Published in final edited form as:
Obesity (Silver Spring). 2012 March ; 20(3): 622–627. doi:10.1038/oby.2011.154.

Genome-Wide Association of BMI in African Americans

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Abstract

Recent genome-wide association studies (GWAS) have identified multiple novel loci associated with obesity in Europeans but results in other ethnicities are less convincing. Here, we report a two-stage GWAS of BMI in African Americans. The GWAS was performed using the Affymetrix 6.0 platform in 816 nondiabetic and 899 diabetic nephropathy subjects. 746,626 single-nucleotide polymorphisms (SNPs) were tested for association with BMI after adjustment for age, gender, disease status, and population structure. Sixty high scoring SNPs that showed nominal association in both GWAS cohorts were further replicated in 3,274 additional subjects in four replication cohorts and a meta-analysis was computed. Meta-analysis of 4,989 subjects revealed five SNPs (rs6794092, rs268972, rs2033195, rs815611, and rs6088887) at four loci showing consistent associations in both GWAS ($P < 0.0001$) and replication cohorts ($P < 0.05$) with combined P values range from 2.4×10^{-6} to 5×10^{-5}. These loci are located near *PP13439-TMEM212*, *CDH12*, *MFAP3-GALNT10*, and *FER1L4* and had effect sizes between 0.091 and 0.167 s.d. unit (or 0.67–1.24 kg/m^2) of BMI for each copy of the effect allele. Our findings suggest the presence of novel loci potentially associated with adiposity in African Americans. Further replication and meta-analysis in African Americans and other populations will shed light on the role of these loci in different ethnic populations.

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Supplementary Material: Supplementary material is linked to the online version of the paper at http://www.nature.com/oby

Disclosure: The authors declared no conflict of interest.

Introduction

Obesity is a global public health problem leading to increased mortality and comorbidities such as type 2 diabetes (T2DM), metabolic syndrome, coronary heart disease, stroke, cancer, liver and gallbladder disease, sleep disorders, and osteoarthritis. In the United States, the age-adjusted prevalence of obesity (defined as BMI ≥30 kg/m^2) has increased from 15 to 34% in adults aged >20 years from 1980 to 2008, although the trend of increase has slowed in the past decade (1,2). Marked racial and gender differences in the prevalence of obesity have been observed. Approximately 32% of European American adults were obese and 5% were morbidly obese (BMI ≥40 kg/m^2) in the 2007–2008 National Health and Nutrition Examination Survey (NHANES). Alarmingly, 44% of African Americans were obese and 11% were morbidly obese, with black women having a substantially higher prevalence of obesity (50%) than black men (37%) (2).

The increasing prevalence of obesity is related to excessive caloric intake and diminished physical activity in the modern environment. However, genetic factors may modulate the impact of the environment in an individual. Considerable evidence from familial segregation and twin studies suggest a significant genetic contribution to BMI (3), with heritability estimates between 60 to 90% in African Americans (4,5). Recently, large-scale genome-wide association studies (GWAS) and meta-analyses conducted in populations of European ancestry revealed over 40 novel adiposity loci associated with BMI, waist circumference, and/or waist-hip-ratio (6–17). Many of these loci have been confirmed in Asian populations by GWAS (18,19) and replication studies (20–22). However, results in other populations are less convincing. Replication studies in African Americans showed a lack of association of *MC4R* (23) and inconclusive association of *FTO* (24,25) with adiposity measures. Here, we report a two-stage study including a GWAS of BMI in 1,715 African Americans followed by replication in additional African-American samples.

Methods and Procedures

Subjects

GWAS—GWAS samples included two cohorts of unrelated African Americans who participated in a GWAS for T2DM and nephropathy. The community nondiabetic GWAS cohort (cohort 1) consisted of 816 subjects who reported no history of diabetes were recruited from the community and internal medicine clinics at Wake Forest University School of Medicine. The diabetic GWAS cohort (cohort 2) consisted of 899 subjects with T2DM and end-stage renal disease (T2DM-ESRD) recruited from dialysis facilities in the southeastern United States (26).

