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Obesity and diabetes genetic variants associated with gestational weight gain

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Abstract

Objective—To determine whether genetic variants associated with diabetes and obesity predict gestational weight gain.

Study Design—960 participants in the Pregnancy, Infection and Nutrition cohorts were genotyped for 27 single-nucleotide polymorphisms (SNPs) associated with diabetes and obesity.

Results—Among white and black women (n=960), *KCNQ1* risk allele carriage was directly associated with weight gain ($p < 0.01$). In Bayesian hierarchical models among white women (N=628), we found posterior odds ratios > 3 for inclusion of *TCF2* and *THADA* SNPs in our models. Among black women (n=332), we found associations between risk allele carriage and weight gain for the *THADA* and *INSIG2* SNPs. In Bayesian variable selection models, we found an interaction between the *TSPAN8* risk allele and pre-gravid obesity, with lower weight gain among obese risk allele carriers.

Conclusion—We found evidence that diabetes and obesity risk alleles interact with maternal pre-gravid BMI to predict gestational weight gain.

Keywords

diabetes; gestational weight gain; genetics; obesity; single nucleotide polymorphisms

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Introduction

Maternal weight gain during pregnancy is an important predictor of health outcomes for both mother and child[1]. Inadequate gestational weight gain is associated with preterm birth[2], intrauterine growth restriction, low birth weight, and offspring obesity risk[3], whereas mothers who gain excessively are more likely to deliver by cesarean section [4–7], have an unsuccessful trial of labor after c-section[8], develop pre-eclampsia[6], retain excessive weight after delivery[9, 10], and become overweight or obese in later life[11, 12]. Infants born to women who gain excessively during pregnancy are more likely to be born preterm[13], be macrosomic at birth (> 9 lbs)[5, 14, 15], and become overweight or obese as toddlers[16] and adults[3]. Based on these well-described epidemiologic associations, gestational weight gain has been targeted as a modifiable risk factor for metabolic disease in both mother and child.

While intervention strategies have targeted health behaviors that affect gestational weight gain, a mother's genotype is also likely to influence her pattern of weight gain. Recent studies in non-pregnant populations have identified common genetic variants associated with diabetes and obesity. Family and twin studies suggest that 50% of obesity is attributable to genetic causes[17]. In a recent multicenter study, subjects homozygous for the *FTO rs9939609* A allele had a 1.6-fold increased risk of obesity[18]. Variants in *MC4R*[19] and *INSIG2*[20], as well as multiple gene regions recently identified by the GIANT consortium[21], are also associated with body mass index (per-allele effect 0.06–0.33 kg/m^2). In addition, association studies have identified common genes associated with type 2 diabetes[22–26], such as *PPARG* and *TCF7L2*.

Elucidating the role of genetic variants in gestational weight gain has important implications for public health. If genetic variants associated with diabetes and obesity are also linked with inappropriate weight gain, then excessive or inadequate gain may a marker for genetic predisposition to metabolic disease. No studies to our knowledge have measured the association between genetic variants associated with diabetes and obesity and gestational weight gain. We hypothesized that such genetic variants predict a mother's total weight gain during pregnancy. We further hypothesized that a woman's complement of diabetes and obesity risk alleles predicts whether she will gain in excess of IOM guidelines. Finally, we hypothesized that genotype modifies the association between pregravid BMI and gestational weight gain. To test these hypotheses, we measured such associations in a subset of women enrolled in the Pregnancy, Infection and Nutrition Study, 1998–2005, a longitudinal pregnancy cohort study.

Materials and Methods

The Pregnancy, Infection and Nutrition Cohort study comprises three prospective cohorts of more than 5000 women enrolled in early to mid-pregnancy. Participants enrolled in PIN1 and PIN2 were 24–29 weeks gestation at study entry, and were recruited from University of North Carolina Resident and Private Physician Obstetrics Clinic and the Wake County Department of Human Services and Wake Area Health Education Center prenatal care clinics from August 1995 through June 2000. Subjects enrolled in PIN3 were less than 20 weeks gestation at study entry and were recruited from the prenatal clinics at UNC hospitals from January 2001 to June 2005.

Extracted DNA was available for 1363 pregnancies that had undergone prior genotyping for case:control studies of preterm birth, small-for-gestational age birth weight, and placental vascular disease (Figure 1). For 132 pregnancies, there was insufficient DNA available for genotyping, leaving 1231 pregnancies eligible for our study. We allowed for only one

pregnancy during the study period. If data were available for multiple pregnancies (N=21), we confirmed that the genotypes were concordant and included the pregnancy with the most complete SNP data. One pair of specimens was not concordant, so this subject was excluded. We further limited our analysis to self- identified black (n = 418) or white (n = 756) women, in order to avoid confounding by population stratification. As we considered ancestry, we removed women missing more than 20% of ancestral data (n = 61). We further removed black women for whom ancestry informative markers indicated a less than 10% probability of Yoruban ancestry (n = 3). Finally, we excluded women who were missing data on gestational age (n = 63), gestational weight gain (n = 64) or pre-gravid BMI (n =12, total removed = 149), leaving 960 women available for analysis (Figure 1).

Determination of pre-gravid BMI

Pre-gravid BMI was calculated based on self-reported pre-gravid weight and height at the first prenatal visit. Self-reported pre-gravid weights were examined for biological plausibility and imputed if deemed appropriate (<5% of weights were imputed). This imputed weight was calculated using the measured weight at the first prenatal visit (if taken prior to 15 weeks) minus the recommended amount of weight to be gained in the first and second trimesters as defined by the Institute of Medicine{Institute of Medicine, 1990 #1097}[27].

Study covariates

The PIN datasets include information from telephone interviews, self-administered questionnaires, medical chart abstraction, and biological specimen collection. Information on race/ethnicity (non-Hispanic white, non-Hispanic black, and other) and maternal age was self-reported by the mother. Gestational age was estimated based on an algorithm that combined ultrasound dating with last menstrual period. If an ultrasound was done before 22 weeks gestation, it was used to date the pregnancy. If no ultrasound was done or it was done later in pregnancy, last menstrual period was used to date the pregnancy. In the PIN cohorts, 90.7% had an ultrasound that was used to date the pregnancy with the remaining 9.3% based on LMP.

Outcome assessment

Clinically obtained weights were recorded at each prenatal visit. We calculated gestational weight gain as the difference between pre-gravid self-reported weight and the last weight prior to delivery. We defined excessive or inadequate weight gain based on the 1990 Institute of Medicine (IOM) recommendations[28]; these were as follows: 28 to 40 lbs for low BMI (<19.8), 25–35 lbs for normal BMI (19.8 to 26.0), 15 to 25 lbs for overweight BMI (>26 to 29) and at least 15 pounds of gain for obese BMI (> 29). The IOM did not specify an upper limit for this group. For purposes of this analysis, excessive gain in the obese group was defined as greater than 18 lbs of gain, consistent with other analyses in the PIN cohorts. To calculate adequacy of gain for any given time point in pregnancy, the upper and lower limits of the weight gain intervals were extrapolated based on IOM-recommended rates of weight gain for the second and third trimesters[29], consistent with earlier studies in this cohort[30–32].

Genotyping

The Sequenom iPLEX platform[33] was used to genotype 27 SNPs associated with obesity and diabetes[19, 21–26, 34]. For the purpose of quality control, 6 SNPs that had been previously assessed in the PIN cohorts were also genotyped. All SNPs were tested for Hardy-Weinberg equilibrium among self-identified white participants.

Population stratification

In genetic association studies, differences in allele frequency among ethnic groups can confound relationships between genotype and disease outcome. To address population stratification in this cohort, genotyping was performed for 37 ancestry-informative markers that have been successfully in other genetic association studies[35]. STRUCTURE was used to infer population substructure and assign individuals to populations using probabilistic clustering methods[36]. We analyzed self-identified white and black participants separately, and we included probability of Yoruban ancestry as a covariate among self-identified black women.

Statistical analysis

The DNA used for this study had been extracted for previous case:control studies of SGA, preterm birth and placental vascular disease, so prevalence of these outcomes was high. In order to produce estimates of the association between genotype and outcome that would approximate what we would have observed for the full study cohort, we calculated the probability of each participant's inclusion in our study population. We used inverse probability weights to adjust our findings in all regression analyses. We used the SAS 9.2 surveylogistic and surveyreg for these analyses.

We used linear regression to model associations between maternal genotype and total gestational weight gain, adjusting for maternal age, linear and quadratic gestational age at birth, as well as probability of Yoruban ancestry among self-identified black women. We similarly used logistic regression to model associations between maternal genotype and probability of excessive gestational weight gain. We did not include in our models reproductive and obstetric factors that may be affected by genotype and may also affect weight gain, such as gestational diabetes and preeclampsia. These factors are potential intermediates on the causal pathway between genotype and weight gain, and including them in our models would attenuate the true association between maternal genotype and the outcome of interest. Moreover, because genotype may impact parity, we did not include parity as a covariate in our models.

We next considered models incorporating pre-gravid BMI in addition to gestational age and maternal age. Because the association between pre-gravid BMI and gestational weight gain is non-linear, both linear and quadratic terms were included. We then used hierarchical selection to model 1) Quadratic models including the joint effects of SNP allele carriage and interactions between SNP carriage and both log BMI and log BMI squared; 2) Linear models including the effects of SNP carriage and interactions between SNP carriage and log BMI; and 3) main effect models including only SNP allele carriage. If the Wald chi square p value for model 1 was < 0.05, the wald chi square p value for the quadratic interaction term was determined. If this was < 0.1, then the quadratic interaction term was retained. We similarly evaluated the linear model, retaining the interaction term if the SNP and SNP * log BMI p was < 0.05 and the SNP * log BMI term was < 0.1. Finally, we retained the main effects model if the p for the SNP term was < 0.05. To avoid false-positive findings due to small cell sizes, we excluded SNPs with fewer than 5 homozygous low or high-risk allele participants from these interaction models.

We did not to adjust alpha levels for multiple comparisons in this analysis. We recognize that this approach is may produce false positive associations. However, the purpose of our pilot study was to investigate the strength and direction of associations between these diabetes and obesity SNPs and gestational weight gain. All results should be viewed as exploratory findings pending confirmation in larger cohorts.

