Published in final edited form as:

Obesity (Silver Spring). 2019 July ; 27(7): 1184–1189. doi:10.1002/oby.22505.

Variants in body mass index-associated genes and adrenergic genes are not associated with gestational weight trajectory

Vivian K. Kawai¹, Samuel K. Nwosu², Daniel Kurnik^{1,3,4}, Frank E. Harrell², and C. Michael Stein¹

¹Division of Clinical Pharmacology, Department of Medicine Vanderbilt University Medical Center, Nashville, TN, USA;

²Department of Biostatistics, Vanderbilt University Medical Center, Nashville, TN, USA;

³Clinical Pharmacology Unit, Rambam Health Care Campus, Haifa, Israel;

⁴Rappaport Faculty of Medicine, Technion – Israel Institute of Technology, Haifa, Israel.

Abstract

Objective: Define the association between a genetic risk score (GRS) that combined the effect of multiple body mass index (BMI)-associated variants and gestational weight trajectory. Because pregnancy is a state of sympathetic activation, we examined the association between gestational weight trajectory and variants in adrenergic pathways previously associated with weight.

Methods: In a previously defined cohort of pregnant women with (n=1504) and without gestational diabetes (GDM) (n=435), we calculated weight trajectory using all weights during pregnancy. We calculated a GRS for BMI (GRS_{BMI}) using 31 common variants associated with BMI and genotyped 10 variants in the adrenergic pathway. Clinical and genetic factors were studied using generalized linear models.

Results: Pre-pregnancy BMI was associated with the GRS_{BMI} ($P=9.3 \times 10^{-11}$) and parity ($P=4.54 \times 10^{-17}$). The GRS_{BMI} was associated with gestational weight trajectory in women with and without GDM ($P=0.041$ and $P<0.0001$, respectively); however, when pre-pregnancy BMI was included in the models, the associations disappeared ($P>0.05$). Variants in adrenergic genes were not associated with gestational weight trajectory.

Conclusions: A GRS for BMI was associated with pre-pregnancy BMI but was not independently associated with gestational weight trajectory in women with and without GDM. Selected variants in adrenergic genes were not associated with gestational weight trajectory.

Keywords

gestational weight; BMI; genetics

Contact Information: Vivian K. Kawai, MD. Division of Clinical Pharmacology, 536 RRB, Vanderbilt University Medical Center, Nashville, TN 37232, USA., Phone: +1-615-343-0041, Fax: +1-615-936-2746., vivian.k.kawai@vumc.org; vivian.k.kawai@vanderbilt.edu.

Author Contribution: VKK, DK and CMS conceived the study design. VKK and SKN extracted and curated the data, VKK, SKN, FEH, DK and CMS analyzed and interpreted the data. All authors were involved in writing the paper and approved the final version of the manuscript.

Disclosure: The authors have no conflict of interest to disclose.

INTRODUCTION

The obesity epidemic has shifted patterns of gestational weight gain so that obesity during pregnancy currently affects more than a fifth of women in the United States (1). Excessive gestational weight gain is an important predictor of adverse outcomes for mother and child, during pregnancy (2–4) and later in life (5, 6). To address this public health concern and improve maternal and child health, the Institute of Medicine (IOM) has published new guidelines for the recommended rate and total amount of weight gained during pregnancy (7). In addition, several studies suggest that compared to total gestational weight, gestational weight trajectory is more informative to identify at-risk pregnancies that may benefit from early interventions (8–10).

Studies performed in twins estimated heritability values of 0.40 and 0.25 for gestational weight gain in the first and second pregnancy, respectively (11). The first and largest genome-wide association study (GWAS) on gestational weight gain did not identify any loci with large effects but found that some variants known to be associated with obesity and body weight were also associated with gestational weight gain with nominal statistical significance (12). Thus, it is possible that a genetic risk score (GRS) that combines the individual contributions of many genetic variants associated with obesity and body weight could predict gestational weight gain.

In addition to common genetic variants known to be associated with obesity and body weight, variants affecting the sympathetic nervous system are likely to affect weight in pregnancy. Pregnancy is a physiologic state associated with increased sympathetic activity (13, 14). The sympathetic nervous system contributes to the regulation of body weight through the activation of α and β -adrenergic signaling pathway (15). Excessive activation of α over β -adrenergic signaling impairs lipolysis and contributes to obesity (15, 16). During pregnancy, insulin secretion increases (17) as a compensatory mechanism for insulin resistance and this increase favors α_2 -adrenergic over β -adrenergic signaling (18, 19), which further aggravates the anti-lipolytic effect (20).

