 (0.006)	3%	6.2E-9	1.8%	0.06	0.006 (0.011)	0.6%	0.57	0.09	0.03 (0.005)	3%	2.9E-8	0.02 (0.02)	2%	0.37	0.09
					Black	0.11	0.03 (0.006)	3%	6.2E-9	1.8%	0.06	0.006 (0.011)	0.6%	0.57	0.09	0.03 (0.005)	3%	2.9E-8	0.02 (0.02)	2%	0.37	0.09
rs59443763	17	*PRKCA*	C/T	Percent glycated albumin (%)	White	0.41	−0.01 (0.002)	−1%	5.9E-9	0.3%	0.43	−0.01 (0.004)	−1%	0.04	0.04	−0.01 (0.002)	−1%	2.3E-8	−0.007 (0.005)	−0.7%	0.14	0.04
					Black	0.06	0.05 (0.009)	5%	4.1E-9	2.0%	–	–	–	–	–	–	–	–	–	–	–	–

Chr, chromosome; diff, difference; freq, frequency. *ARIC: $N = 7,647$ whites, 2,104 blacks; CARDIA: $N = 1,304$ whites, 608 blacks; ARIC+CARDIA is a meta-analysis across the cohorts; ARIC White+Black is a meta-analysis across the ancestries in ARIC. †A1 is the minor allele in whites. ‡Mean change in ln(outcome) for each additional A1 allele. §Percent higher or lower levels of the outcome for each additional copy of the minor allele, calculated as $e^{\beta} * 100$. ‖rs34459162 and rs2438321 not available in CARDIA data set; evaluated proxy SNPs rs8105626 and rs3525014, respectively, in perfect LD ($r^2 = 1$ with ARIC SNP).

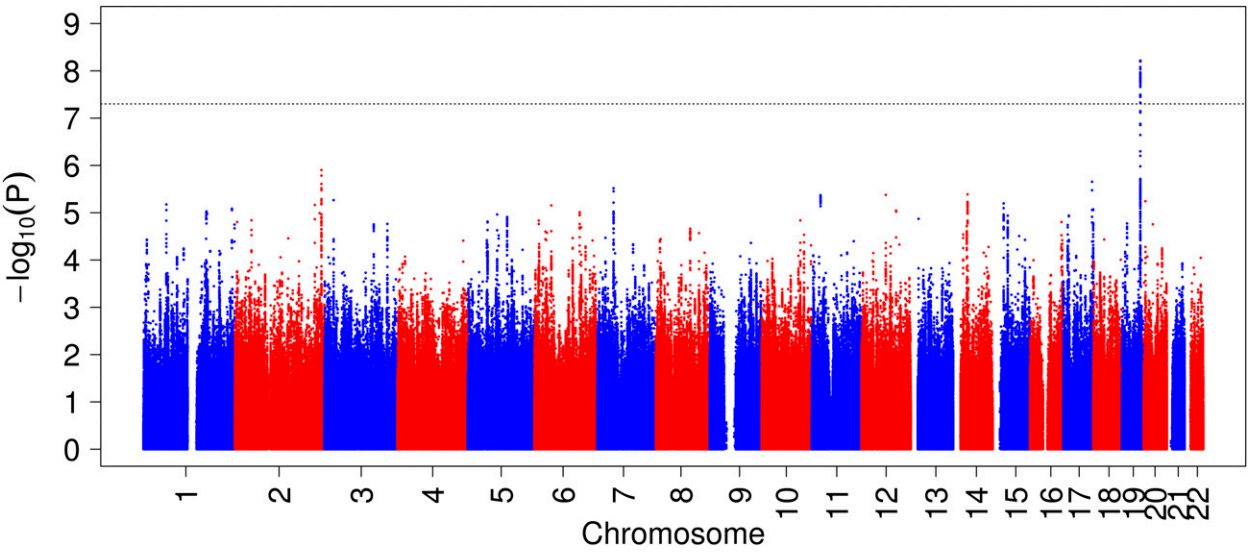

Figure 1—Manhattan plot for GWAS of fructosamine (log transformed) in whites (N = 7,647).

total glycated albumin ($P = 2.0 \times 10^{-6}$) (Table 2). rs2438321 was not associated with HbA_{1c} in blacks and was not associated with any of the markers of hyperglycemia in whites independently or in a meta-analysis across ancestries (Tables 1 and 2). This SNP was not available in the CARDIA data set; however, a proxy SNP in perfect LD ($r^2 = 1$, rs35256014, MAF = 0.06) was present but did not replicate the association with fructosamine in blacks (P = 0.57), and

