# Genetic Predisposition to Central Obesity and Risk of Type 2 Diabetes: Two Independent Cohort Studies

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## OBJECTIVE

**Abdominal obesity is a major risk factor for type 2 diabetes (T2D). We aimed to examine the association between the genetic predisposition to central obesity, assessed by the waist-to-hip ratio (WHR) genetic score, and T2D risk.**

## RESEARCH DESIGN AND METHODS

**The current study included 2,591 participants with T2D and 3,052 participants without T2D of European ancestry from the Nurses' Health Study (NHS) and the Health Professionals Follow-up Study (HPFS). Genetic predisposition to central obesity was estimated using a genetic score based on 14 established loci for the WHR.**

## RESULTS

**We found that the central obesity genetic score was linearly related to higher T2D risk. Results were similar in the NHS (women) and HPFS (men). In combined results, each point of the central obesity genetic score was associated with an odds ratio (OR) of 1.04 (95% CI 1.01–1.07) for developing T2D, and the OR was 1.24 (1.03–1.45) when comparing extreme quartiles of the genetic score after multivariate adjustment.**

## CONCLUSIONS

**The data indicate that genetic predisposition to central obesity is associated with higher T2D risk. This association is mediated by central obesity.**


The dramatic increase in the global incidence of obesity has been accompanied by an increase in incident type 2 diabetes (T2D) (1). Anthropometric measures capturing abdominal adiposity, such as waist circumference or waist-to-hip ratio (WHR), have been related to diabetes risk independent of BMI across various ethnic groups (2–5). Compelling evidence shows that accumulation of visceral fat plays a pivotal role in the etiology of diabetes by overexposing the liver to free fatty acids, which subsequently result in insulin resistance and hyperinsulinemia (6). However, whether central obesity plays a causal role in the development of T2D remains unclear. A meta-analysis of the WHR genome-wide association studies (GWAS) comprising >100,000 individuals of European ancestry established a comprehensive genetic profile for modulating body fat distribution independent of overall adiposity (7). Information on the association of genetic predisposition to central obesity with risk of T2D is limited.

In the current study, we calculated the genetic score based on 14 well-established single nucleotide polymorphisms (SNPs) for WHR (7) as a proxy of genetic

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predisposition to central obesity. We examined the association of this genetic score with T2D risk in women and men of European ancestry from two prospective cohorts: the Nurses' Health Study (NHS) and the Health Professionals Follow-up Study (HPFS).

## RESEARCH DESIGN AND METHODS

The NHS is a prospective cohort study of 121,700 female registered nurses aged 30–55 years at study inception in 1976 when all participants completed a mailed questionnaire about medical history and lifestyle (8). Between 1989 and 1990, 32,826 women provided blood samples. The HPFS is a prospective cohort study of 51,529 U.S. male health professionals who were aged 40–75 years at study inception in 1986 (9). Between 1993 and 1999, 18,159 men provided blood samples. In both cohorts, medical and lifestyle information has been collected biennially by self-administered questionnaires since inception. Both studies were approved by the human research committee at the Brigham and Women's Hospital (Boston, MA), and all participants provided written informed consent.