Sympathetic responses are highly heritable (21, 22) and functional variants in the α_2 and β -adrenergic receptor (AR) genes influence body weight (23, 24). Thus, it is likely that genetic variation in adrenergic pathways may contribute to variability in weight gain, particularly during states of increased sympathetic activation, such as pregnancy.

Based on these observations, we tested the hypotheses that: 1) a GRS that combines the effect of multiple genetic variants known to be associated with body mass index (BMI) is associated with gestational weight trajectory; and 2) common genetic variants in the adrenergic pathway affect gestational weight trajectory, independent of the BMI GRS. Furthermore, since the genetic contribution to weight in pregnancy is likely to differ in women who have gestational diabetes (GDM) and those who do not, we studied both groups using a previously identified cohort of patients with and without GDM.

MATERIAL AND METHODS

Study population:

We previously defined the genetic determinants of GDM in a cohort from Vanderbilt University Medical Center's DNA Biobank, BioVU (25). For the current study, we perform a secondary analysis using the same study population to determine the genetic contribution of common BMI variants and selected variants in adrenergic pathways to the trajectory of gestational weight. The study was approved by the Vanderbilt Institutional Review Board, and the detailed methods have been described previously (25); a brief overview is provided here. Using bioinformatic algorithms combined with manual review of de-identified electronic medical records (EMRs), we selected a cohort of pregnant women of European ancestry who had been screened for GDM. Women with a positive 100 gr oral glucose tolerance test were classified as having GDM using the Carpenter and Coustan criteria (26). Women without GDM had a negative 50 gr glucose screening test at 24–28 weeks of pregnancy (27). We excluded women with a diagnosis of diabetes before pregnancy, those receiving antidiabetic medication at the time of screening, non-singleton pregnancies, and pregnancies with insufficient information on weight during pregnancy.

Measures:

The primary analysis examined the effects of clinical and genetic variables on gestational weight trajectory defined as the change in the average weight during pregnancy (kg). The advantage of using weight trajectory is that any woman with a weight recorded during pregnancy contributes to the outcome and the contribution is proportional to the amount of weight information available for a given woman.

We extracted all maternal weights between the date of conception (DOC) and the date of delivery (DOD) from the EMR. To calculate the DOC, we subtracted the gestational age at delivery from the date of delivery (DOD). Pre-pregnancy weight was defined as the closest weight to the DOC recorded within the previous 2 years. If a weight was not recorded in this time-period, we used a) self-reported pre-pregnancy weight present in the mother's medical record, or b) the closest weight to DOC during the first trimester (<13 weeks). Clinical covariates such as maternal age at pregnancy, parity, and height were extracted from the de-identified EMR. Pre-pregnancy BMI was calculated as the ratio of pre-pregnancy weight in kg and height squared (meters).

Genotyping:

Thirty-one common genetic variants that had been associated with body weight or BMI ($P < 5 \times 10^{-8}$) in 2 or more GWAS published before December 2016 were selected for genotyping (Supplement Table S1) and included in GRS. In addition, we genotyped 10 variants in the adrenergic pathway that had been associated with body weight in the general population. Genotyping was performed by the Vanderbilt Technologies for Advance Genomics (VANTAGE) according to standard protocols using the Sequenom platform supplemented by TaqMan assays for SNPs that failed or did not pool well in Sequenom. For quality control, we required genotyping call rates >90% and calculated Hardy-Weinberg equilibrium (HWE) of genotype distributions.

Statistical analysis:

Demographic and clinical characteristics were described using proportions for categorical variables, and percentiles (i.e. 25th, 50th, 75th) for quantitative variables. To study the combined effect of common variants previously associated with body weight or BMI, we constructed a simple count (0, 1, or 2 for each risk allele) genetic risk score (GRS_{BMI}). In patients where genotype failed for 5 or fewer BMI-associated variants, we assumed that they did not carry the risk allele and assigned a score of 0 for each missing genotype.

For the primary analysis, to test the association between gestational weight trajectory and the clinical and genetic characteristics (age at pregnancy, parity, pre-pregnancy BMI, gestational age in days, GRS_{BMI}, adrenergic variants), we conducted a multivariable repeated measures generalized least squares (GLS) regression analysis to assess the expected change in gestational weight within patients while adjusting for each of the covariates. To fully examine the individual contribution of the GRS_{BMI} and the variants in adrenergic genes to gestational weight trajectory, we fit a full model including all variants, and separate models for each individual variant. Since interventions to prevent excessive weight gain are more likely to be initiated in women with GDM, the models were fit separately for women with and without GDM.