Replication—The replication study samples included four cohorts of African-American subjects. The community nondiabetic replication cohort (cohort 3) includes 621 subjects (616 unrelated subjects and 5 related subjects from two nuclear families) who reported no history of diabetes were recruited from the community and internal medicine clinics similar to that of cohort 1. The diabetic replication cohort (cohort 4) consisted of 891 subjects with T2DM and 617 subjects with T2DM-ESRD (1,005 unrelated subjects and 503 related subjects from 178 nuclear families) recruited from the community, churches, health fairs, medical clinics, and dialysis facilities. The Diabetes Heart Studies cohort (cohort 5) consisted of subjects recruited from the community and internal medicine clinics in two studies that examine the subclinical cardiovascular risk in T2DM. A subset of 211 unrelated subjects from the African American-Diabetes Heart Study (27) and 81 subjects from the family based Diabetes Heart Study (28) were included in this study. All subjects from cohorts 1–5 were recruited in North Carolina, South Carolina, Georgia, Tennessee, or Virginia. The Insulin Resistance Atherosclerosis (IRAS) Studies cohort (cohort 6) consisted

of subjects recruited from two multicenter community-based cohort studies, the IRAS Study (29) and the IRAS Family Study (30), designed to examine the epidemiology and genetics of glucose homeostasis traits, respectively. Among these, 575 related subjects from 42 families of the IRAS Family Study recruited from Los Angeles, CA and 278 unrelated subjects from the IRAS study recruited from Los Angeles and Oakland, CA were included in this study.

The clinical characteristics of all cohorts are summarized in Table 1. Informed consent was obtained from all study participants. Recruitment and sample collection procedures for cohorts 1–5 and cohort 6 were approved by the institutional review boards at Wake Forest University School of Medicine and the respective local institutions.

Clinical studies

All study subjects were measured for anthropometry including body weight and height. BMI is calculated as weight divided by square of height. BMI ≥30 kg/m^2 is considered obese. Blood samples were collected for DNA extraction using the PureGene system (Gentra Systems, Minneapolis, MN).

Genotyping and quality control

GWAS—Genotyping of GWAS samples was performed at the Center for Inherited Disease Research using 1 μg of genomic DNA on Affymetrix Genome-wide Human SNP array 6.0. DNA from cohorts 1 and 2 were equally interleaved on 96-well master plates for genotyping. Genotypes were called using Birdseed version 2, APT 1.10.0 and samples were grouped by DNA plate to determine the genotype cluster boundaries. Among 868,157 autosomal single-nucleotide polymorphisms (SNPs) genotyped, 746,626 SNPs passed quality controls with call rate ≥95%, Hardy–Weinberg Equilibrium *P* value ≥ 0.0001 and minor allele frequency ≥0.05 were included in subsequent data analysis. The average sample call rate was 99.16% for all autosomal SNPs. The genotype concordance rates of 46 blind duplicates and 90 HapMap control samples were 99.59 and 99.76%, respectively. One individual was discordant for gender call from X chromosome genotype data when compared to the patient record and was excluded from the analysis. Cryptic relatedness was estimated by pairwise identity-by-descent (IBD) analysis implemented in PLINK (http://pngu.mgh.harvard.edu/purcell/plink/). Two pairs of duplicate samples and 104 cryptic first degree relative samples were identified and only one unrelated sample from each family was included. Inbreeding coefficient F is calculated as the ratio of observed vs. expected number of homozygous genotypes using PLINK. One subject with *F* value > 4 s.d. suggesting excess homozygosity may be due to population substructure and was removed. The final dataset consisted of 1,715 unrelated samples with BMI data for association analysis.

Replication—SNPs were selected for the replication study based on (i) suggestive association ($P \leq 0.0001$) in the meta-analysis of GWAS cohorts 1 and 2, and (ii) nominal ($P < 0.05$) and same direction of association in both GWAS cohorts. A total of 59 SNPs were successfully genotyped for replication. In addition, rs815611 showed nominal associations in both GWAS cohorts and was genotyped to confirm the association result of the highly correlated SNP rs2033195 ($r^2 = 0.94$ in our GWAS samples). Genotyping of samples from replication cohorts 3–6 was performed using the iPLEX Sequenom MassARRAY platform (San Diego, CA). The minimum and average SNP call rates were 81 and 96%, respectively. The average genotype concordance rate of 45 blind duplicates was 99.8%. All SNPs had Hardy–Weinberg *P* values ≥0.001 in the combined unrelated replication cohorts. For related samples, genotype data identified as Mendelian inconsistencies by PedCheck (v. 1.1) (http://watson.hgen.pitt.edu/register/docs/ pedcheck.html) were removed.