### Ascertainment of T2D

Participants for the current study were selected among those with a blood sample, using a nested case-control study design (10,11). Diabetes cases were defined as self-reported diabetes confirmed by a validated supplementary questionnaire (12,13). For cases before 1998, we used the National Diabetes Data Group criteria to define diabetes (14), which included one of the following: one or more classic symptoms (excessive thirst, polyuria, weight loss, hunger, pruritus, or coma) plus a fasting plasma glucose level of $\geq$7.8 mmol/L (140 mg/dL), a random plasma glucose level of $\geq$11.1 mmol/L (200 mg/dL), or a plasma glucose level 2 h after an oral glucose tolerance test of $\geq$11.1 mmol/L (200 mg/dL); at least two elevated plasma glucose levels on different occasions in the absence of symptoms; or treatment with hypoglycemia medication (insulin or oral hypoglycemic agent). We used the American Diabetes Association diagnostic criteria for diabetes diagnosis since 1998 (15). These criteria were the same as those proposed by the National Diabetes Data Group except for the elevated fasting plasma glucose criterion for which the cut point was changed from 7.8 mmol/L (140 mg/dL) to 7.0 mmol/L (126 mg/dL). Only participants with a diabetes diagnosis after the cohort baseline were included as cases. The validity of diabetes self-report was verified in a subsample from the HPFS and the NHS cohorts. A physician blinded to the information reported on the supplementary questionnaire reviewed the medical records according to the diagnostic criteria. Ninety-seven percent of the diabetes cases were confirmed in the HPFS cohort (13). Similarly, 98% of the diabetes cases reported by the supplementary questionnaire were confirmed by medical record review in a subsample of NHS participants (12). Control participants were defined as those free of diabetes at the time of the diagnosis of cases and remained unaffected through follow-up until 2006. We matched the case participants to control participants by age, month and year of blood draw, and fasting status within their respective cohorts. After applying a quality control filter in the NHS and HPFS T2D GWAS (11), duplicate samples, samples with misidentified sex, related samples (siblings or possible first cousins), samples with evidence of contamination, samples with highly variable intensity data, and samples with missing call rates $\geq$2% were excluded. The population structure was investigated by principal component analysis (16). In this analysis, participants clustered with the HapMap CEU (Utah residents with northern and western European ancestry) samples were genetically inferred to have European ancestry. A total of 3,221 women (1,467 case and 1,754 control participants) and 2,422 men (1,124 case and 1,298 control participants) of genetically inferred European ancestry were included in the current analysis.

### Assessment of WHR and Covariates

Waist and hip circumference were reported to the nearest one-quarter inch in 1986 (NHS), and participants were instructed to measure their waists while standing relaxed at the navel and their hips at the largest circumference, including the buttocks in 1987 (HPFS) (17). Each supplemental questionnaire included a tape measure and detailed instructions, including a diagram. Self-reported anthropometric measures were validated against technician measurements among a subset of participants residing in the Boston area (18). Crude Pearson correlations between self-reported waist circumferences and the average of two technician-measured waist circumferences were 0.95 for men and 0.89 for women. Similarly, correlations for hip measurements were 0.88 for men and 0.84 for women and for WHRs, 0.69 for men and 0.70 for women. Correlations became stronger after correcting for random within-person variability from daily or seasonal fluctuations (18). BMI was calculated as weight in kilograms divided by the square of height in meters. Information about diet and lifestyle factors (e.g., smoking status, alcohol intake), menopausal status and postmenopausal hormone therapy (women only), and medications was derived from the baseline questionnaires (8,9). For men, physical activity was expressed as metabolic equivalents per week by using the reported time spent doing various activities, weighting each activity by its intensity level. For women, physical activity was expressed as hours per week because MET hours were not measured at baseline in the NHS. The Healthy Eating Index, which measures adherence to the U.S. Department of Agriculture Dietary Guidelines for Americans and MyPyramid, was calculated among men and women (19). The validity of the self-reported body weight and physical activity data has been described previously (18,20,21). Self-reported and measured weights were highly correlated at 0.97 for men and 0.97 for women (18).

### Genotyping

SNP genotyping and imputation have been described in detail elsewhere (the NHS and HPFS T2D GWA scans) (11). In brief, samples were genotyped and analyzed using the Affymetrix Genome-Wide Human Array 6.0 (Santa Clara, CA) and the Birdseed calling algorithm. All samples used in the current study achieved a call rate of $>$98%. We used MACH (http://www.sph.umich.edu/csg/abecasis/mach) to impute SNPs on chromosomes 1–22, with National Center for Biotechnology Information build 36 of phase II HapMap CEU data (release 22) as the reference panel.

### Genetic Score Calculation

To estimate the genetic predisposition to central obesity, a genetic score was calculated on the basis of the well-established SNPs in 14 loci (Supplementary Table 1) for the WHR reported by a meta-analysis of GWAS (7). We assumed that each SNP in the panel acts independently in

an additive manner, and the genetic score was calculated by using a weighted method. Each SNP was weighted by its relative effect size (β-coefficient) obtained from the reported meta-analysis data (7). Using the same method for the previously reported BMI genetic score (22–24), we first created a weighted score using the following equation: weighted score = $\beta 1 \times$ SNP1 + $\beta 2 \times$ SNP2 + ... + $\beta n \times$ SNPn, where β is the β-coefficient for each individual SNP, and n is number of SNPs. To reflect the number of WHR-increasing alleles, we rescaled the weighted score using the following equation: weighted genetic risk score (GRS) = weighted score × (total number of SNPs / sum of the β-coefficients). Figure 1 shows the association of genetic score with the WHR. In addition, a BMI genetic score based on 32 SNPs was calculated using a similar method to that described previously (22–24).