We next considered the simultaneous effects of multiple SNPs, using Bayesian models. For these analyses, we analyzed the data for subjects with complete information on genotypes using additive parameterization for SNPs. We used linear regression with gestational weight gain as the response variable, and SNP carriage, obesity and their interactions as covariates, adjusting for maternal age, linear and quadratic terms for gestational age at birth, and probability of Yoruban ancestry among self-identified black women. We avoided using a model with interactions between SNPs and log(BMI), log(BMI) squared as it would lead to a much larger model space and induce high correlations in the design matrix. The Bayesian variable selection framework allows each covariate to be either included or excluded from the model with a pre-assigned prior probability, which we chose as 0.5. After observing the data, the idea is to search over the list of all models, which includes models with no covariates, 1 covariate, …., all covariates, to identify the models which explain the observed data the best. With our choice of prior distributions, the prior odds ratio of including a covariate versus excluding is 1. We report the covariates with posterior (after observing the data) odds ratios greater than 3.

Results

Of the 79 SNPs genotyped, 71 genotyped for more than 90% of samples and were in Hardy-Weinberg equilibrium for the self-described White/Caucasian population. We anticipated that some SNPs would not be in HWE for African American participants due to admixture within African American populations in the US, and we found that one diabetes SNP and 4 of 37 ancestry-informative marker SNPs were not in HWE in this group. Our results were 99.5% concordant for SNPs that had previously been genotyped in the PIN cohort. Compared with white participants in our cohort, African American women were younger, had slightly higher pre-gravid BMIs, lower gestational weight gain and lower birth weight infants than Caucasian women (Table 1).

In linear regression analyses adjusted for maternal age and gestational age at birth and weighted to reflect the full PIN study population, we found associations between risk-allele carriage and gestational weight gain for several diabetes-associated variants (Table 2, Figure 1a and b). The *KCNQ1* risk allele was associated with higher gestational weight gain (Caucasian 1 risk allele: 2.8 kg, 95% CI 0.4–5.1; 2 risk alleles: 2.9 kg, 95% CI 1.3 to 4.6; African American 1 risk allele: 3.4 kg, 95% CI 0.6 to 6.3; 2 risk alleles: 2.7 kg, 95% CI 0.5 to 4.8). Among Caucasian participants, *PPARG* risk allele carriage was associated with lower gestational weight gain (1 risk allele: −7.9 kg, 95% CI −15.4 to −0.4; 2 risk alleles: −7.6 kg, 95% CI −15.1 to −0.2). No African American participants were homozygous for the low-risk *PPARG* variant.

We found different patterns of association for Caucasian and African American participants for several other diabetes-associated SNPs (Table 2, Figure 2a and 2b). Among Caucasian participants, we further identified associations between gestational weight gain and *CKDAL1* as well as *TSPAN8*. Among African American participants, we found associations between gestational weight gain and *CDKAL1*, *CDKN2A2B*, *KCNJ11*, *SLC30A8*, *CDC123*, and *THADA*.

In our adjusted models for obesity-related risk variants (Table 2, Figure 3), we found higher gestational weight gain for African American participants with 2 *MC4R* risk alleles (3.8 kg, 95% CI 0.01 to 2.9), compared with women with no *MC4R* risk alleles. We found no other consistent patterns of association between obesity risk variants and gestational weight gain among African-American women, although individuals with one risk allele for *INSIG2* had higher weight gain than women with 0 or 2 risk alleles. In contrast to our findings for *MC4R* among African American women, among Caucasian women, *MC4R* carriage was inversely

associated with weight gain (1 risk allele: −0.7 kg, 95% CI −1.7 to 0.3; 2 risk alleles: −1.6 kg, 95% CI −3.6 to 0.4), although confidence intervals were wide.

In logistic regression models of associations between diabetes SNPs and excessive gestational weight gain (Table 3, Figure 4a and 4b), we found higher risks for excessive gain among Caucasian participants with 2 copies of the *TCF2* risk allele (OR 1.8, 95% CI 1.1–3.0, vs. 0 copies of the risk allele) or 2 copies of the G6PC2 risk allele (OR 2.4, 95% CI 1.1–5.0), and lower risks among participants with 2 copies of the *TSPAN8* risk allele (OR 0.4, 95% CI 0.2–0.8, vs. 0 copies). Among African American participants, *NOTCH2* risk allele carriage was associated with reduced risk for excess gain (OR for 1 risk allele 0.5, 95% CI 0.3–0.9; OR for 2 risk alleles, 0.5, 95% CI 0.2–1.1, vs 0 risk alleles). *THADA* risk allele carriage was also associated with less excessive gain (OR for 1 risk allele 0.2, 95% CI 0.1–0.8, and for 2 risk alleles, 0.3, 95% CI 0.1–0.9, vs. 0 risk alleles), but confidence intervals were wide. *SLC30A8* risk allele carriage was associated with markedly increased excessive weight gain, but there were only 3 participants with 0 risk alleles in our study population, leading to imprecise effect estimates.

In our analysis of obesity SNPs and excessive weight gain (Table 3, Figure 5), carriage of one copy of the *MTCH2* risk allele was associated with excessive gain among YRI participants (OR 3.1, 95% CI 1.5–6.5, vs 0 risk alleles). There were no statistically significant associations between obesity risk allele carriage and excessive weight gain risk among CEU participants (Figure 5).

We found interactions between risk allele carriage and pre-gravid BMI for *TCF7L2, TCF2, CDKAL1, THADA, ADAMTS9, NOTCH2, FTO* and *TMEM18*, as well as main effects for *TSPAN8* (Figure 6). Among African-American participants, we found interactions between risk allele carriage and pre-gravid BMI for *WFS1, ADAMTS9, TMEM18* and *MTCH2* and main effects for *THADA* and *INSIG2* (Figure 7).

Finally, we used Bayesian variable selection models to test the additive effect of multiple SNPs on gestational weight gain. Among Caucasian women, we found a posterior odds ratio > 3 for greater weight gain with carriage of the *TCF2* risk allele (1.1 kg per allele, 95% CI 0 to 2.7, posterior OR 4.0) and for lower weight gain among obese women carrying the *THADA* risk allele (−1.7 kg per allele, 95% CI −4.2 to 0.07, posterior OR 4.26). Among African-American women, we found a posterior odds ratio >3 for an interaction between the *TSPAN8* risk allele and obesity, with lower weight gain among obese risk allele carriers (−2.4 kg per allele, 95% CI −6.7 to 0.3, posterior OR 3.2).

Comment

In this prospective longitudinal study of pregnant women, we found several associations between diabetes and obesity SNPs and gestational weight gain. The effect of risk allele carriage varied with pre-gravid body mass index, suggesting that genotype may modify the effect of a woman's body composition prior to pregnancy on weight gain trajectory.

Our findings confirm and extend earlier work on associations between diabetes and obesity SNPs and weight trajectory. We found greater weight gain among women with the *Ala12Ala PPARG* genotype than those with *Pro12Pro* genotype, although the number of *Ala12Ala* participants was small (N=7), and our findings may be sensitive to two of the seven Ala12Ala participants with weight gains of 28 and 40 kg. In a small study of women with gestational diabetes (N=62), Tok et al found greater weight gain among women with the *Pro12Ala* genotype than women with the *Pro12Pro* genotype. *PPARG* is expressed primarily in adipocytes, and this gene appears to regulate triglyceride storage in adipose

tissue[37–39]. It is plausible that *Ala12Ala* carriers have increased capacity for triglyceride storage, leading to greater gestational weight gain.

We also found greater gestational weight gain among women with one or two copies of the *KCNQ1* risk allele, compared to homozygous low-risk women, although the number of low-risk homozygotes was low (4 Caucasian women and 2 African-American women). The low-risk *KCNQ1 rs2237892* variant has been associated with increased c-peptide levels at 30 minutes after oral glucose load [40]. It is plausible that more efficient insulin release lowers postprandial glucose concentrations and thus reduces gestational weight gain.

Among African-American participants, we found greater weight gain among *MC4R* high-risk homozygotes. The *MC4R rs17782313* variant is associated with increased energy intake, increased total fat and protein intake, and greater weight gain over time in the predominantly-Caucasian Nurses' Health Study cohort[41]. Interestingly, *MC4R* risk allele carriage was not associated with obesity among African-American children in a large case:control study[42].

We also found interactions between pre-gravid BMI and genotype for several diabetes and obesity risk alleles in our population. These results suggest that a woman's pre-gravid BMI as well as her genotype influence gestational weight gain. For example, in analyses of *FTO rs9939609* risk allele carriage among Caucasian women, thin or obese women homozygous for the high risk allele gained more weight than low-risk allele carriers, but among women of average pre-gravid BMI, weight gain was similar regardless of allele carriage. These results suggest that it may be important to consider baseline BMI in longitudinal studies of genetic determinants of weight trajectory.

Our results must be interpreted within the context of the study design. Strengths of this study include our prospective collection of gestational weight gain data and the use of ancestry informative markers to adjust for population stratification. In addition, we used innovative techniques to model the role of pre-gravid BMI in modifying the effect of genotype on pregnancy phenotype. Our study also has several limitations. This is a secondary analysis of data collected over a 10-year period, and secular changes in medical recommendations, diet and physical activity, as well as the evolving nature of the PIN studies, may have modified the association between genotype and weight gain. Bias is also a concern, because we used samples from a subset of a larger cohort. Our use of sampling weights allowed us to produce estimates that approximate what we may have observed from a complete data set, but we were unable to adjust for the possibility that a woman's willingness to allow genetic analysis or provide a blood sample may be non-random. Moreover, this is a pilot study, and our sample size was small, reducing our ability to detect differences among women with differing genotypes. In GWAS studies of obesity risk alleles and body mass index, risk allele carriage has been associated with differences of 0.10 to 0.33 kg/m^2[21], which are considerably smaller than what we could detect in our population. In addition, pregnancy weight gain was measured in a clinical setting, without assessment of water weight vs. adipose tissue. Associated measurement error may further reduce our power to detect associations between genotype and outcome. At the same time, multiple testing is a concern. To address this issue, we limited our analysis to candidate SNPs that have been validated in multiple large studies. Nevertheless, we recognize that some of our findings may be false positives. With 18 diabetes SNPs and 2 comparisons for each SNP, we would expect to find 1.8 significant associations by chance alone, and with 9 obesity SNPs, we would expect to find 0.9 significant association by chance alone, if we conservatively assume independence of all SNPs.