Population structure

In order to account for the effect of population structure on genetic association in these African-American samples, Principal Components Analysis was computed on the GWAS cohorts using all SNPs that passed quality control standards and after exclusion of regions of high linkage disequilibrium and inversions. The first principal component (PC1) explained the largest proportion of genetic variation (22%). In addition, 70 ancestry informative markers were genotyped in 44 Yoruba Nigerians, 39 European Americans as well as the GWAS and replication samples. The African to European ancestral proportion of each sample was estimated using the EM algorithm implemented in the program Frequentist Estimation of individual ancestry proportion (FRAPPE) under a two-population model. PC1 was highly correlated with ancestry informative markers ($r = -0.87$), suggesting that PC1 largely reflected the ancestry proportions of our GWAS samples. The mean (±s.d.) African ancestry proportions estimated by FRAPPE in cohorts 1–6 were 0.77 ± 0.12, 0.78 ± 0.12, 0.77 ± 0.12, 0.78 ± 0.13, 0.76 ± 0.11, and 0.69 ± 0.14, respectively.

Statistical analyses

Data are presented as mean ± s.d. or percentage, as appropriate. BMI was natural logarithmically transformed to best approximate conditional normality and homogeneity of variance, conditional on cohort, disease status, age, and gender. To account for potential gender and cohort differences in distributions of BMI, subjects were stratified by gender in each cohort and by disease status (ESRD in cohort 4 and T2DM in cohort 6). Within each strata, an individual was considered an outlier if the data was outside of four s.d. A total of three outlier observations were removed from further analyses. The data were then adjusted for age in a linear model and residuals were standardized to a mean of zero and variance of one (i.e., Z-score). These Z-scores are the primary unit of analysis for both within individual cohorts and the meta-analyses.

Association—For the two GWAS cohorts, the associations of BMI Z-scores with SNPs were tested by linear regression under an additive model using the program QSNPGWA (www.phs.wfubmc.edu), with additional covariate adjustment for PC1. For the four replication cohorts, a variance component measured genotype method implemented in SOLAR (31) was used for association tests in order to account for familial relationships within each cohort. Associations of BMI Z-scores with SNPs were tested under an additive model with adjustment for proportion of African ancestry. Familial correlation was accounted for using a kinship coefficient matrix, where a correlation was calculated for each set of related pairs.

Meta-analysis—Association results from the two GWAS cohorts were combined using the inverse variance weighted method implemented in METAL (http://www.sph.umich.edu/csg/abecasis/metal/). Inflation factor was calculated as the ratio of median of the observed vs. expected individual SNP χ^2 statistics. It was adjusted for each GWAS cohort before meta-analysis. Meta-analyses of the four replication cohorts, as well as the six GWAS and replication cohorts were also conducted using the inverse variance weighted method. In order to account for modest relatedness between the GWAS (cohorts 1 and 2) and the replication samples (cohorts 3 and 4), BMI Z-scores of all six cohorts were pooled and analyzed together using variance component method for comparison with the meta-analysis method. To evaluate the potential confounding effect of disease, 2,111 community nondiabetic subjects from cohorts 1, 3, and 6, 1,516 T2DM-ESRD subjects from cohorts 2 and 4, and 1,362 T2DM subjects from cohorts 4, 5, and 6 were separately analyzed using linear regression and variance component methods as appropriate. The association results were then combined using METAL to assess the overall SNP association in nondiabetic, T2DM-ESRD, and T2DM subjects separately.

All statistical tests were performed by QSNPGWA, PLINK or SAS v.9.1 (SAS Institute, Cary, NC) unless specified otherwise. Posterior study power was calculated using genetic power calculator (32). A nominal *P* value <0.0001 in the meta-analysis was considered as suggestive evidence of significance.