### Statistical Analysis

Comparisons of proportions and means between case and control participants were calculated by $\chi^2$ and *t* tests. We used logistic regression to estimate odds ratios (ORs) for T2D risk, adjusting for age and BMI. To examine the accumulative effect of the genetic score, we compared the T2D risk across the quartiles of the genetic score. In multivariate analysis, we further adjusted for smoking (never, past, or current), alcohol intake (0, 0.1–4.9, 5.0–9.9, 10.0–14.9, or ≥15.0 g/day), menopausal hormone therapy use (never, past, or current [women only]), Healthy Eating Index, and physical activity (quintiles). BMI genetic score and WHR were further adjusted for association with WHR genetic score and risk of T2D. Results in women and men were pooled by using inverse variance weights under a fixed model because there was no heterogeneity. A restricted cubic spline regression model was used to test linear relation between the genetic score (as a continuous variable) and risk of T2D (25). This simple method can help to prevent the problems resulting from inappropriate linearity assumptions. We further examined the genetic association with risk of T2D according to joint classification of BMI-GRS and WHR-GRS in which both variables were classified into three categories (tertiles). All reported *P* values are nominal and two sided, and $P \leq 0.05$ was considered statistically significant. The study had 80% power to detect an association with an OR of 1.03 for risk of T2D at a significance level of 0.05. Statistical analyses were performed in SAS version 9.3 software (SAS Institute Inc., Cary, NC).

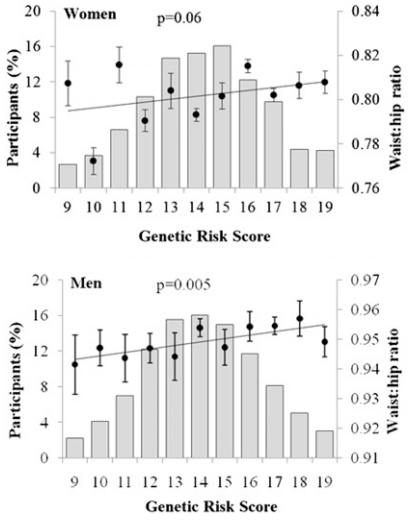


**Figure 1**—WHR genetic score distribution and its association with WHR in the NHS and HPFS cohorts. The histograms represent the percentage of participants, and the mean (± SE) WHRs are plotted with the trend lines across the GRS. The slope of the trend line represents the correction between GHR and WHR in control participants.

## RESULTS

### Characteristics of the Participants at Baseline

Table 1 shows the baseline characteristics of participants of two nested case-control studies from the NHS (women) and HPFS (men). Participants with T2D had a significantly higher BMI and lower physical activity level and were more likely to smoke and have a family history of diabetes than participants without T2D. Female participants with T2D consumed less alcohol and were more likely to be postmenopausal than those without diabetes. In addition, the genetic score was not associated with age, BMI, or lifestyle factors, including smoking, alcohol intake, and physical activity (all $P >$ 0.05). The mean genetic scores among men and women were 14.39 ± 2.4, and 14.53 ± 2.3, respectively. The range of genetic scores among men and women was 6.26–23.01 and 5.33–22.32, respectively. The genetic score was significantly associated with the WHR among men (0.005) and marginally related to the WHR among women (*P* = 0.06) (Fig. 1).

### Central Obesity Genetic Score and T2D

As shown in Table 2, the central obesity genetic score was significantly associated with an increased T2D risk in women (OR 1.03 [95% CI 1.00–1.06] per 1-point genetic score increase) and men (1.03 [1.00–1.07]). Multivariate adjustment for age, family history of diabetes, smoking, menopausal hormone therapy use (women only), physical activity, alcohol intake, and Healthy Eating Index showed a significant association among men (*P* = 0.02) but a borderline of significance among women (*P* = 0.08). The pooled OR for T2D was 1.03 (1.01–1.05) per 1-point genetic score increase, adjusting for age and BMI. The ORs for T2D increased across the quartiles of the genetic score (*P* for trend = 0.014). Compared with those in the lowest quartile of the genetic score, participants in the highest quartile had an OR of 1.22 (1.02–1.42). Multivariate adjustment for age, family history of diabetes, smoking, menopausal hormone therapy use (women only), physical activity, alcohol intake, and Healthy Eating Index did not change the association. Further adjustment of the BMI genetic score did not significantly change the results (*P* = 0.01), whereas the association was abolished after further adjustment for the WHR (*P* = 0.12).