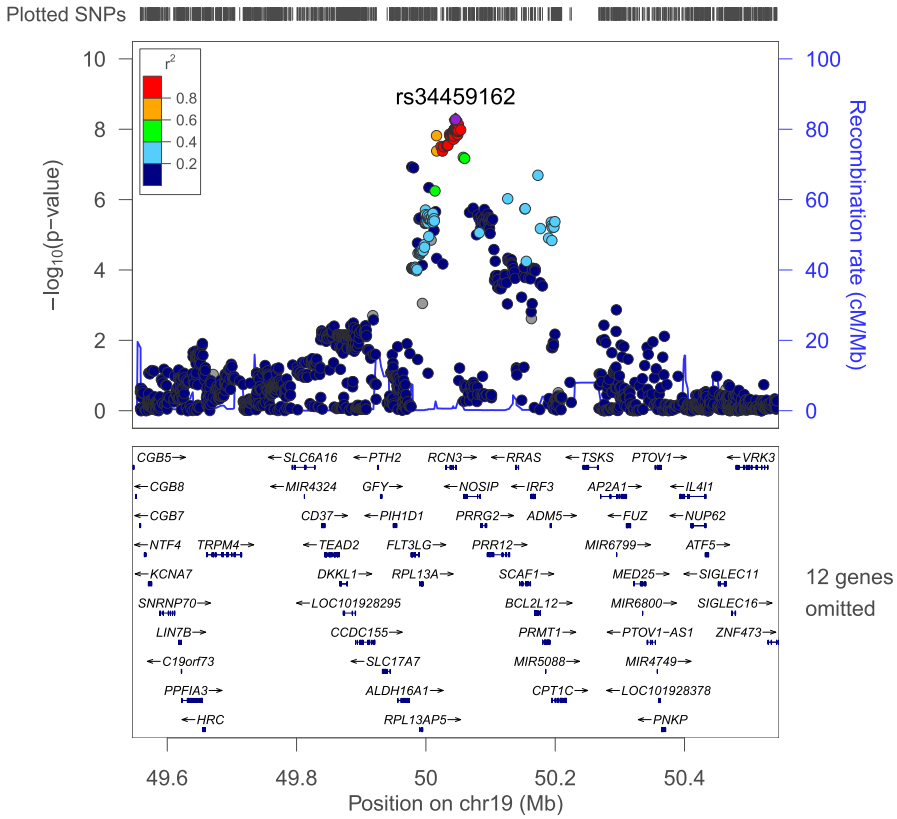

Figure 2—Regional association plot for rs34459162 and fructosamine (log transformed) among whites (included SNPs with MAF ≥5% and imputation quality ≥0.8, insertions and deletions excluded).

meta-analysis results were also nonsignificant (Table 1 and Supplementary Fig. 13).

An intronic variant, rs59443763, in *PRKCA* on chromosome 17 (MAF = 0.06), was significantly associated with 5.4% higher percent glycated albumin per minor allele in blacks ($P = 4.9 \times 10^{-9}$, variance explained = 2%) (Table 1 and Supplementary Figs. 14 and 15). It was also associated with fructosamine ($P = 9.4 \times 10^{-7}$) and total glycated albumin ($P = 5.8 \times 10^{-7}$), although these associations did not meet genome-wide significance (Table 2). This SNP was not significant among whites or in trans-ancestry meta-analysis (Tables 1 and 2), but there was limited power to replicate (Supplementary Table 2). No proxy SNPs with $r^2 > 0.7$ were available in the CARDIA data set, and thus replication was not possible for this association.

Sensitivity Analyses

In analyses that excluded participants with undiagnosed diabetes, genome-wide significant results remained for the white sample (N = 7,229) but were no longer present among the reduced sample of black participants (N = 1,878) (Supplementary Table 3).

Of the SNPs significantly associated with fructosamine or glycated albumin, only rs2438321 in blacks (P = 0.002) was significantly associated with serum albumin with a Bonferroni corrected P value (0.05/(4 SNPs * 2 races) = 0.006) (Supplementary Table 4).

Controlling for fasting glucose or HbA_{1c} variants did not reveal any additional genome-wide significant variants, but for glycated albumin, controlling for fasting glucose score attenuated the P value for rs1260326 (P = 0.002) among whites.

Fructosamine, percent glycated albumin, and total glycated albumin had strong, statistically significant genetic correlations (0.92 to 1.17) indicating a large proportion of shared genetics (Supplementary Table 5). Correlations between fasting glucose and HbA_{1c} with the other biomarkers were moderate to substantial but were not significant.