In conclusion, we found evidence that maternal diabetes- and obesity-risk allele genotype interact with pre-gravid BMI to affect gestational weight gain. These results suggest that excessive or inadequate gain may be marker for maternal genotype, and these differences in genetic risk may explain some observed associations between gestational weight gain and long term health outcomes for mothers and infants. Further studies in larger cohorts will be needed to delineate further the role of genotype in maternal weight gain during pregnancy.

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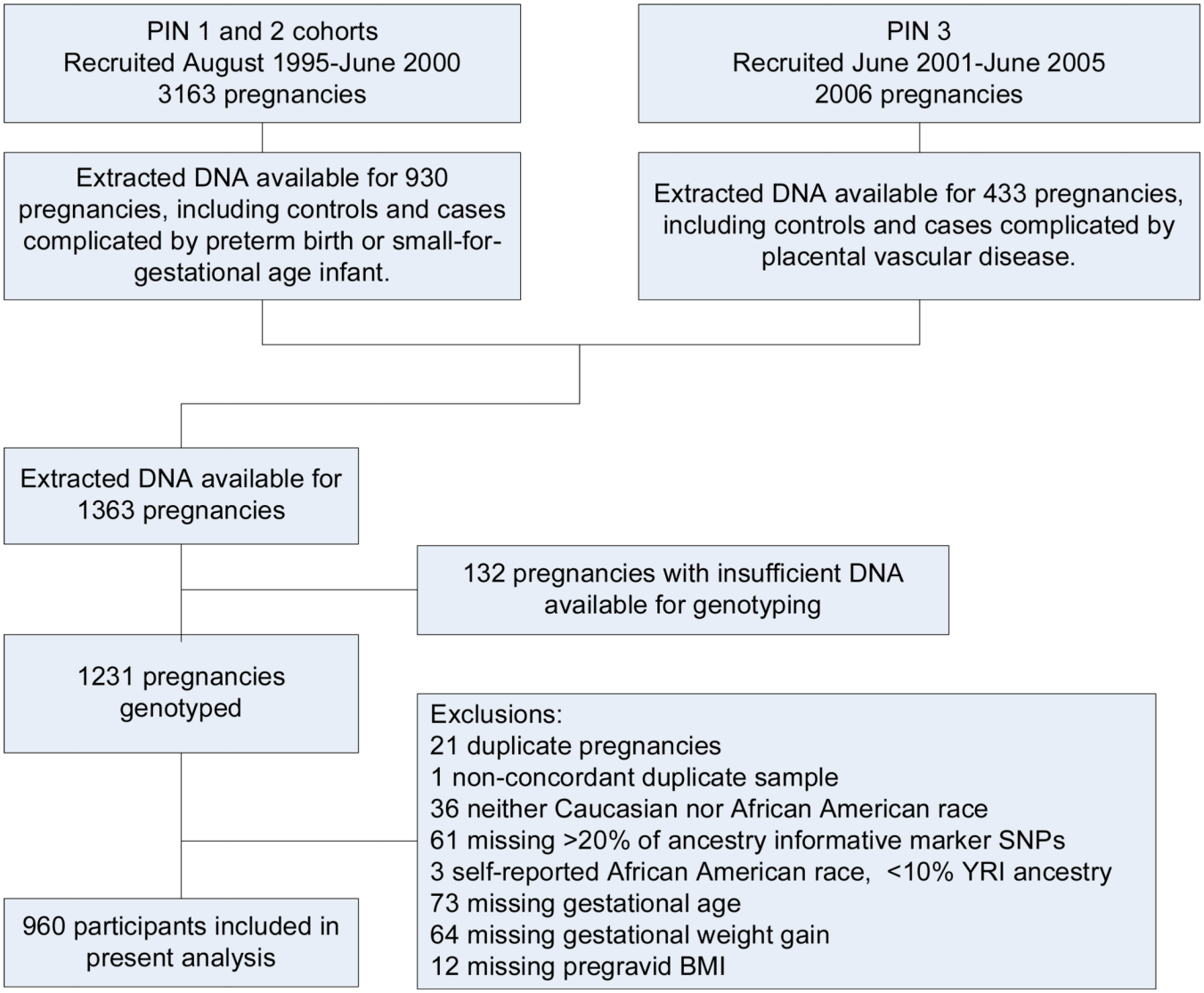
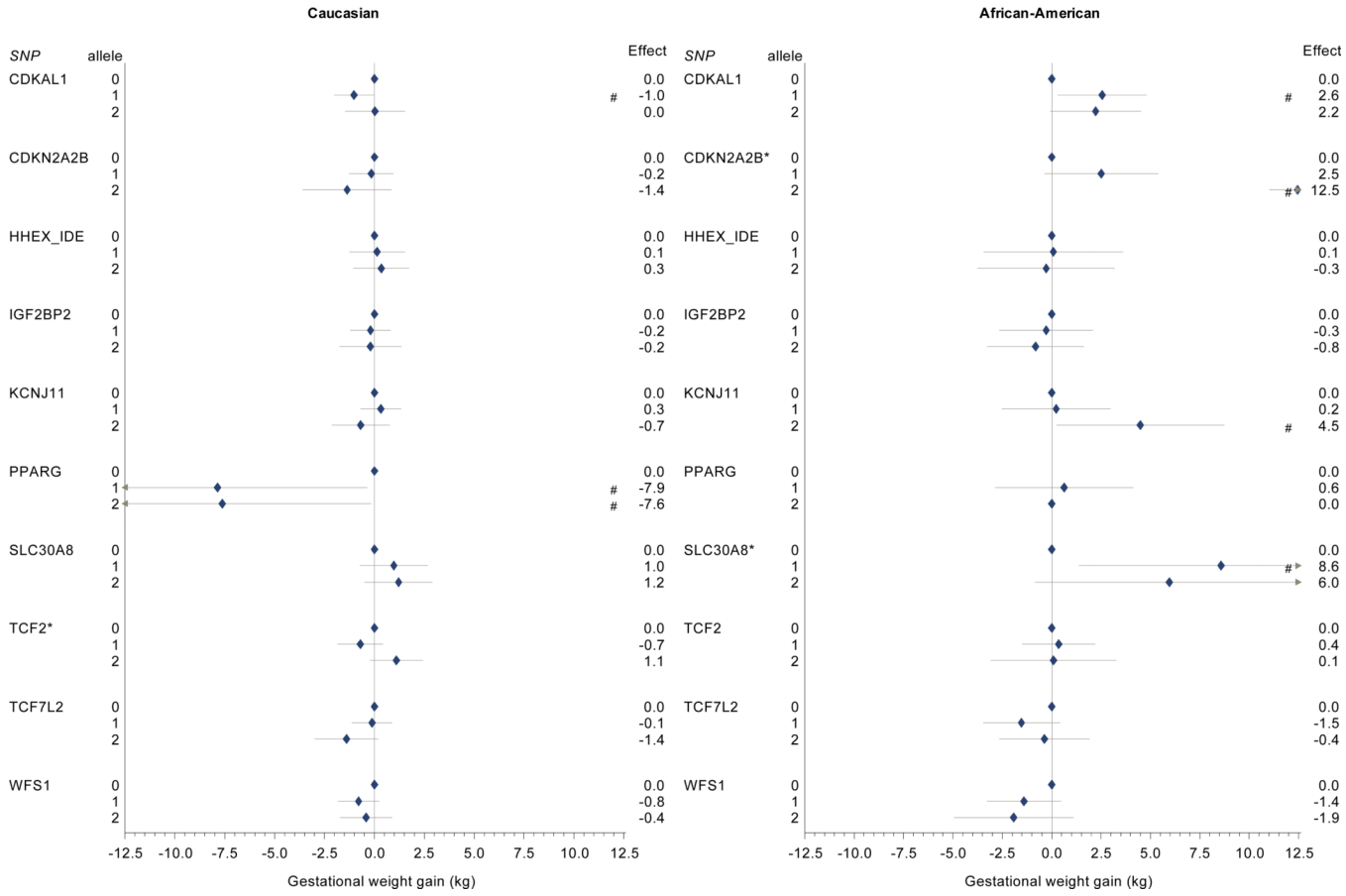