### Stratified Analyses by Lifestyle Risk Factors

We further examined whether the association between the genetic score and T2D risk varied across subgroups stratified by BMI and lifestyle risk factors for T2D (Supplementary Table 2). Although the associations appeared to be more pronounced in participants with a higher BMI and lower physical activity and who consumed modest levels of alcohol and currently smoked, no significant interaction between the genetic score and these risk factors in the combined samples of men and women was found (all *P* for interaction > 0.16). Results were similar in both sexes when analyses were performed in men and women separately (data not shown).

### Linear Relationship Between Genetic Predisposition Score and Risk of T2D

The central obesity genetic predisposition score showed a linear relationship with increasing T2D risk (*P* for linearity = 0.006 in the combined samples) (Supplementary Fig. 1).

**Table 1—Baseline characteristics among 2,422 men in HPFS and 3,221 women in NHS**

| | Men | | | Women | | |
|---|---|---|---|---|---|---|
| | Control | T2D case | *P* value | Control | T2D case | *P* value |
| *n* | 1,298 | 1,124 | — | 1,754 | 1,467 | — |
| Age (years) | 55 ± 8 | 55 ± 7 | 0.85 | 53 ± 8 | 53 ± 9 | 0.17 |
| WHR | 0.93 ± 0.05 | 0.96 ± 0.05 | <0.001 | 0.77 ± 0.07 | 0.84 ± 0.15 | <0.001 |
| BMI (kg/m$^2$) | 23.5 ± 3.9 | 27.4 ± 5.0 | <0.001 | 25.0 ± 2.7 | 29.7 ± 4.0 | <0.001 |
| Family history of T2D | 15.8 | 36.8 | <0.001 | 21.9 | 49.3 | <0.001 |
| Current smokers | 7.6 | 12.1 | <0.001 | 20.9 | 29.5 | 0.02 |
| Alcohol (g/day) | 12.1 ± 15.3 | 11.2 ± 16.1 | 0.18 | 6.6 ± 10.0 | 4.4 ± 9.1 | <0.001 |
| Healthy eating index | 45.8 ± 10.9 | 43.8 ± 10.5 | <0.001 | 42.7 ± 11.3 | 40.2 ± 10.4 | <0.001 |
| Physical activity* | 21.1 ± 25.2 | 14.6 ± 18.9 | <0.001 | 14.3 ± 18.7 | 11.8 ± 15.5 | <0.001 |
| Postmenopausal | — | — | — | 28.9 | 29.0 | 0.19 |
| Hypertension | 208 (16.3) | 359 (32.9) | <0.001 | 210 (12.9) | 467 (35.0) | <0.001 |
| High cholesterol | 140 (10.9) | 188 (17.2) | <0.001 | 283 (17.5) | 398 (29.8) | <0.001 |
| WHR genetic score | 14.0 ± 2.4 | 14.2 ± 2.3 | 0.06 | 14.2 ± 2.4 | 14.3 ± 2.5 | 0.10 |

Data are mean ± SD, %, or *n* (%). *MET hours per week for men and hours per week for women.

### The Joint Effects of BMI-GRS and WHR-GRS on Risk of T2D

We found that the GRS for BMI was significantly associated with risk of T2D in both the NHS ($P_{continuous}$ = 0.01) and the HPFS ($P_{continuous}$ = 0.02) cohorts (Fig. 2). We further examined the joint effects of BMI-GRS and WHR-GRS on risk of T2D (Fig. 3). Among individuals with the highest tertile of BMI-GRS, the risk of T2D was increased by 23%, 47%, and 46% within subgroups defined by increasing tertiles of WHR-GRS. Among individuals with the lowest tertile BMI-GRS, the OR for T2D was 0%, 0%, and 39% within subgroups defined by increasing tertiles of WHR-GRS.