Results

Clinical characteristics of the study samples

Clinical characteristics of the GWAS and replication study samples are shown in Table 1. Due to the nature of sample collection, the GWAS and replication cohorts consisted of either community nondiabetic (cohorts 1 and 3), community-based (cohort 6), or diabetic subjects (cohorts 2, 4, and 5). The distributions of BMI were comparable among all cohorts except for higher mean BMI (35.3 kg/m^2) and higher prevalence of obesity (74.3%) in the Diabetes Heart Studies (cohort 5). In view of the heterogeneous phenotypes among study cohorts, BMI Z-scores were calculated in sex- and disease-specific strata and then combined separately in each cohort for association analyses.

GWAS

A total of 746,626 autosomal SNPs that passed quality control were analyzed in 816 community nondiabetic and 899 T2DM-ESRD subjects (cohorts 1 and 2) separately for association with BMI. The inflation factors were 1.013 and 1.011 for cohorts 1 and 2, respectively before genomic control. The association results combined using an inverse variance weighted meta-analysis and the respective quantile–quantile plot (inflation factor = 1.005 after genomic control) are shown in Supplementary Figures S1 and S2 online, respectively. The inflation factor for heterogeneity *P* values between the two GWAS was 1.002, suggests in general there was no significant heterogeneity in the associations between the two cohorts (Supplementary Figures S3 online). A total of 70 SNPs showed nominal association at $P \leq 1 \times 10^{-4}$ in the meta-analysis. The most significant SNP was rs7791504 located in an intergenic region on chromosome 7 ($P = 5.47 \times 10^{-9}$).

Replication

In the replication stage, SNPs showing nominal association in individual GWAS cohorts ($P < 0.05$) with the same direction of associations and meta-analysis *P* value $\leq 1 \times 10^{-4}$ were followed up. This strategy would likely identify SNPs that were robust to the heterogeneous phenotype of our cohorts. Sixty SNPs were successfully genotyped in 3,274 subjects from four replication cohorts. The association results of these SNPs with BMI in individual GWAS and replication cohorts are shown in Supplementary Table S1 online. The most significant SNP from the GWAS, rs7791504, was not significant in either individual or combined replication cohorts ($P > 0.05$, Supplementary Tables S1 and S2 online). However, four SNPs (rs6794092, rs2033195, rs815611, and rs6088887) located on chromosomes 3, 5, and 20, respectively, were nominally associated with BMI ($0.004 < P < 0.05$) in the meta-analysis of the four replication cohorts (Supplementary Table S2 online). In addition, an excess of association signals (inflation factor = 1.468) was observed in the quantile–quantile plot for the replication cohorts (Supplementary Figures S2 online).

Meta-analysis of GWAS and replication

The association results of these 60 SNPs in all six GWAS and replication cohorts were then combined by meta-analysis to evaluate their overall effects (Supplementary Table S2 online). Among these, five SNPs showed suggestive associations at $P < 1 \times 10^{-4}$ with effect sizes between 0.091 and 0.167 s.d. unit (~0.67 to 1.24 kg/m^2) of BMI for each copy of the effect allele (Table 2). Of note, the four nominally associated SNPs in the replication study

(rs6794092, rs2033195, rs815611, and rs6088887) showed the same direction of associations in all six cohorts (Supplementary Table S1 online). In addition, the former three SNPs became more significant ($2.4 \times 10^{-6} < P < 2.5 \times 10^{-5}$) when compared to the GWAS results alone ($3.9 \times 10^{-6} < P < 2 \times 10^{-4}$). rs2033195 and rs815611 ($5.4 \times 10^{-6} < P < 5.6 \times 10^{-6}$) located between the genes *MFAP3* and *GALNT10* on chromosome 5 were highly correlated in our samples ($r^2 = 0.94$). Major alleles of both SNPs were associated with increased BMI, supporting the confidence of genotyping accuracy and associations. rs268972 showed a trend toward association in the replication phase ($P = 0.06$) but did not show a stronger association than in the GWAS results, as was the case for rs6088887 (Table 2).

Due to modest relatedness between the GWAS and replication cohorts, the association analyses of the 60 SNPs were repeated using variance component method to combine all samples into a single group. The association results were highly consistent with the meta-analysis method (slope = 0.964, intercept = −0.003 by linear regression of variance component –log *P* values on the meta-analysis –log *P* values).