Figure 1. Flow diagram

2a



2b

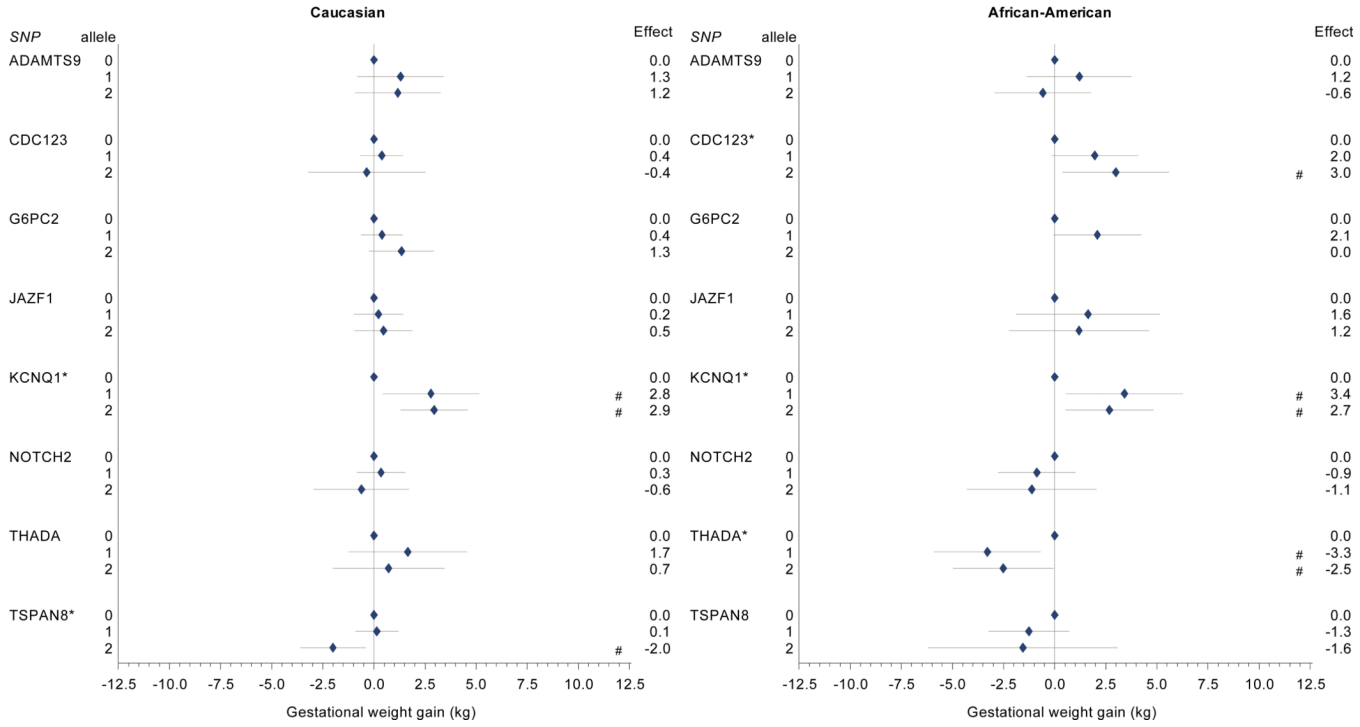


Figure 2. a and 2b: Diabetes-associated SNPs and gestational weight gain

Multivariate-adjusted§ effect estimate (95% CI) for change in gestational weight gain associated with risk allele carriage for single nucleotide polymorphisms associated with diabetes in non-pregnant populations. Caucasian participants (n=628) on left, African-American participants (n=332) on right.

* $p < 0.05$ for partial F test for this SNP. # $p < 0.05$ for comparison with 0 risk alleles (referent).

§ Model covariates include log pregravid BMI, log pregravid BMI squared, gestational age at birth, gestational age at birth squared, and maternal age. Effect estimates among self-identified African American participants further adjusted for probability of Yoruban ancestry. All models weighted to reflect the composition of the full PIN studies population.

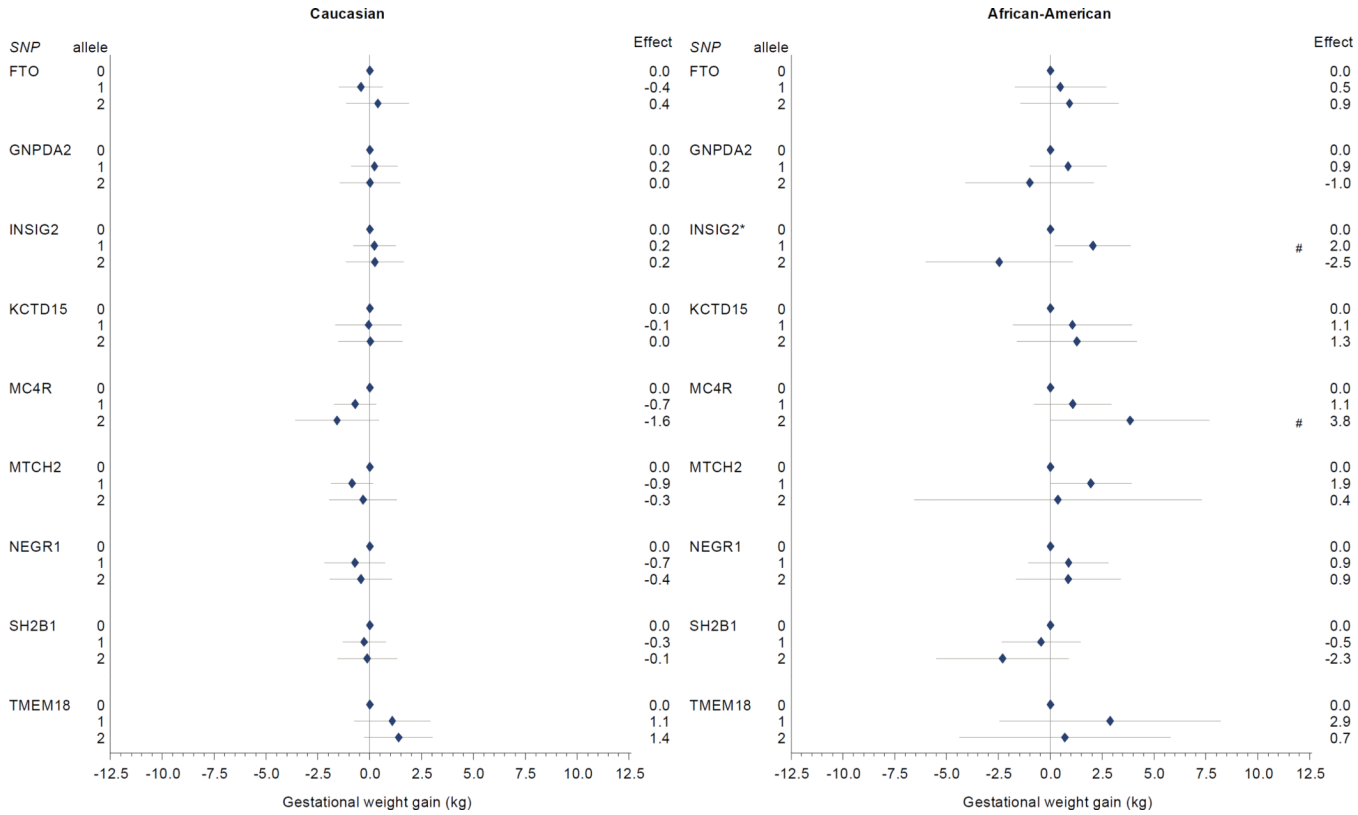


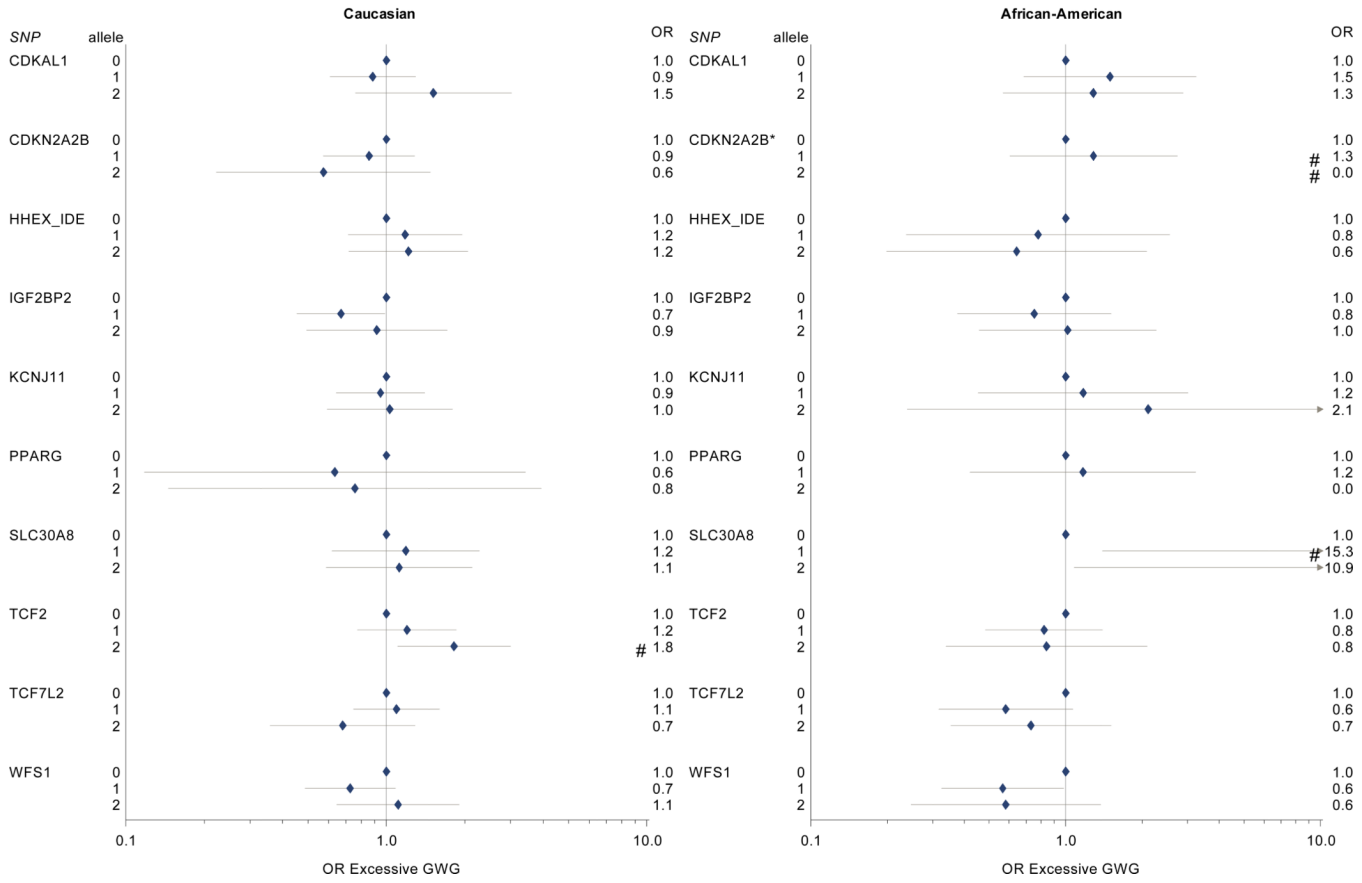
Figure 3. Obesity-associated SNPs and gestational weight gain

Multivariate-adjusted§ effect estimate (95% CI) for change in gestational weight gain associated with risk allele carriage for single nucleotide polymorphisms associated with obesity in non-pregnant populations. Caucasian participants (n=628) on left, African-American participants (n=332) on right.

* $p < 0.05$ for comparison with 0 risk alleles (referent).

§ Model covariates include log pregravid BMI, log pregravid BMI squared, gestational age at birth, gestational age at birth squared, and maternal age. Effect estimates among self-identified African American participants further adjusted for probability of Yoruban ancestry. All models weighted to reflect the composition of the full PIN studies population.