## CONCLUSIONS

In two well-established, prospective, nested case-control studies of U.S. women and men, we examined the association between a genetic score comprising 14 independent central obesity–associated variants and risk of T2D. The results indicate that the genetic predisposition to central obesity was significantly associated with an increased T2D risk independent of BMI, dietary, and lifestyle risk factors.

Consistent with our previous analyses (22,26), we estimated a genetic score to evaluate the overall susceptibility to central obesity based on 14 well-established WHR-predisposing variants identified from GWAS. The current study shows robust associations between the central obesity genetic score and risk of T2D in pooled results. Although the genetic association with T2D was weaker in women than in men, there was no significant sex difference. The association between GRS and WHR was also weaker in women than in men. Of note, the findings may partly support the potential causal relationship between central obesity and T2D risk. Because genetic variants are randomly assigned and generally uncorrelated with environmental factors, the observed association between the genetic score and T2D is free of risk for reverse causation and less likely to be affected by confounding (27–29). The current findings provide consistent evidence

**Table 2—Association between the genetic predisposition score of the WHR and T2D risk**

| | Continuous score (per allele) | Quartile of genetic predisposition score | | | | *P* value for trend |
|---|---|---|---|---|---|---|
| | | Quartile 1 | Quartile 2 | Quartile 3 | Quartile 4 | |
| Men | | | | | | |
| *n* (case/control participants) | — | 230/327 | 284/318 | 311/328 | 299/325 | — |
| Score [median (range)] | — | 11.6 (6.27–12.6) | 13.47 (12.63–14.16) | 15.06 (14.19–15.96) | 17.09 (16–23.01) | — |
| OR (95% CI) | — | | | | | |
| Age and BMI adjusted | 1.03 (1.00–1.07) | 1 | 1.35 (1.05–1.74) | 1.40 (1.09–1.80) | 1.31 (1.02–1.68) | 0.04 |
| Multivariate adjusted* | 1.05 (1.01–1.09) | 1 | 1.33 (1.04–1.70) | 1.40 (1.10–1.78) | 1.43 (1.12–1.82) | 0.02 |
| + BMI score adjusted | 1.04 (1.00–1.08) | 1 | 1.39 (1.07–1.81) | 1.44 (1.11–1.87) | 1.40 (1.08–1.82) | 0.02 |
| + WHR adjusted | 1.03 (0.99–1.07) | 1 | 1.32 (1.00–1.76) | 1.31 (0.99–1.75) | 1.29 (0.97–1.73) | 0.12 |
| Women | | | | | | |
| *n* (case/control subjects) | | 339/436 | 344/441 | 382/441 | 402/436 | |
| Score [median (range)] | | 11.66 (5.33–12.78) | 13.69 (12.82–14.47) | 15.28 (14.5–16.12) | 17.31 (16.15–22.73) | |
| OR (95% CI) | | | | | | |
| Age and BMI adjusted | 1.03 (1.00–1.06) | 1 | 0.97 (0.78–1.21) | 1.17 (0.94–1.45) | 1.17 (0.94–1.45) | 0.05 |
| Multivariate adjusted* | 1.03 (0.99–1.06) | 1 | 0.93 (0.74–1.18) | 1.12 (0.89–1.41) | 1.13 (0.90–1.42) | 0.08 |
| + BMI score adjusted | 1.03 (0.99–1.07) | 1 | 0.89 (0.69–1.15) | 1.12 (0.87–1.44) | 1.14 (0.89–1.46) | 0.08 |
| + WHR adjusted | 0.99 (0.95–1.04) | 1 | 0.99 (0.73–1.34) | 0.96 (0.71–1.29) | 0.91 (0.68–1.23) | 0.88 |
| Combined OR (95% CI)† | | | | | | |
| Age and BMI adjusted | 1.03 (1.01–1.05) | 1 | 1.08 (0.89–1.26) | 1.25 (1.04–1.46) | 1.22 (1.02–1.42) | 0.01 |
| Multivariate adjusted* | 1.04 (1.01–1.07) | 1 | 1.05 (0.87–1.24) | 1.22 (1.02–1.43) | 1.24 (1.03–1.45) | 0.01 |
| + BMI score adjusted | 1.04 (1.01–1.06) | 1 | 1.03 (0.83–1.23) | 1.24 (1.01–1.46) | 1.24 (1.01–1.46) | 0.01 |
| + WHR adjusted | 1.01 (0.98–1.04) | 1 | 1.12 (0.88–1.36) | 1.09 (0.86–1.32) | 1.04 (0.82–1.26) | 0.12 |

*Adjusted for age, family history of diabetes, smoking, menopausal hormone therapy use (women only), physical activity, alcohol intake, and Healthy Eating Index. †Results of men and women were combined using inverse variance weights under a fixed model because no heterogeneity existed between women and men (all *P* for heterogeneity > 0.17).