We further investigated the association of these five SNPs separately in 2,111 community nondiabetic, 1,516 T2DM-ESRD, and 1,362 T2DM subjects from cohorts 1 to 6 (Table 3). The effect sizes ranged from 0.102 to 0.181, 0.068 to 0.228, and 0.063 to 0.089 s.d. units, respectively, for the three groups. Although the effect sizes and association signals tended to be weaker in the T2DM group as compared to the nondiabetic or T2DM-ESRD groups, there were no significant heterogeneity of effect sizes among the three groups ($P_{\text{heterogeneity}} > 0.05$). For the T2DM-ESRD group, additional adjustment for duration of ESRD revealed similar association results for the 60 tested SNPs (slope = 0.948, intercept = 0.197 by linear regression of –log *P* values for ESRD duration adjustment analysis on the–log *P* values for the analysis without ESRD duration adjustment).

When we considered community nondiabetic subjects only, the effect sizes were comparable while the significance of associations were weaker than that in all combined samples due to reduced sample size (Supplementary Table S2 online). Of note, the strongest association was observed for rs268972 (β = 0.131 s.d. unit, $P = 0.0002$) and four of the five SNPs with suggestive association from meta-analysis of all combined samples (Table 2) were among the top 10 hits in the nondiabetic subjects.

Discussion

We performed a high-density GWAS on BMI to examine the genetic determinants of adiposity in African Americans. Meta-analysis of two GWAS and four replication cohorts revealed five SNPs (rs6794092, rs2033195, rs815611, rs6088887, and rs268972) at four loci showing suggestive association to BMI ($2.4 \times 10^{-6} < P < 2.5 \times 10^{-5}$) (Table 2). Although no signals reached genome-wide significance ($P < 5 \times 10^{-8}$) potentially due to modest sample size and power at the respective α level, the consistent direction of associations in all six cohorts and nominal association in both GWAS and replication stages in the former four SNPs implicates them in the modulation of BMI levels.

rs6794092 is located on chromosome 3q26.31 near the gene transmembrane protein 212 (*TMEM212*) with unknown function. However, another family member *TMEM18* has recently been identified as a BMI locus in GWAS studies of European ancestry (14,15).

The two highly correlated SNPs rs2033195 and rs815611 are located on chromosome 5q33.2 near the genes microfibrillar-associated protein 3 isoform 1 (*MFAP3*) and *GALNT10*. MFAP3 is a microfibrillar protein, in which the microfibrils family acts to control tumor growth factor β bioavailability (33). *GALNT10* encodes a member of the GalNAc

polypeptide *N*-acetylgalactosaminyltransferase involved in the synthesis of mucin-type oligosaccharides. GALNT10 is highly expressed in the central nervous system including the hypothalamus, thalamus, and amygdala (34). A related family member, *GALNT2*, is associated with high-density lipoprotein levels in European-ancestry GWAS (35,36). The close relationship between adiposity and lipid levels and the recent identification of central nervous system regulating adiposity loci makes *GALNT10* a new potential candidate for regulation of adiposity.

rs268972 is located at the cadherin 12 type 2 (*CDH12*) locus which belongs to the cadherin superfamily that mediate calcium-dependent cell–cell adhesion and cadherins adhesion are regulated by the canonical wnt signaling pathway (37). CDH12 is expressed in the brain and may play a role in neuronal development. rs6088887 is located in the intron of fer-1-like 4 (*FER1L4*) which has an unknown function.

We have identified four potential loci associated with BMI in African Americans but none of these loci have been reported in prior GWAS. Moreover, among 22 SNPs from 17 BMI loci previously identified predominantly in European-derived populations (14–16), none of them showed associations in our GWAS ($P > 0.05$), except for a nominal association of *MC4R* rs17782313 ($P = 0.02$ with negative effect size for the European effect allele) (data not shown). The sample size of our GWAS alone has modest power to detect weak effect sizes. Assuming an effect size of 0.1 s.d. unit of BMI for a BMI-increasing allele with a frequency of 0.5 under the additive model, such as those reported for *FTO* in Europeans (7), we have only 17% power to detect association at α level of 1×10^{-4}. Although the absence of association in European-identified loci in this study may be due to lack of power, these loci have demonstrated inconclusive association with BMI in African Americans (23,25,38), which may reflect allelic (39), locus heterogeneity and difference in linkage disequilibrium in African American as compared to European-derived populations. Larger sample sizes and thorough examination of these loci will be required to delineate their effects in African Americans. A recent GWAS on anthropometric traits has been conducted in two populations of Africans and African Americans. Nominal association was observed at rs8077681 in *SLC39A11* in the African-American GWAS samples ($P = 0.0011$) but this SNP was not replicated in additional samples (40). In our GWAS, we observed nominal association ($P = 0.0001$) in a nearby SNP rs9893303 but showed no replication ($P = 0.11$) (Supplementary Table S2 online). rs8077681 and rs9893303 were not in linkage disequilibrium ($D' = 0$, $r^2 = 0$) in our African American samples. This locus may warrant further investigation.