4a



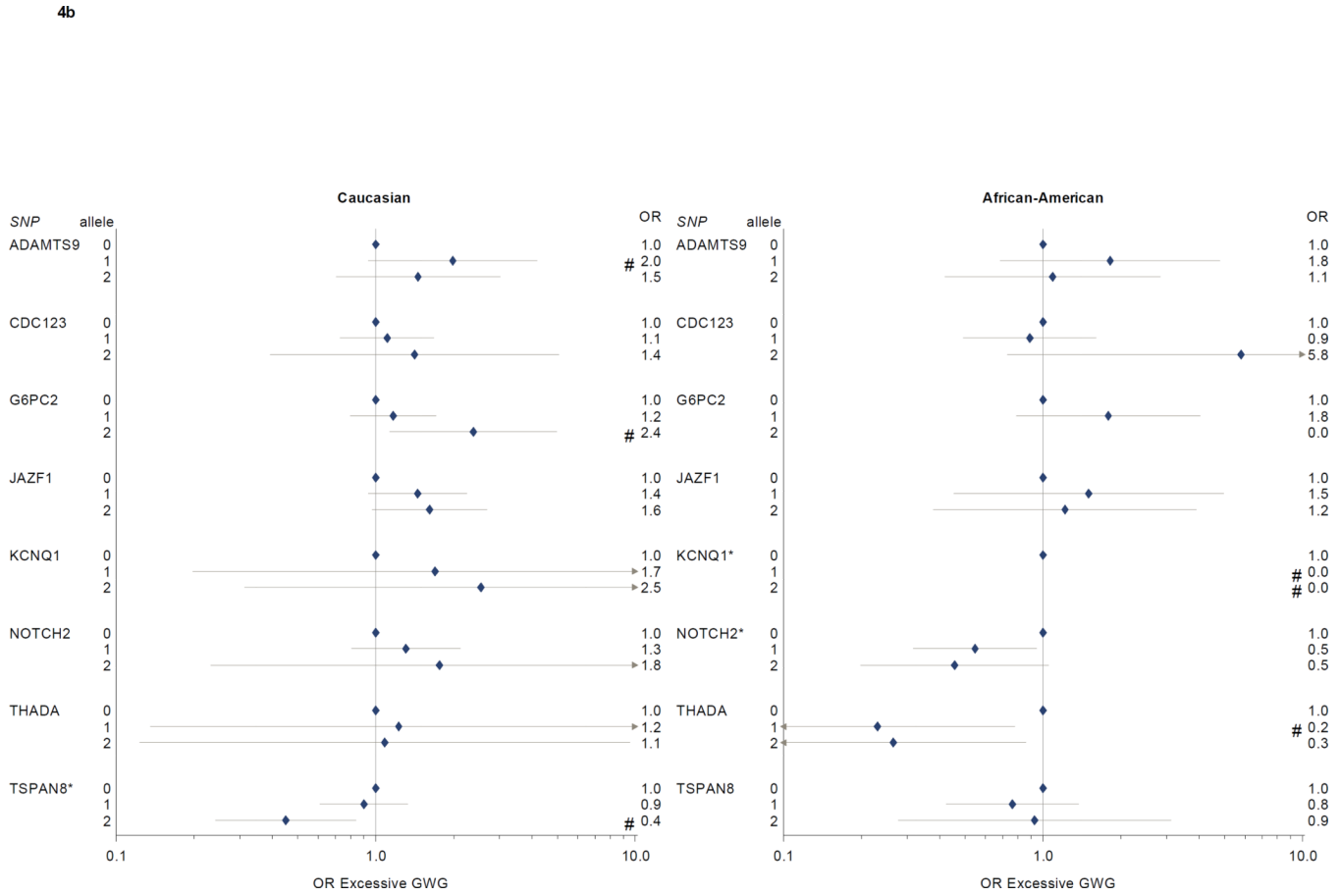


Figure 4. a and 4b: Diabetes-associated SNPs and excessive gestational weight gain

Multivariate-adjusted§ odds ratio (95% CI) for excessive weight gain by risk allele carriage for single nucleotide polymorphisms associated with diabetes in non-pregnant populations. Caucasian participants (n=628) on left, African-American participants (n=332) on right.

* $p < 0.05$ for Wald Chi Square test; # $p < 0.05$ for comparison with 0 risk alleles (referent).

§ Model covariates include log pregravid BMI, log pregravid BMI squared, and maternal age. Effect estimates among self-identified African American participants further adjusted for probability of Yoruban ancestry. All models weighted to reflect the composition of the full PIN studies population.

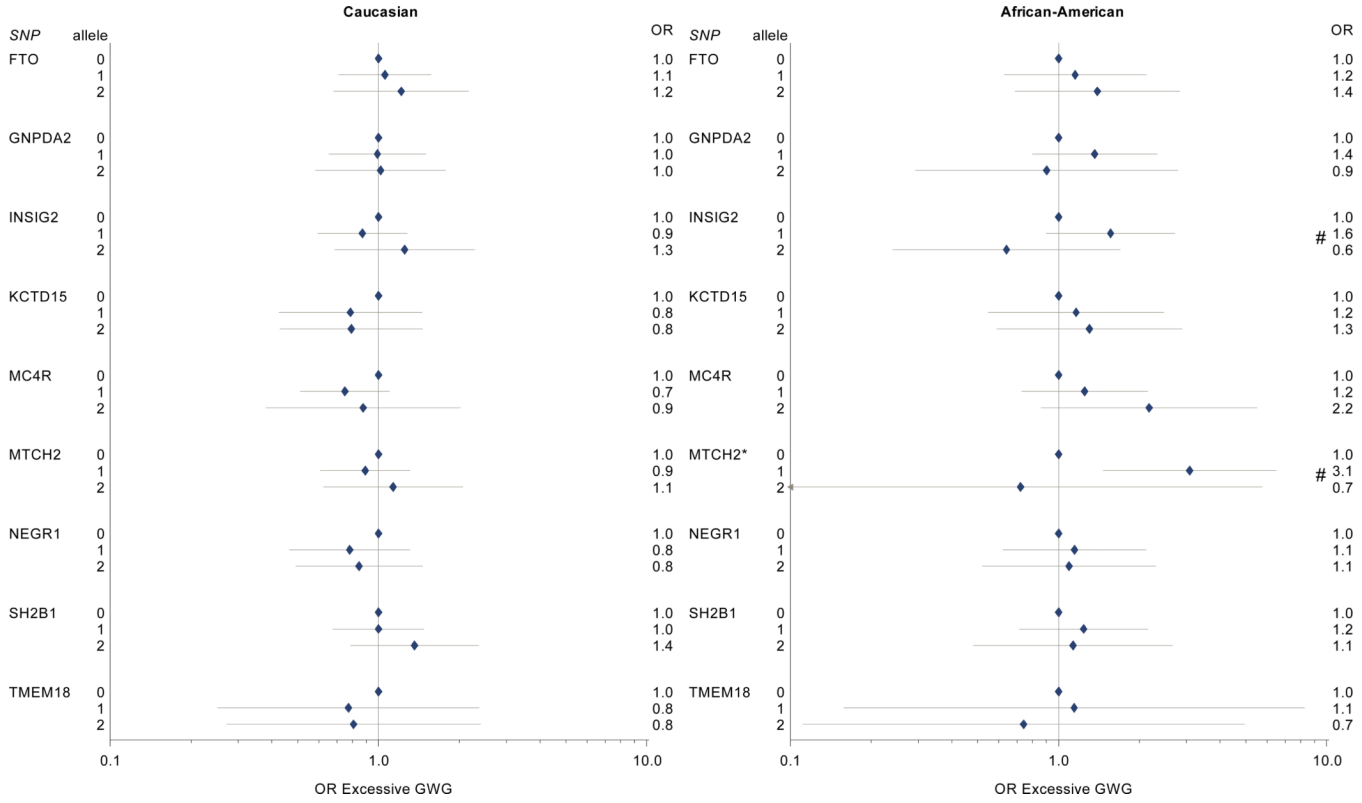


Figure 5. Obesity-associated SNPs and excessive gestational weight gain

Multivariate-adjusted§ odds ratio (95% CI) for excessive weight gain by risk allele carriage for single nucleotide polymorphisms associated with obesity in non-pregnant populations. Caucasian participants (n=628) on left, African-American participants (n=332) on right.

* $p < 0.05$ for Wald Chi Square test; # $p < 0.05$ for comparison with 0 risk alleles (referent).

§ Model covariates include log pregravid BMI, log pregravid BMI squared, and maternal age. Effect estimates among self-identified African American participants further adjusted for probability of Yoruban ancestry. All models weighted to reflect the composition of the full PIN studies population.

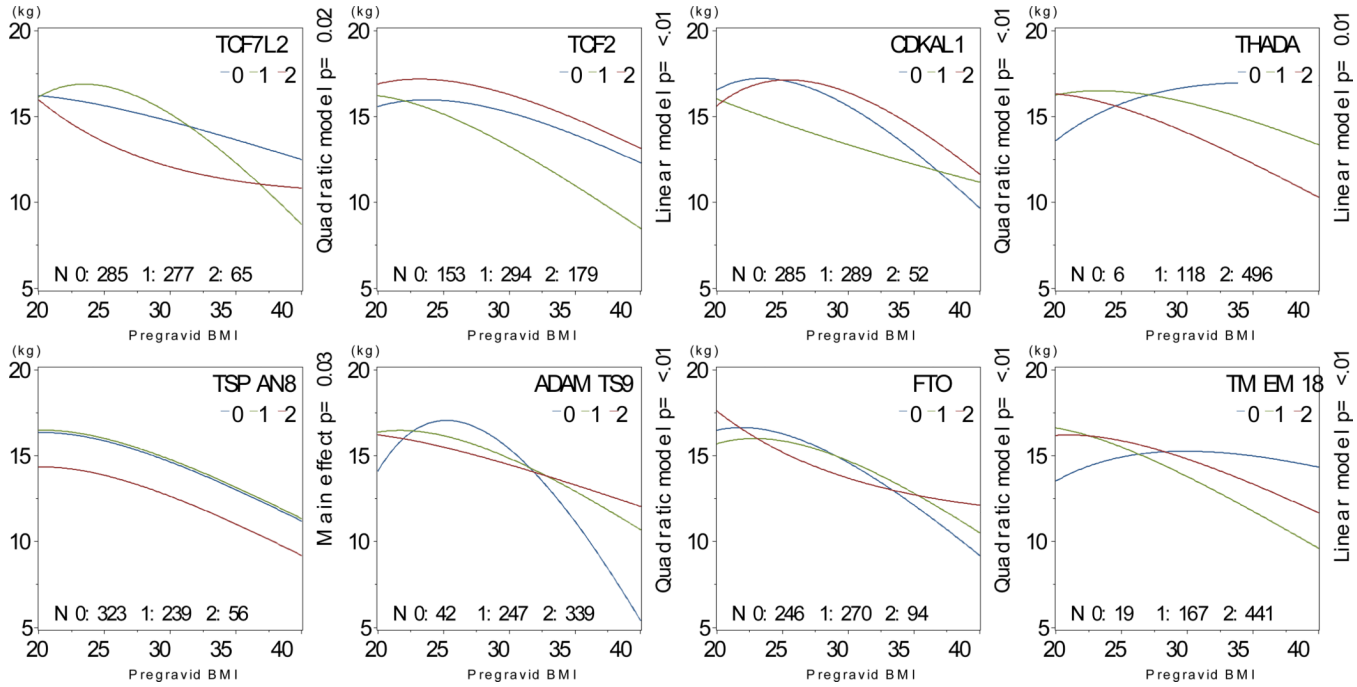


Figure 6. Interactions between pre-gravid BMI and SNP carriage, Caucasian participants