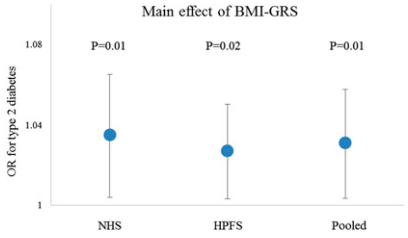


**Figure 2**—Association of GRS for BMI with risk of T2D among NHS and HPFS participants. Data are pooled from women and men and adjusted for age, genotype data source, family history of diabetes, smoking, alcohol intake, menopausal hormone therapy use (women only), Healthy Eating Index, and total energy intake.

from two cohorts to show associations between the WHR genetic score and risk of T2D.

Several lines of evidence support the potential causal relationship. The visceral depots of fat most likely contribute to the creation of insulin resistance, with additional effects of elevated fatty acids from central fat depots (3). The higher visceral adipose tissue-to-subcutaneous adipose tissue ratio, a measure of relative body fat distribution, is associated with higher dyslipidemia, insulin resistance, and prevalence of diabetes independent of overall obesity and absolute visceral fat mass (4). Therefore, the waist circumference and WHR have been described as superior measures in predicting diabetes risk in the Diabetes Prevention Program (30).

The potential causal relation between central obesity and diabetes is also supported by evidence from randomized clinical trials. For example, an intervention study showed that twice-weekly progressive resistance training significantly decreases abdominal fat and improves insulin sensitivity and glycemia in older men with T2D (31). A shift of fat distribution from visceral to adipose depots after pioglitazone treatment has been associated with improvements in hepatic and peripheral tissue sensitivity to insulin (32).

In the stratified analysis by lifestyle risk factors for T2D, the associations of WHR genetic score and risk of T2D appeared to be more pronounced in participants who had low physical activity and modest alcohol intake and who currently smoked, although there was no significant interaction between the genetic score and these risk factors. These results suggest that lifestyle factors might modify the genetic association with risk of T2D. High physical activity and smoking cessation may attenuate the genetic susceptibility to T2D. The current findings are in line with a previous study showing that genetic risk for T2D modifies the overall protective effect of physical activity on T2D (33). Furthermore, the joint effects of BMI and WHR genetic scores on T2D suggest that a high BMI genetic score might accentuate the WHR genetic effect on risk of T2D. Of note, the current results highlight the importance in considering the gene-environment interaction when studying the risk factors for diabetes.

The major strengths of this study are the prospective design, high-quality genetic data, and minimal population stratification (11). Although the central obesity genetic score captured the combined information from most of the established genetic variants for the WHR, these variants only explained ~4% variation of the WHR (7). This may explain the observed moderate effect of the genetic score on T2D risk.

We also acknowledge several limitations. First, although this nested case-control study was conducted in well-established prospective cohorts, some degree of measurement error in self-reported waist and hip circumferences and covariates is inevitable. However, the self-reported waist and hip circumferences were validated with high correlation, and we confirmed the association between genetic score and WHR in this study. Second, residual and unmeasured confounding from other lifestyle behaviors or factors is still possible. Third, although the meta-analysis of GWAS for WHR showed that most individual SNPs had a much stronger genetic association with WHR in women than in men, the study found a weak association of WHR genetic score with WHR and T2D among women. The reason for this discrepancy might be partly due to population variation, which was also observed in the original GWAS meta-analysis and warrants further investigation. Finally, the study was restricted to white participants. Therefore, further investigations in other ethnic groups are needed to validate the findings.