As a sensitivity analysis, we fit two additional models to both cohorts: 1) a model excluding both the adrenergic variants and the pre-pregnancy BMI, and 2) a model excluding only the adrenergic variants. Per number of levels, categorical variables were fit according to their degrees of freedom (i.e. $n-1$) and continuous variables were fit as non-linear effects (i.e. 4-knot splines). Results are displayed with effect estimates, 95% C.I., and p-values. Effect estimates for continuous variables represent the expected change in the average weight per interquartile range (IQR) change (from 25th to the 75th percentile). To minimize case-wise deletion of records with missing covariates, we employed multiple imputation with 20 imputation samples using predictive mean matching.

To define the contribution of the GRS_{BMI} to pre-pregnancy BMI, we analyzed natural log transformed pre-pregnancy BMI (in the combined group of women with and without GDM) using linear regression adjusted for maternal age and parity.

Statistical analysis was performed using R software version 3.3.0 (www.R-project.org) and SPSS (v.25, IBM® SPSS® Inc. Chicago, IL). A p-value <0.05 was considered statistically significant for the association between GRS_{BMI} and gestational weight trajectory; for the analysis that include all the adrenergic variants, a Bonferroni correction was applied and P-values <0.005 were considered statistically significant.

RESULTS

Study population:

The study included 1504 (77%) pregnant women without GDM and 435 (22%) pregnant women with GDM. The median age at pregnancy was 29 years for women without GDM and 30 years for women with GDM (Table 1). Pre-pregnancy weight was available in 1744 women, of these 216 had a pre-pregnancy weight measured more than 1 year before the

conception date. As reported previously (22), women with GDM were more likely to have higher parity, higher pre-pregnancy weight and BMI, and higher pre-delivery weight, but less weight gain than pregnant women without GDM (all $P < 0.05$). For repeated gestational weights, the overall average weight was approximately 79.7 (kgs). The average number of repeated gestational weight measured was approximately 10 measurements per subject.

BMI-associated genetic variants and pre-pregnancy BMI:

Risk allele frequencies (RAF) for the 31 variants included in the GRS_{BMI} were within expected ranges (see Supplementary Table S1) and BMI-associated variants were in HWE. The prevalence of the BMI-associated variants was similar among women with and without GDM, except for rs2307111 (*POC5*), which was more frequent among patients with GDM ($P = 0.042$) (Supplementary Table S1). The GRS_{BMI} was similar in the two groups ($P = 0.958$, Table 1). Pre-pregnancy BMI was available in 1744 women (322 with GDM) and was associated with parity ($\beta = 0.045$, $P = 4.54 \times 10^{-17}$) and the GRS_{BMI} ($\beta = 0.010$, $P = 9.1 \times 10^{-11}$) (Table S2) and was nominally associated with six of the individual variants in the GRS_{BMI} (Table S1).

Clinical and genetic determinants of gestational weight trajectory:

In the primary analysis, the results from the full GLS regression model showed that gestational age and pre-pregnancy BMI were significantly associated with gestational weight trajectory in women with and without GDM, but the GRS_{BMI} and variants in adrenergic genes were not (Table 2). For example, per IQR change in gestational age (from 136 to 251 days) the estimated gestational weight was associated with a 5.77 kg (95% CI: 5.08 – 6.46, p -value < 0.0001) change in women with GDM, and a 9.28 kg (95% CI: 9.01 – 9.55, p -value < 0.0001) change in women without GDM. For pre-pregnancy BMI, per IQR change in BMI (from 21.69 to 28.96) the estimated gestational weight was associated with a 17.85 kg (95% CI: 14.06 – 21.64, p -value < 0.0001) change in women with GDM, and an 18.00 kg (95% CI: 16.73 – 19.27, p -value < 0.0001) change in women without GDM (Table 2).

Minor allele frequencies (MAF) for the variants in adrenergic genes were within expected ranges, except for rs1801252 (*ADRB1*) that was out of HWE ($P < 1 \times 10^{-6}$) and was excluded from the analysis (Table S3). None of the adrenergic variants were significantly associated with gestational weight in both groups (rs4994 was nominally but not Bonferroni-adjusted significantly associated in women without GDM in the single SNP analysis ($P = 0.040$, Table S3) and in the full adjusted model (P -value = 0.042, Table 2)).

In the sensitivity analyses, excluding only the variants in adrenergic genes from the models (Table 3), the findings were very similar to those of the primary analysis. However, in models that excluded variants in adrenergic genes and pre-pregnancy BMI, the GRS_{BMI} was significantly associated with gestational weight change in women with and without GDM (Table 3). For instance, per IQR change in GRS_{BMI} (from 27 to 32) the estimated gestational weight was associated with a 5.35 kg (95% CI: -0.38 – 11.07, p -value < 0.041) change in women with GDM, and a 2.96 kg (95% CI: 0.76 – 5.13, p -value < 0.0001) change in women without GDM.