Multivariate-adjusted§ mean predicted gestational weight gain as a function of body mass index and risk allele carriage among self-identified Caucasian participants, N=628.

§ Model covariates include log pregravid BMI, log pregravid BMI squared, and maternal age. All models weighted to reflect the composition of the full PIN studies population.

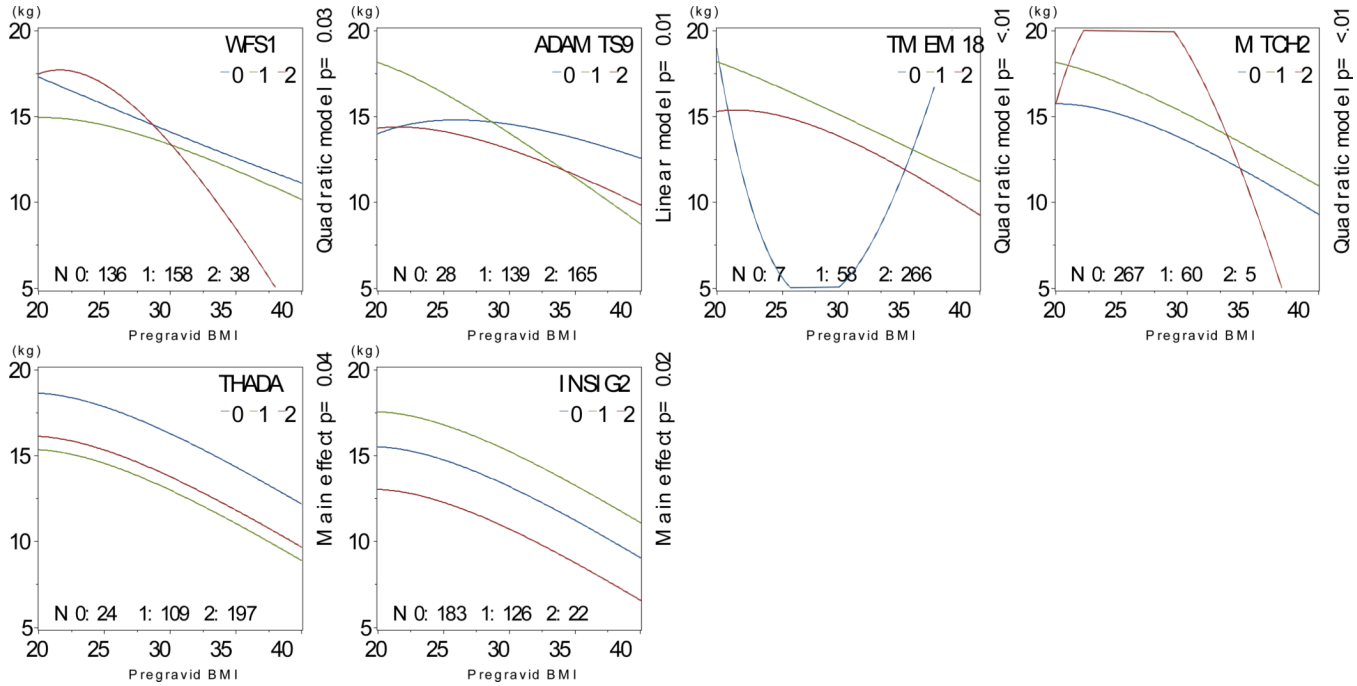


Figure 7. Interactions between pre-gravid BMI and SNP carriage, African-American participants

Multivariate-adjusted§ mean predicted gestational weight gain as a function of body mass index and risk allele carriage among self-identified African-American participants, N=332.

§ Model covariates include log pregravid BMI, log pregravid BMI squared, and maternal age, and probability of Yoruban ancestry. All models weighted to reflect the composition of the full PIN studies population.

Table 1

Characteristics of participants in the PIN3 study, n=960, mean (SD).

	Caucasian	African American
N	628	332
Maternal age	27.7 (6.2)	23.9 (5.3)
Pregravid BMI, kg/m^2	25.0 (6.6)	27.4 (8.1)
GA at delivery, wks	40.1 (0.9)	39.9 (1.1)
Infant birth weight, g	3258 (672)	2939 (753)
Gestational weight gain, kg	15.3 (6.2)	13.4 (7.8)
Glucose loading test, mg/dL	108.4 (25.9)	105.6 (31.0)
Gestational diabetes, % (n)	7.2 (45)	5.7 (19)
Small-for-gestational age, % (n)	12.3 (77)	18.7 (62)
Birth<37 wks, % (n)	21.2 (133)	28.0 (93)
Excessive weight gain, % (n)	65.5 (411)	58.4 (194)

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Table 2

SNP frequencies and total gestational weight gain, kg, for Caucasian and African American participants in the PIN studies, n=960.

			Gestational Weight Gain, kg Caucasian			African-American		
Gene / SNP	**Effect allele / other allele**	**Risk alleles**	**N***	**Mean (SD)**	**Adjusted† effect estimate (95% CI)**	**N***	**Mean (SD)**	**Adjusted† effect estimate (95% CI)**
N			628			332		
PPARG	C/G	0	7	21.7 (9.5)	0.00 (ref)	0	-	-
rs1801282		1	118	14.8 (5.9)	−7.9 (−15.4, −0.4)	20	13.4 (8.5)	0.6 (−2.9, 4.1)
		2	500	15.4 (6.2)	−7.6 (−15.1, −0.2)	309	13.4 (7.8)	0.00 (ref)
KCNJ11	C/T	0	243	15.5 (6.3)	0.00 (ref)	295	13.4 (7.8)	0.00 (ref)
rs5215		1	291	15.5 (6.1)	0.3 (−0.7, 1.3)	34	13.7 (7.8)	0.2 (−2.5, 3.0)
		2	94	14.3 (6.6)	−0.7 (−2.1, 0.8)	3	17.6 (4.1)	4.5 (0.2, 8.7)
TCF7L2	T/C	0	285	15.5 (6.1)	0.00 (ref)	109	14.0 (7.4)	0.00 (ref)
rs7901695		1	277	15.4 (6.4)	−0.1 (−1.1, 0.9)	152	12.8 (8.1)	−1.5 (−3.5, 0.4)
		2	65	14.2 (6.0)	−1.4 (−3.0, 0.2)	71	13.9 (7.7)	−0.4 (−2.6, 1.9)
TCF2	A/G	0	153	15.0 (5.9)	0.00 (ref)	145	13.1 (7.1)	0.00 (ref)
rs4430796		1	294	14.9 (6.2)	−0.7 (−1.8, 0.4)	150	13.5 (8.3)	0.4 (−1.5, 2.2)
		2	179	16.3 (6.5)	1.1 (−0.2, 2.4)	37	14.7 (8.0)	0.1 (−3.1, 3.3)
WFS1	A/G	0	236	15.7 (6.0)	0.00 (ref)	136	14.2 (7.7)	0.00 (ref)
rs10010131		1	286	15.1 (6.5)	−0.8 (−1.8, 0.2)	158	12.9 (7.3)	−1.4 (−3.3, 0.5)
		2	105	14.9 (6.1)	−0.4 (−1.7, 0.9)	38	12.8 (9.7)	−1.9 (−4.9, 1.1)
HHEX_IDE	C/T	0	108	15.3 (6.6)	0.00 (ref)	17	13.3 (6.1)	0.00 (ref)
rslll875		1	297	15.2 (6.6)	0.1 (−1.3, 1.5)	127	14.2 (7.9)	0.1 (−3.4, 3.6)
		2	221	15.5 (5.5)	0.3 (−1.0, 1.7)	188	12.9 (7.8)	−0.3 (−3.7, 3.2)
SLC30A8	C/T	0	55	14.3 (7.2)	0.00 (ref)	3	12.3 (8.0)	0.00 (ref)
rs13266634		1	273	15.4 (6.2)	1.0 (−0.7, 2.7)	61	15.0 (8.5)	8.6 (1.4, 15.8)
		2	300	15.4 (6.1)	1.2 (−0.5, 2.9)	268	13.1 (7.6)	6.0 (−0.8, 12.8)
CDKAL1	C/A	0	285	15.7 (6.7)	0.00 (ref)	45	12.0 (6.6)	0.00 (ref)
rs10946398		1	289	14.9 (5.9)	−1.0 (−2.0, 0.0)	162	13.9 (8.5)	2.6 (0.3, 4.8)
		2	52	15.6 (5.3)	0.0 (−1.5, 1.5)	121	13.4 (7.2)	2.2 (−0.1, 4.5)