Candidate SNP Analysis

We investigated SNPs previously identified in fasting glucose and HbA_{1c} GWAS for association with fructosamine and percent glycated albumin. Nineteen of the 41 fasting glucose SNPs were nominally ($P < 0.05$) associated with fasting glucose, and 13 of these associations were in the same direction in blacks and whites (Table 3 and Supplementary Table 6) and 33 had consistent direction with the discovery cohort in whites. Four variants (10%) were study-wide significantly associated with fructosamine and percent glycated albumin in whites, three of which were associated with percent glycated albumin and one of which was associated with fructosamine. No variants were study-wide significantly associated with fructosamine or percent glycated albumin in blacks.

Thirty-one of 46 previously identified HbA_{1c} SNPs were nominally associated with HbA_{1c}, 15 of which were associated

Table 2—Genome-wide significant loci for fructosamine and percent glycated albumin and their association with total glycated albumin, fasting glucose, and HbA_{1c} in ARIC

SNP	Closest gene	A1/A2‡	Race	1000 Genomes A1 freq§	A1 freq	Fructosamine (μmol/L)		Percent glycated albumin (%)		Total glycated albumin (g/dL)		Fasting glucose (mg/dL)		HbA_{1c} (%)	
						β (SE)	*P* value	β (SE)	*P* value	β (SE)	*P* value	β (SE)	*P* value	β (SE)	*P* value
rs34459162	*RCN3*	C/T	White	0.08	0.08	**-0.02 (0.003)**	**5.3E-9**	−0.02 (0.004)	7.3E-8	**−0.03 (0.005)**	**3.8E-8**	0.26 (0.56)	0.64	−0.02 (0.02)	0.25
			Black	—	—	—	—	—	—	—	—	—	—	—	—
rs1260326	*GCKR*	T/C	White	0.43	0.41	−0.003 (0.002)	0.02	**−0.01 (0.002)**	**5.9E-9**	−0.01 (0.003)	1.3E-5	−1.13 (0.28)	4.5E-5	−0.01 (0.008)	0.09
			Black	0.10	0.14	0.0005 (0.005)	0.93	−0.0003 (0.006)	0.96	0.001 (0.009)	0.9	−0.53 (1.16)	0.64	−0.01 (0.04)	0.76
rs2438321	*CNTN5*	G/A	White	0.30	0.24	−0.001 (0.002)	0.44	0.0005 (0.002)	0.82	−0.001 (0.003)	0.71	−0.21 (0.32)	0.52	0.001 (0.01)	0.95
			Black	0.11	0.11	**0.03 (0.006)**	**6.2E-9**	0.03 (0.007)	6.4E-5	0.05 (0.009)	2.0E-6	4.19 (1.24)	8.3E-4	0.14 (0.04)	6.8E-4
rs59443763	*PRKCA*	C/T	White	0.005	—	—	—	—	—	—	—	—	—	—	—
			Black	0.09	0.06	0.04 (0.008)	9.4E-7	**0.05 (0.009)**	**4.1E-9**	0.06 (0.01)	5.8E-7	7.2 (1.65)	9.6E-6	0.18 (0.05)	8.3E-4

freq, frequency. Genome-wide significant results are in boldface type. Fructosamine, glycated albumin percent, and total glycated albumin are log transformed. ‡A1 is the minor allele in whites. §1000 Genomes populations: white, Utah residents (CEPH) with Northern and Western European ancestry (CEU); black, Americans of African ancestry in Southwest U.S. (ASW).

Table 3—Significance of associations between fasting glucose known genetic determinants and fructosamine and percent glycated albumin in ARIC