DISCUSSION

We found that a GRS composed of BMI-associated genetic variants was associated with pre-pregnancy BMI but not with gestational weight trajectory in women with and without GDM; however, the GRS_{BMI} was associated with gestational weight trajectory when pre-pregnancy BMI was excluded from the model. None of the variants in adrenergic genes were significantly associated with gestational weight trajectory.

Family and twin studies have shown that BMI is a highly heritable trait (28); however, GWAS studies in the general population that included hundreds of thousands of individuals have reported that the loci identified account for 6% of variability in BMI (29, 30). Gestational weight gain is also a heritable trait with h^2 values of 0.40 and 0.25 for the first and second pregnancy, respectively (11), but the specific genetic determinants of this heritability are undefined.

We hypothesized that the combined effect of known BMI-associated variants would be associated with weight trajectory during pregnancy. We found that a GRS_{BMI} that included 31 loci was associated with pre-pregnancy BMI but not with gestational weight trajectory when pre-pregnancy BMI was considered. Similar to these findings, Lawlor found that a risk score that included the four variants most strongly associated with BMI in GWAS studies was associated with pre-pregnancy BMI but not with weight gain during pregnancy (31). Li et al reported similar results using an unweighted risk score for 83 BMI-associated genetic variants, but no associations were found with a weighted GRS (32). Also, in other studies individual BMI-associated variants were not associated with weight gain during pregnancy (12, 33).

In aggregate, these findings suggest that BMI-associated genetic variants, although they are associated with pre-pregnancy BMI, do not have major independent effects on weight gain during pregnancy. Moreover, a previous GWAS performed in more than 10,000 women found no loci significantly associated with weight gain during pregnancy, suggesting that variants with large effect size are unlikely (12).

Pregnant women go through many metabolic changes in order to sustain the growing fetus, and the effect of these, together with environmental factors, are likely to contribute more to the variability of gestational weight than genetic factors (11). This is particularly likely for women with GDM because treatment is started to limit excessive weight gain.

All the variants in the adrenergic pathway selected for study have been associated body weight in the general population (23). Moreover, some of them were also associated with variability in weight change during weight loss interventions (34, 35), anti-psychotic therapy (36), and pregnancy (24, 37–39). Because pregnancy is a hyperadrenergic state (13, 14), we postulated that adrenergic pathway variants would be likely to have even greater effects on gestational weight than on non-pregnant weight. However, there was only a nominally significant association between rs4994, a missense mutation in *ADRB3*, and weight trajectory during pregnancy.

The study had some limitations. First, because we studied pregnant women at a tertiary care hospital, our findings may not be generalizable to other populations. Second, because weight at the beginning of the pregnancy was not available in all the patients, pre-pregnancy BMI was calculated using different definitions of pre-pregnancy weight. In approximately 12% of patients, pre-pregnancy BMI was calculated using a weight measured more than 12 months before the date of conception, which could have affected our results. Third, although the study had better power to detect a genetic signal for adrenergic variants than previous studies in pregnant women, the sample size does not exclude small effects. For alleles with a MAF of 0.01, we were powered (0.80) to detect a 1.0 kg and 0.25 kg change for women with and without GDM, respectively assuming a normal distribution for weight trajectory, an additive model, and a type I error 0.05. Our study population consisted of a total of 1939 subjects, including 1504 pregnant women without GDM and 435 pregnant women with GDM. With continuous variables fit as non-linear terms (i.e. 4-knot splines) taking up $n-1$ degrees of freedom (d.f.) and categorical variables taking up one d.f. per category minus one, we implemented the 10–20 rule to account for the appropriate number of d.f.. Using a mildly conservative number of approximately 15 observations per d.f., where our model fits used no more than a maximum of 25 d.f., this estimate yielded a minimum number of 375 patients. Given our study population of 1504 women without GDM and 435 women with GDM, our sample size was adequate as to not over-fit our models thus ensuring stable point estimates. Fourth, we cannot exclude the possibility that variants other than those tested contribute to variability in weight during pregnancy; however, much larger studies will be needed to detect a genetic signal since large effects are unlikely (12) as occurs with BMI, where the variability in BMI explained by the addition of 30 new significant loci increased only ~0.3% (40) and 3% with the addition of more than 480 new significant loci (30). Fifth, although previous studies using BMI-associated genetic variants for other phenotypes suggested that weighted and unweighted GRSs produce similar results (41), we cannot exclude the possibility that a weighted GRS would have performed better than the unweighted GRS. An alternative approach would be to construct a polygenic risk score using thousands of BMI-associated genetic variants to explore their contribution to gestational weight trajectory. Although, Yengo et al reported that the BMI variance explained by SNPs with $P < 0.001$ is ~13.9% compared to 6% for SNPs with $P < 10^{-8}$ (30), studies in other complex traits show that there is limited improvement in the performance of the GRS when thousands of variants are used as opposed to only GWAS-significant SNPs (42). Nevertheless, the performance of a polygenic risk score in gestational weight traits would be of interest, considering that half of the heritability of GWG variability is likely explained by the maternal genome (12).