			Gestational Weight Gain, kg					
			Caucasian			African-American		
Gene / SNP	Effect allele / other allele	Risk alleles	N*	Mean (SD)	Adjusted† effect estimate (95% CI)	N*	Mean (SD)	Adjusted† effect estimate (95% CI)
CDKN2A2B	C/T	0	425	15.5 (6.2)	0.00 (ref)	287	13.1 (7.7)	0.00 (ref)
rs10811661	C/T	1	172	15.0 (6.3)	−0.2 (−1.3, 1.0)	42	15.1 (7.8)	2.5 (−0.4, 5.4)
		2	21	13.6 (5.9)	−1.4 (−3.6, 0.8)	1	26.8 (.)	12.5 (11.0, 13.9)
IGF2BP2	T/G	0	276	15.6 (6.2)	0.00 (ref)	68	14.3 (7.0)	0.00 (ref)
rs4402960		1	275	15.2 (6.3)	−0.2 (−1.2, 0.8)	176	13.2 (8.3)	−0.3 (−2.6, 2.1)
		2	74	14.8 (6.3)	−0.2 (−1.8, 1.4)	81	13.3 (7.4)	−0.8 (−3.3, 1.6)
JAZF1	T/C	0	152	14.8 (6.3)	0.00 (ref)	18	12.9 (8.0)	0.00 (ref)
rs864745		1	303	15.4 (6.0)	0.2 (−1.0, 1.4)	126	13.7 (7.7)	1.6 (−1.9, 5.1)
		2	169	15.7 (6.5)	0.5 (−0.9, 1.9)	188	13.3 (7.8)	1.2 (−2.2, 4.6)
CDC123	G/A	0	424	15.3 (6.3)	0.00 (ref)	242	12.9 (7.8)	0.00 (ref)
rs12779790		1	176	15.5 (5.9)	0.4 (−0.7, 1.4)	82	14.8 (7.9)	2.0 (−0.1, 4.1)
		2	18	15.2 (6.8)	−0.4 (−3.2, 2.5)	4	15.0 (7.1)	3.0 (0.4, 5.6)
TSPAN8	C/T	0	323	15.3 (6.0)	0.00 (ref)	220	13.5 (7.6)	0.00 (ref)
rs7961581		1	239	15.6 (6.6)	0.1 (−0.9, 1.2)	97	13.5 (8.0)	−1.3 (−3.2, 0.7)
		2	56	13.5 (6.2)	−2.0 (−3.6, −0.4)	12	10.3 (9.1)	−1.6 (−6.2, 3.1)
THADA	T/C	0	6	15.5 (2.5)	0.00 (ref)	24	15.5 (6.3)	0.00 (ref)
rs7578597		1	118	15.7 (6.8)	1.7 (−1.2, 4.5)	109	13.1 (7.9)	−3.3 (−5.9, −0.7)
		2	496	15.2 (6.1)	0.7 (−2.0, 3.4)	197	13.4 (7.8)	−2.5 (−5.0, −0.1)
ADAMTS9	C/T	0	42	13.0 (7.1)	0.00 (ref)	28	12.6 (5.2)	0.00 (ref)
rs4607103		1	247	15.8 (5.9)	1.3 (−0.8, 3.4)	139	14.0 (9.2)	1.2 (−1.3, 3.8)
		2	339	15.3 (6.3)	1.2 (−0.9, 3.3)	165	13.1 (6.8)	−0.6 (−2.9, 1.8)
NOTCH2	T/G	0	506	15.3 (6.2)	0.00 (ref)	153	13.8 (8.1)	0.00 (ref)
rs10923931		1	115	15.4 (6.5)	0.3 (−0.8, 1.5)	140	13.2 (7.5)	−0.9 (−2.8, 1.0)
		2	4	16.0 (3.5)	−0.6 (−2.9, 1.7)	39	12.8 (7.8)	−1.1 (−4.3, 2.0)
KCNQ1	C/T	0	4	13.4 (1.6)	0.00 (ref)	2	5.9 (1.3)	0.00 (ref)
rs2237892		1	61	14.6 (6.6)	2.8 (0.4, 5.1)	51	14.1 (7.6)	3.4 (0.6, 6.3)
		2	542	15.4 (6.2)	2.9 (1.3, 4.6)	273	13.3 (7.7)	2.7 (0.5, 4.8)
G6PC2	A/G	0	309	15.3 (6.1)	0.00 (ref)	286	13.2 (8.0)	0.00 (ref)

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			Gestational Weight Gain, kg					
			Caucasian			African-American		
Gene / SNP	Effect allele / other allele	Risk alleles	N*	Mean (SD)	Adjusted† effect estimate (95% CI)	N*	Mean (SD)	Adjusted† effect estimate (95% CI)
rs560887		1	262	15.1 (6.5)	0.4 (−0.6, 1.4)	42	14.7 (6.5)	2.1 (−0.1, 4.2)
		2	52	15.9 (5.9)	1.3 (−0.2, 2.9)	0	-	-
INSIG2	C/G	0	301	15.2 (6.6)	0.00 (ref)	183	12.8 (7.5)	0.00 (ref)
rs7566605		1	255	15.5 (6.1)	0.2 (−0.8, 1.2)	126	14.9 (8.0)	2.0 (0.2, 3.9)
		2	72	15.4 (5.2)	0.2 (−1.1, 1.6)	22	10.5 (7.7)	−2.5 (−6.0, 1.1)
FTO	A/T	0	246	15.5 (6.8)	0.00 (ref)	83	12.9 (8.5)	0.00 (ref)
rs9939609		1	270	14.9 (5.7)	−0.4 (−1.5, 0.6)	158	13.4 (8.0)	0.5 (−1.7, 2.7)
		2	94	15.9 (6.4)	0.4 (−1.1, 1.9)	81	13.8 (7.0)	0.9 (−1.4, 3.3)
MC4R	C/T	0	369	15.7 (6.1)	0.00 (ref)	162	12.5 (7.0)	0.00 (ref)
rs17782313		1	219	14.9 (6.5)	−0.7 (−1.7, 0.3)	135	14.2 (8.4)	1.1 (−0.8, 2.9)
		2	34	13.9 (6.6)	−1.6 (−3.6, 0.4)	33	14.8 (8.7)	3.8 (0.0, 7.7)
TMEM18	C/T	0	19	14.4 (3.4)	0.00 (ref)	7	13.9 (6.1)	0.00 (ref)
rs6548238		1	167	15.2 (7.1)	1.1 (−0.8, 2.9)	58	15.1 (8.0)	2.9 (−2.4, 8.2)
		2	441	15.4 (6.0)	1.4 (−0.3, 3.0)	266	13.0 (7.7)	0.7 (−4.4, 5.8)
GNPDA2	G/A	0	195	15.5 (6.6)	0.00 (ref)	185	13.0 (8.2)	0.00 (ref)
rs10938397		1	308	15.5 (5.7)	0.2 (−0.9, 1.3)	131	14.1 (7.4)	0.9 (−1.0, 2.7)
		2	114	14.8 (6.4)	0.0 (−1.4, 1.5)	15	12.8 (5.9)	−1.0 (−4.1, 2.1)
SH2B1	G/A	0	249	15.5 (5.9)	0.00 (ref)	178	14.1 (7.8)	0.00 (ref)
rs7498665		1	280	15.2 (6.3)	−0.3 (−1.3, 0.8)	121	12.9 (7.3)	−0.5 (−2.4, 1.4)
		2	98	15.4 (6.7)	−0.1 (−1.6, 1.3)	33	11.9 (9.2)	−2.3 (−5.5, 0.9)
MTCH2	G/A	0	257	15.8 (6.3)	0.00 (ref)	267	13.1 (7.8)	0.00 (ref)
rs10838738		1	289	14.9 (6.1)	−0.9 (−1.9, 0.2)	60	14.6 (7.4)	1.9 (0.0, 3.9)
		2	82	15.1 (6.4)	−0.3 (−1.9, 1.3)	5	15.1 (9.1)	0.4 (−6.6, 7.3)
KCTD15	G/A	0	73	15.5 (6.1)	0.00 (ref)	50	11.3 (9.1)	0.00 (ref)
rs11084753		1	288	15.2 (6.6)	−0.1 (−1.6, 1.5)	155	13.7 (7.6)	1.1 (−1.8, 3.9)
		2	262	15.3 (5.8)	0.0 (−1.5, 1.6)	126	13.9 (7.4)	1.3 (−1.6, 4.2)
NEGR1	T/C	0	97	16.1 (6.9)	0.00 (ref)	87	13.3 (6.6)	0.00 (ref)
rs2815752		1	285	15.1 (6.0)	−0.7 (−2.2, 0.7)	169	13.7 (8.0)	0.9 (−1.0, 2.8)

Gene / SNP	Effect allele / other allele	Risk alleles	Gestational Weight Gain, kg Caucasian N*	Caucasian Mean (SD)	Caucasian Adjusted† effect estimate (95% CI)	African-American N*	African-American Mean (SD)	African-American Adjusted† effect estimate (95% CI)
		2	244	15.3 (6.2)	−0.4 (−1.9, 1.1)	76	13.0 (8.6)	0.9 (−1.7, 3.4)

*Frequencies sum to less than 628 or 332 because participants were excluded from an analysis if their samples did not genotype successfully.

†Model covariates include log pregravid BMI, log pregravid BMI squared, gestational age at birth, gestational age at birth squared, and maternal age. Effect estimates among self-identified African American participants further adjusted for probability of Yoruban ancestry. All models weighted to reflect the composition of the full PIN studies population.

Table 3

Risk allele carriage and odds of excessive gestational weight gain* for Caucasian and African American participants in the PIN studies, n=960.