				Whites				Blacks			
SNP	Chr:position	Closest gene	A1/A2	A1 freq	*P* value fructosamine	*P* value glycated albumin	*P* value fasting glucose	A1 freq	*P* value fructosamine	*P* value glycated albumin	*P* value fasting glucose
rs10747083	12:133041618	*P2RX2*	G/A	0.33	0.95	0.76	0.14	0.16	0.17	0.11	0.95
rs10830963	11:92708710	*MTNR1B*	G/C	0.28	0.001	0.003	**3.3E-07**	0.07	0.13	0.03	0.38
rs10885122	10:113042093	*ADRA2A*	T/G	0.12	0.82	0.75	0.76	0.68	0.24	0.72	0.21
rs11071657	15:62433962	*C2CD4B*	G/A	0.38	0.50	0.81	0.52	0.12	0.98	0.95	0.43
rs11558471	8:118185733	*SLC30A8*	G/A	0.32	0.005	**8.2E-05**	**1.8E-05**	0.09	0.31	0.18	0.65
rs11603334	11:72432985	*ARAP1*	A/G	0.16	0.01	0.08	0.47	0.06	0.79	0.95	0.76
rs11605924	11:45873091	*CRY2*	A/C	0.47	0.36	0.58	0.66	0.84	0.58	0.72	0.44
rs11708067	3:123065778	*ADCY5*	G/A	0.23	0.07	0.001	**0.01**	0.16	0.002	0.003	**0.03**
rs11715915	3:49455330	*AMT*	T/C	0.30	0.30	0.74	**0.04**	0.23	0.06	0.37	0.31
rs11920090	3:170717521	*SLC2A2*	A/T	0.13	0.004	0.002	0.34	0.35	0.47	0.30	0.28
rs13179048	5:95542726	*PCSK1*	A/C	0.31	0.11	0.13	0.51	0.08	0.18	0.52	0.78
rs1371614	2:27152874	*DPYSL5*	T/C	0.25	0.47	0.78	0.69	0.36	0.18	0.11	0.21
rs143399767	9:96182703	*YRNA*	C/A	0.01	0.65	0.24	0.55				
rs1483121	11:48333360	*OR4S1*	A/G	0.13	0.41	0.36	0.74	0.04	0.46	0.42	0.94
rs16913693	9:111680359	*IKBKAP*	G/T	0.03	0.60	0.78	0.11	0.25	0.73	0.68	0.91
rs174550	11:61571478	*FADS1*	C/T	0.33	0.16	0.28	0.54	0.08	0.37	0.15	0.93
rs17762454	6:7213200	*RREB1*	T/C	0.26	0.13	0.32	**0.001**	0.16	0.16	0.76	0.75
rs2191349	7:15064309	*TMEM195, DGKB*	G/T	0.46	0.17	0.36	**0.02**	0.44	0.58	0.73	**0.004**
rs2293941	13:28491198	*PDX1*	A/G	0.22	0.02	0.005	**0.03**	0.17	0.38	0.60	0.77
rs2302593	19:46196634	*GIPR*	G/C	0.50	1.00	0.40	**0.02**	0.30	0.64	0.94	0.97
rs2657879	12:56865338	*GLS2*	G/A	0.18	0.93	0.94	0.31	0.06	0.05	0.23	**0.04**
rs2722425	8:40484239	*ZMAT4*	T/C	0.12	0.01	0.01	0.78	0.37	0.25	0.35	0.41
rs340874	1:214159256	*PROX1*	T/C	0.45	0.42	0.82	0.40	0.17	0.36	0.74	0.15
rs35767	12:102875569	*IGF1*	G/A	0.16	0.76	0.54	0.62	0.55	0.43	0.10	**0.02**
rs3736594	2:27995781	*MRPL33*	C/A	0.26	0.11	0.07	0.25	0.43	0.07	0.03	0.62
rs3783347	14:100839261	*WARS*	T/G	0.22	0.45	0.51	0.57	0.06	0.44	0.60	0.94
rs3829109	9:139256766	*DNLZ*	A/G	0.29	0.003	0.13	0.16	0.18	0.51	0.39	0.46
rs4506565	10:114756041	*TCF7L2*	T/A	0.31	3.9E-04	**2.5E-05**	**2.7E-05**	0.44	0.09	0.40	0.83
rs4607517	7:44235668	*GCK*	A/G	0.17	**2.0E-04**	0.003	**5.0E-04**	0.11	0.09	0.10	0.08
rs4841132	8:9183596	*PPP1R3B*	A/G	0.09	0.33	0.32	**0.05**	0.13	0.74	0.29	**0.05**