CONCLUSION

In summary, we found that a GRS_{BMI} was associated with pre-pregnancy BMI but was not independently associated with gestational weight trajectory in women with and without GDM. None of the selected variants in adrenergic genes were associated with gestational weight trajectory.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Funding:

The study was supported by NIH/NHLBI grant HL56693. The datasets used in the analysis were obtained from Vanderbilt University Medical Center's BioVU and supported by the 1S10RR025141-01 instrumentation award and by the Vanderbilt CTSA grant UL1TR000445 from NCATS/NIH. Additional support included NIH/NIGMS K23 GM117395 (VKK), NIH/NHLBI 3P01HL56693-17S (VKK).

References

1. Kim SY, Dietz PM, England L, Morrow B, Callaghan WM. Trends in pre-pregnancy obesity in nine states, 1993–2003. *Obesity (Silver Spring)*. 2007;15(4):986–93. [PubMed: 17426334]
2. Kiel DW, Dodson EA, Artal R, Boehmer TK, Leet TL. Gestational weight gain and pregnancy outcomes in obese women: how much is enough? *Obstet Gynecol*. 2007;110(4):752–8. [PubMed: 17906005]
3. Hedderson MM, Gunderson EP, Ferrara A. Gestational weight gain and risk of gestational diabetes mellitus. *Obstet Gynecol*. 2010;115(3):597–604. [PubMed: 20177292]
4. Viswanathan M, Siega-Riz AM, Moos MK, Deierlein A, Mumford S, Knaack J, et al. Outcomes of maternal weight gain. *Evid Rep Technol Assess (Full Rep)*. 2008(168):1–223.
5. Herring SJ, Rose MZ, Skouteris H, Oken E. Optimizing weight gain in pregnancy to prevent obesity in women and children. *Diabetes Obes Metab*. 2012;14(3):195–203. [PubMed: 21851516]
6. Oken E, Kleinman KP, Belfort MB, Hammitt JK, Gillman MW. Associations of gestational weight gain with short- and longer-term maternal and child health outcomes. *Am J Epidemiol*. 2009;170(2):173–80. [PubMed: 19439579]
7. In: Rasmussen KM, Yaktine AL, editors. *Weight Gain During Pregnancy: Reexamining the Guidelines* The National Academies Collection: Reports funded by National Institutes of Health. Washington (DC)2009.
8. Pugh SJ, Albert PS, Kim S, Grobman W, Hinkle SN, Newman RB, et al. Patterns of gestational weight gain and birthweight outcomes in the Eunice Kennedy Shriver National Institute of Child Health and Human Development Fetal Growth Studies-Singletons: a prospective study. *Am J Obstet Gynecol*. 2017;217(3):346 e1– e11. [PubMed: 28502760]
9. Galjaard S, Pexsters A, Devlieger R, Guelinckx I, Abdallah Y, Lewis C, et al. The influence of weight gain patterns in pregnancy on fetal growth using cluster analysis in an obese and nonobese population. *Obesity (Silver Spring)*. 2013;21(7):1416–22. [PubMed: 23408453]
10. Catov JM, Abatemarco D, Althouse A, Davis EM, Hubel C. Patterns of gestational weight gain related to fetal growth among women with overweight and obesity. *Obesity (Silver Spring)*. 2015;23(5):1071–8. [PubMed: 25865858]
11. Andersson ES, Silventoinen K, Tynelius P, Nohr EA, Sorensen TI, Rasmussen F. Heritability of gestational weight gain--a Swedish register-based twin study. *Twin Res Hum Genet*. 2015;18(4):410–8. [PubMed: 26111621]
12. Warrington NM, Richmond R, Fenstra B, Myhre R, Gaillard R, Paternoster L, et al. Maternal and fetal genetic contribution to gestational weight gain. *Int J Obes (Lond)*. 2018;42(4):775–84. [PubMed: 28990592]
13. Greenwood JP, Scott EM, Stoker JB, Walker JJ, Mary DA. Sympathetic neural mechanisms in normal and hypertensive pregnancy in humans. *Circulation*. 2001;104(18):2200–4. [PubMed: 11684631]
14. Jarvis SS, Shibata S, Bivens TB, Okada Y, Casey BM, Levine BD, et al. Sympathetic activation during early pregnancy in humans. *J Physiol*. 2012;590(15):3535–43. [PubMed: 22687610]
15. Lafontan M, Bousquet-Melou A, Galitzky J, Barbe P, Carpenne C, Langin D, et al. Adrenergic receptors and fat cells: differential recruitment by physiological amines and homologous regulation. *Obes Res*. 1995;3 Suppl 4:507S–14S. [PubMed: 8697051]
16. Galitzky J, Lafontan M, Nordenstrom J, Arner P. Role of vascular alpha-2 adrenoceptors in regulating lipid mobilization from human adipose tissue. *J Clin Invest*. 1993;91(5):1997–2003. [PubMed: 8387538]