			Caucasian			African-American		
	Effect allele / other allele	**Risk alleles**	**Excessive / Total†**	**Excessive weight gain, %**	**Adjusted‡ OR excessive gain (95% CI)**	**Excessive / Total†**	**Excessive weight gain, %**	**Adjusted‡ OR excessive gain (95% CI)**
			411/628	65.5		194/332	58.4	
PPARG	C/G	0	5/7	71.4	1.0 (ref)	./.	.	
rs1801282		1	72/118	61.0	0.6 (0.1, 3.4)	12/20	60.0	1.0 (ref)
		2	332/500	66.4	0.8 (0.1, 3.9)	180/309	58.3	1.2 (0.4, 3.2)
KCNJ11	C/T	0	160/243	65.8	1.0 (ref)	171/295	58.0	1.0 (ref)
rs5215		1	188/291	64.6	0.9 (0.6, 1.4)	21/34	61.8	1.2 (0.5, 3.0)
		2	63/94	67.0	1.0 (0.6, 1.8)	2/3	66.7	2.1 (0.2, 18.6)
TCF7L2	T/C	0	188/285	66.0	1.0 (ref)	68/109	62.4	1.0 (ref)
rs7901695		1	184/277	66.4	1.1 (0.7, 1.6)	83/152	54.6	0.6 (0.3, 1.1)
		2	38/65	58.5	0.7 (0.4, 1.3)	43/71	60.6	0.7 (0.4, 1.5)
TCF2	A/G	0	92/153	60.1	1.0 (ref)	85/145	58.6	1.0 (ref)
rs4430796		1	190/294	64.6	1.2 (0.8, 1.9)	87/150	58.0	0.8 (0.5, 1.4)
		2	129/179	72.1	1.8 (1.1, 3.0)	22/37	59.5	0.8 (0.3, 2.1)
WFS1	A/G	0	159/236	67.4	1.0 (ref)	87/136	64.0	1.0 (ref)
rs10010131		1	179/286	62.6	0.7 (0.5, 1.1)	87/158	55.1	0.6 (0.3, 1.0)
		2	73/105	69.5	1.1 (0.6, 1.9)	20/38	52.6	0.6 (0.2, 1.4)
HHEX_IDE	C/T	0	67/108	62.0	1.0 (ref)	12/17	70.6	1.0 (ref)
rslll875		1	195/297	65.7	1.2 (0.7, 2.0)	79/127	62.2	0.8 (0.2, 2.6)
		2	149/221	67.4	1.2 (0.7, 2.1)	103/188	54.8	0.6 (0.2, 2.1)
SLC30A8	C/T	0	37/55	67.3	1.0 (ref)	1/3	33.3	1.0 (ref)
rs13266634		1	182/273	66.7	1.2 (0.6, 2.3)	41/61	67.2	15.3 (1.4–167.5)
		2	192/300	64.0	1.1 (0.6, 2.1)	152/268	56.7	10.9 (1.1–110.8)
CDKAL1	C/A	0	185/285	64.9	1.0 (ref)	25/45	55.6	1.0 (ref)
rs10946398		1	188/289	65.1	0.9 (0.6, 1.3)	100/162	61.7	1.5 (0.7, 3.3)
		2	38/52	73.1	1.5 (0.8, 3.0)	67/121	55.4	1.3 (0.6, 2.9)
CDKN2A2B	C/T	0	284/425	66.8	1.0 (ref)	165/287	57.5	1.0 (ref)

			Caucasian			African-American		
	Effect allele / other allele	**Risk alleles**	**Excessive / Total†**	**Excessive weight gain, %**	**Adjusted‡ OR excessive gain (95% CI)**	**Excessive / Total†**	**Excessive weight gain, %**	**Adjusted‡ OR excessive gain (95% CI)**
rs10811661		1	109/172	63.4	0.9 (0.6, 1.3)	27/42	64.3	1.3 (0.6, 2.7)
		2	11/21	52.4	0.6 (0.2, 1.5)	1/1	100.0	-
IGF2BP2	T/G	0	190/276	68.8	1.0 (ref)	43/68	63.2	1.0 (ref)
rs4402960		1	169/275	61.5	0.7 (0.5, 1.0)	96/176	54.5	0.8 (0.4, 1.5)
		2	51/74	68.9	0.9 (0.5, 1.7)	52/81	64.2	1.0 (0.5, 2.3)
JAZF1	T/C	0	91/152	59.9	1.0 (ref)	10/18	55.6	1.0 (ref)
rs864745		1	202/303	66.7	1.4 (0.9, 2.2)	76/126	60.3	1.5 (0.5, 5.0)
		2	115/169	68.0	1.6 (1.0, 2.7)	108/188	57.4	1.2 (0.4, 3.9)
CDC123	G/A	0	275/424	64.9	1.0 (ref)	142/242	58.7	1.0 (ref)
rs12779790		1	119/176	67.6	1.1 (0.7, 1.7)	47/82	57.3	0.9 (0.5, 1.6)
		2	13/18	72.2	1.4 (0.4, 5.1)	3/4	75.0	5.8 (0.7, 45.9)
TSPAN8	C/T	0	217/323	67.2	1.0 (ref)	128/220	58.2	1.0 (ref)
rs7961581		1	154/239	64.4	0.9 (0.6, 1.3)	57/97	58.8	0.8 (0.4, 1.4)
		2	32/56	57.1	0.4 (0.2, 0.8)	6/12	50.0	0.9 (0.3, 3.1)
THADA	T/C	0	4/6	66.7	1.0 (ref)	18/24	75.0	1.0 (ref)
rs7578597		1	78/118	66.1	1.2 (0.1, 11.1)	63/109	57.8	0.2 (0.1, 0.8)
		2	322/496	64.9	1.1 (0.1, 9.5)	112/197	56.9	0.3 (0.1, 0.9)
ADAMTS9	C/T	0	23/42	54.8	1.0 (ref)	14/28	50.0	1.0 (ref)
rs4607103		1	174/247	70.4	2.0 (0.9, 4.2)	89/139	64.0	1.8 (0.7, 4.8)
		2	214/339	63.1	1.5 (0.7, 3.0)	91/165	55.2	1.1 (0.4, 2.8)
NOTCH2	T/G	0	326/506	64.4	1.0 (ref)	101/153	66.0	1.0 (ref)
rs10923931		1	79/115	68.7	1.3 (0.8, 2.1)	74/140	52.9	0.5 (0.3, 0.9)
		2	3/4	75.0	1.8 (0.2, 13.4)	19/39	48.7	0.5 (0.2, 1.1)
KCNQ1	C/T	0	2/4	50.0	1.0 (ref)	2/2	100.0	1.0 (ref)
rs2237892		1	37/61	60.7	1.7 (0.2, 14.5)	34/51	66.7	-
		2	357/542	65.9	2.5 (0.3, 20.6)	154/273	56.4	-
G6PC2	A/G	0	197/309	63.8	1.0 (ref)	164/286	57.3	1.0 (ref)
rs560887		1	174/262	66.4	1.2 (0.8, 1.7)	28/42	66.7	1.8 (0.8, 4.0)
		2	38/52	73.1	2.4 (1.1, 5.0)	./.	.	

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			Caucasian			African-American		
	Effect allele / other allele	**Risk alleles**	**Excessive / Total†**	**Excessive weight gain, %**	**Adjusted‡ OR excessive gain (95% CI)**	**Excessive / Total†**	**Excessive weight gain, %**	**Adjusted‡ OR excessive gain (95% CI)**
INSIG2	C/G	0	200/301	66.4	1.0 (ref)	101/183	55.2	1.0 (ref)
rs7566605		1	160/255	62.7	0.9 (0.6, 1.3)	82/126	65.1	1.6 (0.9, 2.7)
		2	51/72	70.8	1.3 (0.7, 2.3)	11/22	50.0	0.6 (0.2, 1.7)
FTO	A/T	0	162/246	65.9	1.0 (ref)	43/83	51.8	1.0 (ref)
rs9939609		1	172/270	63.7	1.1 (0.7, 1.6)	93/158	58.9	1.2 (0.6, 2.1)
		2	65/94	69.1	1.2 (0.7, 2.2)	50/81	61.7	1.4 (0.7, 2.8)
MC4R	C/T	0	251/369	68.0	1.0 (ref)	88/162	54.3	1.0 (ref)
rs17782313		1	137/219	62.6	0.7 (0.5, 1.1)	84/135	62.2	1.2 (0.7, 2.1)
		2	21/34	61.8	0.9 (0.4, 2.0)	21/33	63.6	2.2 (0.9, 5.5)
TMEM18	C/T	0	13/19	68.4	1.0 (ref)	5/7	71.4	1.0 (ref)
rs6548238		1	107/167	64.1	0.8 (0.3, 2.4)	36/58	62.1	1.1 (0.2, 8.3)
		2	290/441	65.8	0.8 (0.3, 2.4)	152/266	57.1	0.7 (0.1, 4.9)
GNPDA2	G/A	0	127/195	65.1	1.0 (ref)	103/185	55.7	1.0 (ref)
rs10938397		1	200/308	64.9	1.0 (0.7, 1.5)	82/131	62.6	1.4 (0.8, 2.3)
		2	77/114	67.5	1.0 (0.6, 1.8)	8/15	53.3	0.9 (0.3, 2.8)
SH2B1	G/A	0	160/249	64.3	1.0 (ref)	100/178	56.2	1.0 (ref)
rs7498665		1	180/280	64.3	1.0 (0.7, 1.5)	74/121	61.2	1.2 (0.7, 2.2)
		2	70/98	71.4	1.4 (0.8, 2.4)	20/33	60.6	1.1 (0.5, 2.7)
MTCH2	G/A	0	174/257	67.7	1.0 (ref)	148/267	55.4	1.0 (ref)
rs10838738		1	182/289	63.0	0.9 (0.6, 1.3)	43/60	71.7	3.1 (1.5, 6.5)
		2	55/82	67.1	1.1 (0.6, 2.1)	3/5	60.0	0.7 (0.1, 5.7)
KCTD15	G/A	0	53/73	72.6	1.0 (ref)	24/50	48.0	1.0 (ref)
rs11084753		1	184/288	63.9	0.8 (0.4, 1.4)	95/155	61.3	1.2 (0.5, 2.5)
		2	170/262	64.9	0.8 (0.4, 1.5)	74/126	58.7	1.3 (0.6, 2.9)
NEGR1	T/C	0	65/97	67.0	1.0 (ref)	49/87	56.3	1.0 (ref)
rs2815752		1	184/285	64.6	0.8 (0.5, 1.3)	103/169	60.9	1.1 (0.6, 2.1)
		2	161/244	66.0	0.8 (0.5, 1.5)	42/76	55.3	1.1 (0.5, 2.3)

*1990 Institute of Medicine (IOM) recommendations

[†]Frequencies sum to less than 628 or 332 because participants were excluded from an analysis if their samples did not genotype successfully.

[‡]Model covariates include log pregravid BMI, log pregravid BMI squared and maternal age. Effect estimates among self-identified African American participants further adjusted for probability of Yoruban ancestry. All models weighted to reflect the composition of the full PIN studies population.