Continued on p. 1691

Table 3—Continued

SNP	Chr:position	Closest gene	A1/A2	Whites				Blacks			
				A1 freq	*P* value fructosamine	*P* value glycated albumin	*P* value fasting glucose	A1 freq	*P* value fructosamine	*P* value glycated albumin	*P* value fasting glucose
rs560887	2:169763148	*G6PC2*	T/C	0.30	0.08	0.003	**7.3E-05**	0.05	0.81	0.58	0.91
rs576674	13:33554302	*KL*	G/A	0.16	0.45	0.50	0.33	0.61	0.17	0.26	0.11
rs6048205	20:22559601	*FOXA2*	G/A	0.05	0.79	0.95	0.07	0.18	0.02	0.25	**0.05**
rs6072275	20:39743905	*TOP1*	A/G	0.16	0.57	0.30	**0.01**	0.08	0.13	0.12	0.08
rs6943153	7:50791579	*GRB10*	T/C	0.31	0.67	0.46	0.16	0.70	0.09	0.77	0.61
rs7034200	9:4289050	*GLIS3*	A/C	0.49	0.19	0.04	**0.03**	0.61	0.18	0.02	0.11
rs7651090	3:185513392	*IGF2BP2*	G/A	0.31	0.01	0.03	**0.003**	0.56	0.32	0.58	0.40
rs7708285	5:76425867	*ZBED3*	G/A	0.30	0.32	0.64	0.71	0.15	0.56	0.52	0.16
rs780094	2:27741237	*GCKR*	T/C	0.40	0.05	**5.7E-05**	**1.0E-04**	0.18	0.75	0.96	0.90
rs7944584	11:47336320	*MADD*	T/A	0.27	0.56	0.76	**0.05**	0.04	0.98	0.38	0.77
rs9368222	6:20686996	*CDKAL1*	A/C	0.27	0.19	0.09	0.27	0.20	0.96	0.80	0.68

freq, frequency. Candidate SNPs selected from NHGRI database based on previous genome-wide significant associations. *P* values that reach study-wide significance for fructosamine and glycated albumin, $P < 3.0 \times 10^{-4}$ (0.05/(2*2*41)), and *P* values that reach nominal significance ($P < 0.05$) for fasting glucose are in boldface type.

in the same direction in blacks and whites (Table 4 and Supplementary Table 7), and 43 had consistent direction with the discovery cohort in whites. Five SNPs (11%) demonstrated a study-wide significant association with fructosamine or glycated albumin in whites. All variants associated with multiple glycemic biomarkers had effects in the same direction.

Percent Variance Explained

SNPs associated with fasting glucose (N = 41) (Table 3) explained 1.4% of the variance in fructosamine, 3.2% of the variance in percent glycated albumin, and 1.9% of the variance in total glycated albumin among whites. Taking SNPs associated with serum albumin from the GWAS catalog explained 0.4% of the variance of fructosamine, 1.1% of the variance of percent glycated albumin, and 0.7% of the variance of total glycated albumin among the white sample.

DISCUSSION

We identified four SNPs significantly associated with fructosamine and glycated albumin among either whites or blacks, one which replicated in a second cohort and three not previously associated with glycemic traits. Several known fasting glucose and HbA_{1c} SNPs were significantly associated with fructosamine or glycated albumin.

Among whites, rs1260326 was associated with percent glycated albumin. This variant reflects the same signal associated with type 2 diabetes and fasting glucose: it is in perfect LD with a known type 2 diabetes variant (r^2 = 1 among 1000 Genomes phase 3 Europeans with rs145819220, from a recent large type 2 diabetes GWAS [38]) and in strong LD with a known fasting glucose variant (r^2 = 0.91 with rs780094 [37,38]). rs1260326 is located in glucokinase (hexokinase 4) regulator (*GCKR*), which encodes a regulatory protein primarily active in the liver that inhibits glucokinase (GCK), the enzyme in the first step of glycolysis and involved in converting glucose to glycogen for storage. GCK is considered a glucose sensor that helps maintain glucose homeostasis. The *GCKR* protein product inhibits the activity of GCK, increasing serum glucose levels. *GCKR* is an established type 2 diabetes gene (39–41) and is associated with multiple other traits including kidney disease, triglyceride levels, and Crohn disease (42–44). Thus, this variant likely represents part of a glycemic pathway, but it is interesting that in our study it is only significantly associated with one measure of hyperglycemia, approached significance with fasting glucose (although controlling for fasting glucose score made this variant nonsignificant) and total glycated albumin, but is not associated with fructosamine or HbA_{1c}, given the moderate to strong correlations and genetic correlations among the biomarkers (Supplementary Tables 5 and 8). That *GCKR* is primarily expressed in the liver rather than the pancreas (45,46) aligns with the finding of association with fasting glucose, which measures hepatic glucose output. Albumin is also produced by the liver, while erythrocytes

Table 4—Significance of associations between HbA_{1c} known genetic determinants and fructosamine and percent glycated albumin in ARIC