17. Etiology Kuhl C. and pathogenesis of gestational diabetes. *Diabetes Care*. 1998;21 Suppl 2:B19–26. [PubMed: 9704223]
18. Moberg E, Enoksson S, Hagstrom-Toft E. Importance of phosphodiesterase 3 for the lipolytic response in adipose tissue during insulin-induced hypoglycemia in normal man. *Horm Metab Res*. 1998;30(11):684–8. [PubMed: 9918386]
19. Stich V, Pelikanova T, Wohl P, Sengenès C, Zakaroff-Girard A, Lafontan M, et al. Activation of alpha2-adrenergic receptors blunts epinephrine-induced lipolysis in subcutaneous adipose tissue during a hyperinsulinemic euglycemic clamp in men. *Am J Physiol Endocrinol Metab*. 2003;285(3):E599–607. [PubMed: 12900381]
20. Bousquet-Melou A, Munoz C, Galitzky J, Berlan M, Lafontan M. Pregnancy modifies the alpha2-beta-adrenergic receptor functional balance in rabbit fat cells. *J Lipid Res*. 1999;40(2):267–74. [PubMed: 9925656]
21. Williams PD, Puddey IB, Beilin LJ, Vandongen R. Genetic influences on plasma catecholamines in human twins. *J Clin Endocrinol Metab*. 1993;77(3):794–9. [PubMed: 8370701]
22. Seasholtz TM, Wessel J, Rao F, Rana BK, Khandrika S, Kennedy BP, et al. Rho kinase polymorphism influences blood pressure and systemic vascular resistance in human twins: role of heredity. *Hypertension*. 2006;47(5):937–47. [PubMed: 16585408]
23. Masuo K, Lambert GW. Relationships of adrenoceptor polymorphisms with obesity. *J Obes*. 2011;2011:609485. [PubMed: 21603275]
24. Dishy V, Gupta S, Landau R, Xie HG, Kim RB, Smiley RM, et al. G-protein beta(3) subunit 825 C/T polymorphism is associated with weight gain during pregnancy. *Pharmacogenetics*. 2003;13(4):241–2. [PubMed: 12668921]
25. Kawai VK, Levinson RT, Adefurin A, Kurnik D, Collier SP, Conway D, et al. A genetic risk score that includes common type 2 diabetes risk variants is associated with gestational diabetes. *Clin Endocrinol (Oxf)*. 2017;87(2):149–55. [PubMed: 28429832]
26. Carpenter MW, Coustan DR. Criteria for screening tests for gestational diabetes. *Am J Obstet Gynecol*. 1982;144(7):768–73. [PubMed: 7148898]
27. American Diabetes A. 2. Classification and Diagnosis of Diabetes. *Diabetes Care*. 2016;39 Suppl 1:S13–22. [PubMed: 26696675]
28. Bell CG, Walley AJ, Froguel P. The genetics of human obesity. *Nat Rev Genet*. 2005;6(3):221–34. [PubMed: 15703762]
29. Locke AE, Kahali B, Berndt SI, Justice AE, Pers TH, Day FR, et al. Genetic studies of body mass index yield new insights for obesity biology. *Nature*. 2015;518(7538):197–206. [PubMed: 25673413]
30. Yengo L, Sidorenko J, Kemper KE, Zheng Z, Wood AR, Weedon MN, et al. Meta-analysis of genome-wide association studies for height and body mass index in approximately 700000 individuals of European ancestry. *Hum Mol Genet*. 2018;27(20):3641–9. [PubMed: 30124842]
31. Lawlor DA, Fraser A, Macdonald-Wallis C, Nelson SM, Palmer TM, Davey Smith G, et al. Maternal and offspring adiposity-related genetic variants and gestational weight gain. *Am J Clin Nutr*. 2011;94(1):149–55. [PubMed: 21593506]
32. Li A, Teo KK, Morrison KM, McDonald SD, Atkinson SA, Anand SS, et al. A genetic link between prepregnancy body mass index, postpartum weight retention, and offspring weight in early childhood. *Obesity (Silver Spring)*. 2017;25(1):236–43. [PubMed: 27883278]
33. Stuebe AM, Lyon H, Herring AH, Ghosh J, Wise A, North KE, et al. Obesity and diabetes genetic variants associated with gestational weight gain. *Am J Obstet Gynecol*. 2010;203(3):283 e1–17. [PubMed: 20816152]
34. Szendrei B, Gonzalez-Lamuno D, Amigo T, Wang G, Pitsiladis Y, Benito PJ, et al. Influence of ADRB2 Gln27Glu and ADRB3 Trp64Arg polymorphisms on body weight and body composition changes after a controlled weight-loss intervention. *Appl Physiol Nutr Metab*. 2016;41(3):307–14. [PubMed: 26888112]
35. Sakane N, Yoshida T, Umekawa T, Kogure A, Takakura Y, Kondo M. Effects of Trp64Arg mutation in the beta 3-adrenergic receptor gene on weight loss, body fat distribution, glycemic control, and insulin resistance in obese type 2 diabetic patients. *Diabetes Care*. 1997;20(12):1887–90. [PubMed: 9405912]