In conclusion, the findings indicate that the genetic predisposition to central adiposity, as estimated by the WHR genetic score, is associated with a higher risk of T2D among women and men from two prospective cohorts. This association is mediated by central obesity. The findings support a potential causal

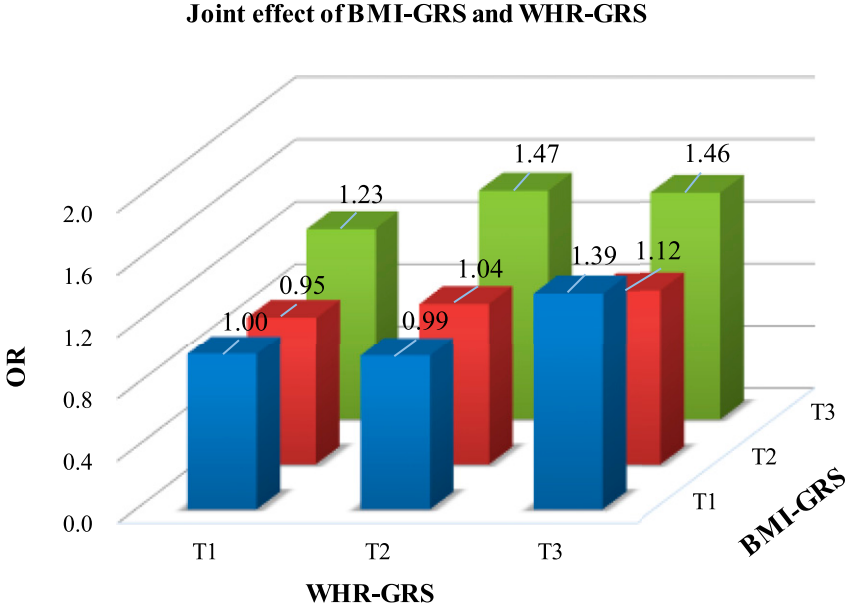


**Figure 3**—Joint effects of BMI-GRS and WHR-GRS on risk of T2D. Data are pooled from women and men and adjusted for age, genotype data source, family history of diabetes, smoking, alcohol intake, menopausal hormone therapy use (women only), Healthy Eating Index, and total energy intake.

relationship between central obesity and T2D.

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**Author Contributions.** T.H. and Q.Q. contributed to study concept and design; data acquisition, analysis, and interpretation; statistical analysis; drafting of the manuscript; and critical revision of the manuscript. Y.Z. and S.H.L. contributed to study concept and design and critical revision of the manuscript. J.E.M. contributed to the data acquisition and critical revision of the manuscript. F.B.H. contributed to the study administration, material support, and supervision. L.Q. contributed to the study concept and design; study administration, material support, and supervision; data acquisition, analysis, and interpretation; drafting of the manuscript; and critical revision of the manuscript. L.Q. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