				Whites				Blacks			
SNP	Chr:position	Closest gene	A1/A2	A1 freq	*P* value fructosamine	*P* value glycated albumin	*P* value HbA_{1c}	A1 freq	*P* value fructosamine	*P* value glycated albumin	*P* value HbA_{1c}
rs1046896	17:80685533	*FN3KRP*	T/C	0.31	0.034	0.048	0.052	0.24	0.661	0.455	0.585
rs10774625	12:111910219	*ATXN2*	G/A	0.48	0.571	0.032	**0.008**	0.09	0.221	0.142	0.503
rs10823343	10:71091013	*HK1*	G/A	0.26	0.452	0.065	**1.1E-06**	0.45	0.808	0.529	0.899
rs10830963	11:92708710	*MTNR1B*	G/C	0.28	0.001	0.003	**0.006**	0.07	0.134	0.035	0.222
rs11248914	16:293562	*ITFG3*	C/T	0.35	0.011	0.229	0.055	0.36	0.067	0.354	0.485
rs11558471	8:118185733	*SLC30A8*	G/A	0.32	0.005	**8.2E-05**	**0.010**	0.09	0.309	0.176	0.989
rs11603334	11:72432985	*ARAP1*	A/G	0.16	0.005	0.078	0.228	0.06	0.788	0.950	0.734
rs11708067	3:123065778	*ADCY5*	G/A	0.23	0.070	0.001	**0.034**	0.16	0.002	0.003	0.074
rs11954649	5:157055491	*SOX30*	G/C	0.00	NA	NA	NA	0.05	0.812	0.220	0.184
rs11964178	6:109562035	*C6orf183*	G/A	0.43	0.861	0.844	0.702	0.36	0.180	0.748	0.475
rs12621844	2:48414735	*FOXN2*	C/T	0.39	0.732	0.294	0.358	0.84	0.829	0.853	0.666
rs12819124	12:48409054	*RP1*	A/C	0.47	0.765	0.930	**0.001**	0.21	0.500	0.826	0.146
rs13134327	4:144659795	*FREM3*	A/G	0.32	0.800	0.662	**0.031**	0.30	0.220	0.854	0.772
rs1402837	2:169757354	*G6PC2*	T/C	0.22	0.016	**9.3E-05**	**2.7E-07**	0.31	0.471	0.728	0.656
rs1558902	16:53803574	*FTO*	A/T	0.41	0.545	0.017	0.131	0.11	0.065	0.176	0.514
rs17509001	2:24021231	*ATAD2B*	C/T	0.14	0.309	0.152	**0.027**	0.09	0.604	0.524	0.802
rs17533903	19:17256523	*MYO9B*	A/G	0.21	0.577	0.167	**5.0E-04**	0.24	0.403	0.232	0.689
rs17747324	10:114752503	*TCF7L2*	C/T	0.23	**1.7E-04**	**3.2E-05**	**1.8E-04**	0.07	0.396	0.755	0.890
rs1800562	6:26093141	*HFE*	A/G	0.06	0.337	0.128	**0.001**	0.01	0.846	0.670	0.146
rs198846	6:26107463	*HFE*	A/G	0.16	0.390	0.198	0.123	0.88	0.533	0.270	0.260
rs2110073	12:7075882	*PHB2*	T/C	0.10	0.321	0.938	**0.002**	0.42	0.177	0.349	0.160
rs2383208	9:22132076	*MTAP*	G/A	0.18	0.008	0.019	**0.007**	0.19	0.293	0.763	0.596
rs2408955	12:48499131	*SENP1*	G/T	0.48	0.567	0.879	**0.002**	0.63	0.813	0.824	0.632
rs267738	1:150940625	*CERS2*	G/T	0.21	0.444	0.434	0.511	0.04	0.853	0.745	0.297
rs2779116	1:158585415	*SPTA1*	T/C	0.27	0.714	0.792	**9.9E-06**	0.22	0.111	0.167	0.961
rs282587	13:113351662	*ATP11A*	G/A	0.12	0.586	0.248	**1.0E-04**	0.69	0.050	0.142	0.246
rs3824065	7:44247258	*GCK*	T/C	0.42	3.3E-04	0.002	0.125	0.24	0.086	0.134	0.910
rs4607517	7:44235668	*GCK*	A/G	0.17	**2.0E-04**	0.003	**5.7E-05**	0.11	0.088	0.097	0.244
rs4737009	8:41630405	*ANK1*	A/G	0.24	0.126	0.515	**0.018**	0.46	0.274	0.461	0.361
rs4745982	10:71089843	*HK1*	G/T	0.07	0.190	0.263	**5.8E-06**	0.10	0.889	0.921	0.602
rs4820268	22:37469591	*TMPRSS6*	G/A	0.46	0.264	0.350	**0.010**	0.72	0.073	0.029	0.181