36. Sickert L, Muller DJ, Tiwari AK, Shaikh S, Zai C, De Souza R, et al. Association of the alpha 2A adrenergic receptor –1291C/G polymorphism and antipsychotic-induced weight gain in European-Americans. *Pharmacogenomics*. 2009;10(7):1169–76. [PubMed: 19604092]
37. Festa A, Krugluger W, Shnawa N, Hopmeier P, Haffner SM, Schernthaner G. Trp64Arg polymorphism of the beta3-adrenergic receptor gene in pregnancy: association with mild gestational diabetes mellitus. *J Clin Endocrinol Metab*. 1999;84(5):1695–9. [PubMed: 10323402]
38. Gutersohn A, Naber C, Muller N, Erbel R, Siffert W. G protein beta3 subunit 825 TT genotype and post-pregnancy weight retention. *Lancet*. 2000;355(9211):1240–1. [PubMed: 10770309]
39. Yanagisawa K, Iwasaki N, Sanaka M, Minei S, Kanamori M, Omori Y, et al. Polymorphism of the beta3-adrenergic receptor gene and weight gain in pregnant diabetic women. *Diabetes Res Clin Pract*. 1999;44(1):41–7. [PubMed: 10414939]
40. Hoffmann TJ, Choquet H, Yin J, Banda Y, Kvale MN, Glymour M, et al. A Large Multiethnic Genome-Wide Association Study of Adult Body Mass Index Identifies Novel Loci. *Genetics*. 2018;210(2):499–515. [PubMed: 30108127]
41. Hung CF, Breen G, Czamara D, Corre T, Wolf C, Kloiber S, et al. A genetic risk score combining 32 SNPs is associated with body mass index and improves obesity prediction in people with major depressive disorder. *BMC Med*. 2015;13:86. [PubMed: 25903154]
42. Khera AV, Chaffin M, Aragam KG, Haas ME, Roselli C, Choi SH, et al. Genome-wide polygenic scores for common diseases identify individuals with risk equivalent to monogenic mutations. *Nat Genet*. 2018;50(9):1219–24. [PubMed: 30104762]

Important questions:

- Gestational weight gain is known to be a heritable trait, with h^2 values of 0.40 and 0.25 for the first and second pregnancy, respectively; however, the genetic determinants have not been defined.
- Some studies have reported nominally significant associations between BMI-related variants and gestational weight gain, but their combined effect has not been explored.
- Pregnancy is a state of increased adrenergic activity. A few small studies have reported an association between gestational weight and common variants in the adrenergic pathway.

What does this study add?

- This study sought to define the combined effects of BMI-related variants and common variants in the adrenergic pathway on gestational weight trajectory using a cohort of 1939 pregnant women with and without gestational diabetes.

Table 1:

Clinical characteristics of pregnant women with and without gestational diabetes (GDM)

Characteristics	No GDM (n=1504)	GDM (n=435)
Age at pregnancy (years)	29 (25, 32)	30 (25, 34)
Parity	0 (0, 1)	1 (0, 2)
Pre-pregnancy weight (kg) ^a	65.3 (58.1, 75.0)	77.0 (62.6, 92.5)
Pre-delivery weight (kg) ^b	80.9 (72.8, 91.2)	86.1 (75.3, 103.4)
Weight gain during pregnancy (kg) ^c	14.5 (10.9, 18.7)	10.0 (5.9, 15.4)
Pre-pregnancy BMI (kg/m ²) ^a	23.9 (21.3, 27.6)	28.8 (23.9, 35.2)
Gestational age at pre-delivery weight (weeks) ^b	39.0 (38.0, 39.9)	38.4 (37.3, 39.1)
Genetic risk score for BMI	29 (27, 32)	29 (27, 32)

Data are expressed as median (interquartile range) or number (percent). BMI: body mass index.