The combined sample of 4,989 subjects in this report had reasonable power to detect modest effect sizes at α level of 1×10^{-4}, the threshold used for follow-up replication. The power was 65% to detect a difference of 0.09 s.d. unit per BMI-increasing allele at a frequency of 0.66 (as for rs268972) and 89% to detect a difference of 0.17 s.d. unit per BMI-increasing allele at frequency of 0.9 (as for rs6794092). The power for these loci was low for α level of 5×10^{-8} (12 and 36%, respectively), thus additional samples are required to confirm or refute these association signals at the genome-wide significance level.

This study has several limitations as do all GWAS. In order to increase sample size and study power, we used both community nondiabetic and diabetic subjects with or without nephropathy for gene discovery and replication. Since obesity is a risk factor for diabetes, it is unclear if the presence of diabetes would affect the genetic effect on adiposity measures. T2DM-ESRD subjects in the GWAS may impact nutritional parameters. Indeed, some of the prior GWAS on adiposity also included patients with metabolic disease (e.g., T2DM, coronary artery disease, hypertension) as part of the gene discovery cohorts to increase study power (14,15) and did not show strong heterogeneity of effect size between the healthy subjects and affected patients. In the present study, we selected SNPs for follow-up based on

the presence of GWAS association in both nondiabetic and T2DM-ESRD subjects. The overall association signals were comparable in these two groups as shown by the similar observed vs. expected distribution of heterogeneity *P* values in the respective quantile–quantile plot (Supplementary Figure S3 online). The effect sizes of the five most associated SNPs were also not significantly different among the nondiabetic, T2DM-ESRD, and T2DM groups (Table 3). This suggests that the presence of disease had minimal effect, if any, on the genetic associations of the top signals although cautious interpretation is needed.

In conclusion, we identified four putative BMI loci at *PP13439-TMEM212*, *CDH12*, *MFAP3-GALNT10*, and *FER1L4* that demonstrated consistent association in six African-American GWAS and replication cohorts. We observed excess association signals in both the GWAS and replication studies, suggest there are additional loci remained to be identified. Given the differences in environment, body composition, and genetic backgrounds among different ethnic groups, additional studies and meta-analyses in African Americans and comparison of results to other ethnic groups is necessary to shed light on whether allelic and locus heterogeneity have a significant contribution to the genetics of adiposity in various ethnic groups.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank the study subjects for their participation. Genotyping services were provided by the Center for Inherited Disease Research (CIDR). CIDR is fully funded through a federal contract from the National Institutes of Health to The Johns Hopkins University, contract number HHSC268200782096C. This work was supported by NIH grants R01 DK087914 (M.C.Y.N.), R01 DK066358 (D.W.B.), R01 DK053591 (D.W.B.), R01 HL56266 (B.I.F.), R01 DK070941 (B.I.F.), R01 HL060944 (L.W.), R01 HL061210 (M.B.), K99 DK081350 (N.D.P.), and by the Wake Forest University School of Medicine grant M01 RR07122 and Venture Fund (M.C.Y.N.).