Continued on p. 1693

Table 4—Continued

				Whites				Blacks			
SNP	Chr:position	Closest gene	A1/A2	A1 freq	*P* value fructosamine	*P* value glycated albumin	*P* value HbA_{1c}	A1 freq	*P* value fructosamine	*P* value glycated albumin	*P* value HbA_{1c}
rs560887	2:169763148	*G6PC2*	T/C	0.30	0.080	0.003	**0.003**	0.95	0.811	0.583	0.861
rs579459	9:136154168	*ABO*	C/T	0.23	0.268	0.340	**0.001**	0.13	0.210	0.487	0.600
rs592423	6:139840693	*CITED2*	A/C	0.46	0.514	0.535	0.063	0.61	0.323	0.605	0.333
rs6474359	8:41549194	*ANK1*	C/T	0.03	0.979	0.486	**4.3E-04**	0.27	0.077	0.047	0.879
rs6980507	8:42383084	*SLC20A2*	A/G	0.39	0.256	0.873	**0.015**	0.48	0.514	0.557	0.663
rs7040409	9:91503236	*C9orf47*	G/C	0.07	0.499	0.765	**0.001**	0.26	0.028	0.005	0.115
rs7616006	3:12267648	*SYN2*	G/A	0.43	0.705	0.385	0.181	0.36	0.974	0.959	0.836
rs761772	17:76122078	*TMC6*	C/T	0.13	0.077	0.109	**0.009**	0.13	0.480	0.361	0.861
rs7756992	6:20679709	*CDKAL1*	G/A	0.27	0.180	0.094	0.292	0.42	0.856	0.997	0.995
rs8192675	3:170724883	*SLC2A2*	C/T	0.30	**5.4E-05**	**6.1E-05**	**0.010**	0.29	0.232	0.239	**0.024**
rs837763	16:88853729	*CDT1*	C/T	0.44	0.591	0.804	**0.046**	0.56	0.492	0.554	0.533
rs857691	1:158626378	*SPTA1*	T/C	0.25	0.803	0.492	**5.6E-06**	0.30	0.092	0.226	0.894
rs9604573	13:114542858	*GAS6*	A/G	0.26	0.482	0.300	0.687	0.24	0.902	0.833	0.425
rs9818758	3:49382925	*USP4*	A/G	0.17	0.240	0.870	0.780	0.09	0.297	0.297	0.642
rs9914988	17:27183104	*ERAL1*	G/A	0.21	0.307	0.993	0.058	0.66	0.252	0.080	0.342

freq, frequency. Candidate SNPs selected from NHGRI database based on previous genome-wide significant associations. *P* values that reach study-wide significance for fructosamine and glycated albumin, $P < 2.7 \times 10^{-4}$ (0.05/(2*2*46)), and *P* values that reach nominal significance ($P < 0.05$) for HbA_{1c} are in boldface type.

and hemoglobin are not likely affected by liver function, thus perhaps hepatic-specific genetic factors would be more likely to associate with percent glycated albumin levels than with HbA_{1c}. It is also possible that HbA_{1c}, affected by other glucose-altering factors, may mask the effect of rs1260326 on *GCKR*. Adjustment for serum albumin may explain the association with percent glycated albumin but not fructosamine.

We also identified several variants of potential interest that were significant in ARIC but lacked replication. Among whites, rs34459162, in *RCN3*, was associated with fructosamine and total glycated albumin. *RCN3* encodes reticulocalbin 3, an EF-hand calcium binding domain (47). This SNP was not associated with serum albumin in our analysis, but a SNP in perfect LD with rs34459162, rs2280401, was associated with total protein in a Japanese population (48) and serum albumin in an East Asian population (49), indicating a possible impact on fructosamine and glycated albumin through nonglycemic pathways. Among blacks, we found two novel variants: rs2438321 (intergenic and closest to *CNTN5*, which encodes a glycosylphosphatidylinositol-anchored neuronal membrane protein, a member of the immunoglobulin superfamily and the contactin family) associated with fructosamine and rs59443763 (*PRKCA*, which encodes protein kinase C alpha, ubiquitous in cellular processes) associated with percent glycated albumin at a genome-wide level of significance. There is no prior literature on either of these as potential glycemic loci in diabetes. While we had sufficient power to replicate the results for whites in CARDIA (Supplementary Table 2), we had low power among blacks, which may be why these SNPs did not replicate. These variants became nonsignificant after excluding undiagnosed diabetes, which may be due to the greater number of individuals with undiagnosed diabetes among blacks than whites. Blacks had higher values of glycemic biomarkers, thus removing case subjects with undiagnosed diabetes could have had a greater impact on associations among blacks than whites. These variants should be evaluated in larger African ancestry data sets as they become available. rs34459162, rs2438321, and rs59443763 are of potential interest, but as these SNPs currently lack replication, we cannot rule out false positive results.