^aPre-pregnancy weight was missing in 82 (5.8%) women without GDM and in 113 (26%) women with GDM

^bPre-delivery weight and gestational age at time of pre-delivery weight was missing in 70 (4.7%) women without GDM and in 50 (11.5%) women with GDM. Pre-delivery weight was defined as the closest weight to the delivery date recorded at 37 weeks of gestation or within 15 days before delivery for pre-term births.

^cWeight gain was calculated as the difference between pre-delivery weight and pre-pregnancy weight. Weight gain could not be estimated in 145 (9.6%) women without GDM and in 138 (31.7%) women with GDM.

Table 2:

Association of gestational weight trajectory with clinical and genetic factors in pregnant women with and without gestational diabetes (GDM)

Covariates	IQR		No GDM		GDM	
	25 th	75 th	Effect (95%CI) ^a	P-value	Effect (95%CI) ^a	P-value
Maternal age (years)	25	32	2.45 (1.19, 3.72)	<0.0001	0.44 (-2.66, 3.54)	0.199
Parity	0	1	-2.55 (-3.51, -1.59)	<0.0001	-1.62 (-4.05, 0.80)	0.202
Gestational age (days)	136	251	9.28 (9.01, 9.55)	<0.0001	5.77 (5.08, 6.46)	<0.0001
Pre-pregnancy BMI (kg/m ²)	21.69	28.96	18.00 (16.73, 19.27)	<0.0001	17.85 (14.06, 21.64)	<0.0001
GRS _{BMI}	27	32	-0.42 (-1.68, 0.83)	0.266	1.38 (-2.02, 4.78)	0.692
rs36022820	---	---	1.69 (-2.51, 5.89)	0.430	5.2 (-7.36, 17.76)	0.417
rs1800544	---	---	-0.60 (-2.91, 1.71)	0.612	-1.11 (-6.70, 4.77)	0.711
rs553668	---	---	-0.36(-2.92, 2.20)	0.783	-1.42 (-8.22, 5.39)	0.683
rs1801253	---	---	0.18 (1.26, 1.62)	0.809	-1.01 (-4.98, 2.95)	0.617
rs1800888	---	---	0.30 (-2.54, 3.13)	0.838	1.97 (-8.39, 12.34)	0.709
rs1042713	---	---	-0.72 (-2.53, 1.09)	0.434	1.15 (-3.92, 6.22)	0.656
rs1042714	---	---	-0.73 (-2.48, 1.03)	0.416	1.68 (-2.94, 6.31)	0.476
rs4994	---	---	2.43 (0.09, 4.76)	0.042	2.64 (-4.38, 9.65)	0.461
rs5443	---	---	-0.41 (-1.74, 0.93)	0.550	-3.31 (-4.00, 3.37)	0.868

Generalized least squared regression model for changes in gestational weight adjusted for all covariates in the table.

IQR: Interquartile range for the covariates; shows the 25th and 75th percentile for the covariates (not applicable for individual genetic variants).

^aEffect size refers to the change in gestational weight (kg) per IQR change (from 25th to 75th percentile) of the covariates.

Table 3:

Association of gestational weight trajectory with clinical variables and GRS_{BMI} in pregnant women with and without gestational diabetes (GDM)

Covariates	IQR		No GDM			GDM		
	25th	75th	Effect (95%CI) ^a	P value	Effect (95%CI) ^a	P value	Effect (95%CI) ^{a,b}	P value
Maternal age (years)	25	32	2.32 (1.18, 3.46)	<0.0001	1.04 (-1.21, 3.19)	0.043	0.60 (-2.45, 3.64)	0.173
Parity	0	1	-2.56 (-3.43, -1.69)	<0.0001	1.67 (-0.01, 3.35)	0.004	-1.68 (-4.04, 0.67)	0.131
Gestational age (days)	136	251	9.30 (9.02, 9.57)	<0.0001	9.28 (9.00, 9.55)	<0.0001	5.77 (5.08, 6.46)	<0.0001
GRS _{BMI}	27	32	-0.76 (-1.87, 0.35)	0.215	2.95 (0.76, 5.13)	<0.0001	1.51 (-1.85, 4.86)	0.595
Pre-pregnancy BMI (kg/m ²)	21.69	28.96	18.52 (17.42, 19.62)	<0.0001	*	*	17.71 (14.00, 21.43)	<0.0001

GRS: Genetic risk score; BMI: Body mass index; GDM: Gestational diabetes; 95%CI: 95% confidence interval

IQR: Interquartile range for the covariates; shows the 25th and 75th percentile values for covariates (not applicable for individual genetic variants)

^a Effect sizes represent the expected change in gestational weight per interquartile range change (from 25th to 75th percentile) in the covariates

* Excludes pre-pregnancy BMI in the GLS model