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Table 1

clinical characterization of study samples

	GWAS		Replication			
	Nondiabetic GWAS (Cohort 1)	**T2DM-ESRD GWAS (Cohort 2)**	**Nondiabetic replication (Cohort 3)**	**T2DM replication (Cohort 4)**	**Diabetes Heart Studies (Cohort 5)**	**Insulin Resistance Atherosclerosis Studies (Cohort 6)**
N	816	899	621	1,508	292	853
Female (%)	55.9	60.6	50.4	61.0	62.3	58.9
Age (year)	49.0 ± 11.9	61.5 ± 10.5	48.4 ± 12.7	58.8 ± 11.6	55.8 ± 9.6	46.9 ± 13.8
BMI (kg/m^2)	30.1 ± 7.1	29.7 ± 7.1	29.4 ± 7.6	31.7 ± 7.6	35.3 ± 7.8	30.2 ± 6.5
Obesity (%)	44.1	43.0	36.7	54.6	74.3	43.1

Data are shown as *N*, mean ± s.d., or %.

ESRD, end-stage renal disease; GWAS, genome-wide association studies; T2DM, type 2 diabetes.

Table 2

GWas, replication, and meta-analysis results of BMI for SNPs with $P < 1 \times 10^{-4}$ in the combined meta-analysis

						GWAS (n = 1,715)		Replication (n = 3,274)		Combined (n = 4,989)	
SNP	Chr	Position	Effect/ other alleles[a]	Effect allele freq	Nearest gene(s)[b]	β(s.e.)[c]	P	P (s.e.)[c]	P	β (s.e.)[c]	P
rs6794092	3	173041038	G/A	0.90	*PP13439-TMEM212*	0.269 (0.058)	3.86×10^{6}	0.107 (0.045)	0.0166	0.167 (0.036)	2.44×10^{6}
rs268972	5	22692284	C/A	0.66	***CDH12***	0.149 (0.036)	3.46×10^{5}	0.054 (0.029)	0.0603	0.091 (0.023)	5.00×10^{5}
rs2033195	5	153489789	C/T	0.57	*MFAP3-GALNT10*	0.145 (0.035)	4.05×10^{5}	0.067 (0.025)	0.0082	0.094 (0.021)	5.57×10^{6}
rs815611	5	153498959	G/A	0.58	*MFAP3-GALNT10*	0.133 (0.035)	0.0002	0.074 (0.026)	0.004	0.095 (0.021)	5.36×10^{6}
rs6088887	20	33634738	G/A	0.79	***FER1L4***	0.178 (0.042)	1.81×10^{5}	0.064 (0.032)	0.0427	0.106 (0.025)	2.53×10^{5}

ESRD, end-stage renal disease; GWAS, genome-wide association studies; SNP, single-nucleotide polymorphisms; T2DM, type 2 diabetes.

[a] Alleles were indexed to the forward strand of NCBI Build 36. Effect allele referred to the BMI-increasing allele in the GWAS meta-analysis.

[b] The nearest annotated gene(s) or gene enclosing the index SNP (bolded) are shown.

[c] β and s.e.s were reported for the changes in s.d. unit per copy of the effect allele.

Table 3

Association results for BMI in nondiabetic, T2DM-ESRD, and T2DM subjects in the combined GWAS and replication cohorts for SNPs with $P < 1 \times 10^{-4}$ in the combined meta-analysis

		Nondiabetic subjects (n = 2,111)		T2DM-ESRD subjects (n = 1,516)		T2DM subjects (n = 1,362)	
SNP	**Effect/other alleles**[a]	β(s.e.)[b]	***P***	β(s.e.)[b]	***P***	β(s.e.)[b]	***P***
rs6794092	G/A	0.181 (0.056)	0.0014	0.228 (0.061)	0.0002	0.063 (0.068)	0.3583
rs268972	C/A	0.131 (0.035)	0.0002	0.068 (0.039)	0.0778	0.064 (0.045)	0.1575
rs2033195	T/C	0.104 (0.032)	0.0013	0.098 (0.037)	0.0079	0.071 (0.038)	0.0623
rs815611	G/A	0.110 (0.033)	0.0007	0.075 (0.037)	0.0422	0.089 (0.039)	0.0234
rs6088887	G/A	0.102 (0.038)	0.0075	0.142 (0.045)	0.0018	0.074 (0.049)	0.1302

ESRD, end-stage renal disease; GWAS, genome-wide association studies; SNP, single-nucleotide polymorphisms; T2DM, type 2 diabetes.

[a] Alleles were indexed to the forward strand of NCBI Build 36. Effect allele referred to the BMI-increasing allele in the GWAS meta-analysis.

[b] β and s.e.s were reported for the changes in s.d. unit per copy of the effect allele.