Results varied by ancestry for the SNPs available in both blacks and whites: neither SNP was significant in both blacks and whites, and meta-analyses results were nonsignificant. While this may partially be explained by differing allele frequencies (rs1260326: 0.41 in whites, 0.14 in blacks; rs2438321: 0.24 in whites, 0.11 in blacks), a differential effect by ancestry on fructosamine and glycated albumin is also possible. This may be particularly true for rs2438321, where the direction of effect differs across ancestries.

In addition to investigating fructosamine and glycated albumin individually, comparing to traditional glycemic markers (fasting glucose and HbA_{1c}) can help to clarify the biological pathways involved in diabetes. Fasting glucose–related SNPs explained almost twice the variance of percent glycated albumin than that of fructosamine. This may reflect the adjustment for serum albumin with percent glycated albumin and not with fructosamine, allowing percent glycated albumin levels to be influenced more by glucose levels and less by albumin levels. However, albumin SNPs also explained more variance of percent glycated albumin than that of fructosamine or total glycated albumin. Given the small percentages, it is difficult to draw first conclusions from these results.

Only five HbA_{1c} variants were significantly associated with fructosamine or glycated albumin. This is consistent with the findings that the majority of HbA_{1c} variants are related to erythrocyte and hemoglobin factors that we would not expect to be related to fructosamine or glycated albumin. Many associations of fructosamine or glycated albumin with HbA_{1c} SNPs or fasting glucose SNPs were present in whites but not blacks. This is not surprising given that the SNPs were originally detected in whites and that our sample size was larger for whites, with corresponding higher power to detect moderate associations. Not all of the previously discovered SNPs for fasting glucose and HbA_{1c} replicated for those outcomes in our sample, but this again may have to do with lack of power.

We found that both glycemic and nonglycemic genetic factors influenced fructosamine and glycated albumin levels. We identified a likely glycemic variant in a gene associated with type 2 diabetes (*GCKR*), supporting its role in diabetes biology, and a likely nonglycemic variant in a gene (*RCN3*) that may reflect the biology of a biomarker (i.e., influencing amount of serum protein available to be glycated) rather than the biology of type 2 diabetes. This contribution of glycemic and nonglycemic variants is similar to the pattern of genetic contribution to HbA_{1c}, for which the majority of genetic variants are nonglycemic (18,19). In our study, previously identified nonglycemic variants (18–20) explained 3.4% of the variance in HbA_{1c} and the glycemic variants explained 2.1% (Supplementary Table 9). Despite the previous studies having much larger sample sizes (and thus more power to detect associations with HbA_{1c}), the percent variance explained we found for fructosamine (0.6% by likely nonglycemic rs34459162) and glycated albumin (0.3% by likely glycemic rs1260326) was of a similar magnitude. Both Soranzo et al. (18) and Chen et al. (19) found that taking nonglycemic variants into account modestly impacted diabetes reclassification, and Wheeler et al. (20) found a more substantial effect. Given that that future larger studies on fructosamine and glycated albumin will likely reveal other significant variants, it will be important to determine whether the effect of nonglycemic variants is substantial enough to impact the clinical interpretation of fructosamine and glycated albumin.

A major limitation of this study was the limited sample size, particularly the smaller sample size in blacks. The differences in ancestries make replication of results difficult, particularly if allele frequencies differ, and warrant

more studies focused on multiethnic populations. Also, the lack of an available SNP or proxy for rs59443763 in CARDIA, possibly due to the imputation reference panel (HapMap Phase II), impeded our ability to evaluate replication of this finding. In addition, the sample size for our replication cohort was much smaller than our discovery cohort, limiting our power to replicate the significant ARIC findings in blacks.

In summary, through GWAS in a community-based population of blacks and whites, we identified and replicated two significant variants associated with fructosamine and/or glycated albumin, one of which was novel. These variants map into a likely glycemic, known diabetes gene and a likely nonglycemic gene. This highlights the utility of examining genetics of diabetes biomarkers both for providing insight into the pathophysiology of diabetes and for better understanding glucose-independent influences on measures of hyperglycemia.

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