## References

1. Morris AP, Voight BF, Teslovich TM, et al.; Wellcome Trust Case Control Consortium; Meta-Analyses of Glucose and Insulin-related traits Consortium (MAGIC) Investigators; Genetic Investigation of ANthropometric Traits (GIANT) Consortium; Asian Genetic Epidemiology Network–Type 2 Diabetes (AGEN-T2D) Consortium; South Asian Type 2 Diabetes (SAT2D) Consortium; DIAbetes Genetics Replication And Meta-analysis (DIAGRAM) Consortium. Large-scale association analysis provides insights into the genetic architecture and pathophysiology of type 2 diabetes. Nat Genet 2012;44:981–990
2. Qiao Q, Nyamdorj R. Is the association of type II diabetes with waist circumference or waist-to-hip ratio stronger than that with body mass index? Eur J Clin Nutr 2010;64:30–34
3. McKeigue PM, Shah B, Marmot MG. Relation of central obesity and insulin resistance with high diabetes prevalence and cardiovascular risk in South Asians. Lancet 1991;337:382–386
4. Snijder MB, Dekker JM, Visser M, et al. Associations of hip and thigh circumferences independent of waist circumference with the incidence of type 2 diabetes: the Hoorn Study. Am J Clin Nutr 2003;77:1192–1197
5. Vazquez G, Duval S, Jacobs DR Jr, Silventoinen K. Comparison of body mass index, waist circumference, and waist/hip ratio in predicting incident diabetes: a meta-analysis. Epidemiol Rev 2007;29:115–128
6. Björntorp P. Metabolic implications of body fat distribution. Diabetes Care 1991;14:1132–1143
7. Heid IM, Jackson AU, Randall JC, et al.; MAGIC. Meta-analysis identifies 13 new loci associated with waist-hip ratio and reveals sexual dimorphism in the genetic basis of fat distribution. Nat Genet 2010;42:949–960
8. Colditz GA, Manson JE, Hankinson SE. The Nurses' Health Study: 20-year contribution to the understanding of health among women. J Womens Health 1997;6:49–62
9. Dupuis J, Langenberg C, Prokopenko I, et al.; DIAGRAM Consortium; GIANT Consortium; Global BPgen Consortium; Anders Hamsten on behalf of Procardis Consortium; MAGIC Investigators. New genetic loci implicated in fasting glucose homeostasis and their impact on type 2 diabetes risk. Nat Genet 2010;42:105–116
10. Cornelis MC, Qi L, Zhang C, et al. Joint effects of common genetic variants on the risk for type 2 diabetes in U.S. men and women of European ancestry. Ann Intern Med 2009;150:541–550
11. Levitt NS, Lambert EV. The foetal origins of the metabolic syndrome–a South African perspective. Cardiovasc J S Afr 2002;13:179–180
12. Manson JE, Rimm EB, Stampfer MJ, et al. Physical activity and incidence of non-insulin-dependent diabetes mellitus in women. Lancet 1991;338:774–778
13. Hu FB, Leitzmann MF, Stampfer MJ, Colditz GA, Willett WC, Rimm EB. Physical activity and television watching in relation to risk for type 2 diabetes mellitus in men. Arch Intern Med 2001;161:1542–1548
14. National Diabetes Data Group. Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. Diabetes 1979;28:1039–1057
15. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 1997;20:1183–1197
16. Patterson N, Price AL, Reich D. Population structure and eigenanalysis. PLoS Genet 2006;2:e190
17. Kotsopoulos J, Baer HJ, Tworoger SS. Anthropometric measures and risk of epithelial ovarian cancer: results from the Nurses' Health Study. Obesity (Silver Spring) 2010;18:1625–1631
18. Rimm EB, Stampfer MJ, Colditz GA, Chute CG, Litin LB, Willett WC. Validity of self-reported waist and hip circumferences in men and women. Epidemiology 1990;1:466–473
19. Chiuve SE, Fung TT, Rimm EB, et al. Alternative dietary indices both strongly predict risk of chronic disease. J Nutr 2012;142:1009–1018
20. Willett W, Stampfer MJ, Bain C, et al. Cigarette smoking, relative weight, and menopause. Am J Epidemiol 1983;117:651–658
21. Bahadoran Z, Mirmiran P, Hosseini-Esfahani F, Azizi F. Fast food consumption and the risk of metabolic syndrome after 3-years of follow-up: Tehran Lipid and Glucose Study. Eur J Clin Nutr 2013;67:1303–1309
22. Qi Q, Chu AY, Kang JH, et al. Fried food consumption, genetic risk, and body mass index: gene-diet interaction analysis in three US cohort studies. BMJ 2014;348:g1610
23. Rung J, Cauchi S, Albrechtsen A, et al. Genetic variant near IRS1 is associated with type 2 diabetes, insulin resistance and hyperinsulinemia. Nat Genet 2009;41:1110–1115
24. Been LF, Hatfield JL, Shankar A, et al. A low frequency variant within the GWAS locus of MTNR1B affects fasting glucose concentrations: genetic risk is modulated by obesity. Nutr Metab Cardiovasc Dis 2012;22:944–951
25. Durrleman S, Simon R. Flexible regression models with cubic splines. Stat Med 1989;8:551–561
26. Qi Q, Chu AY, Kang JH, et al. Sugar-sweetened beverages and genetic risk of obesity. N Engl J Med 2012;367:1387–1396
27. Qi L. Mendelian randomization in nutritional epidemiology. Nutr Rev 2009;67:439–450
28. Leong A, Rehman W, Dastani Z, et al.; METASTROKE. The causal effect of vitamin D binding protein (DBP) levels on calcemic and cardiometabolic diseases: a Mendelian randomization study. PLoS Med 2014;11:e1001751
29. Yaghootkar H, Lamina C, Scott RA, et al.; GENESIS Consortium; RISC Consortium. Mendelian randomization studies do not support a causal role for reduced circulating adiponectin levels in insulin resistance and type 2 diabetes. Diabetes 2013;62:3589–3598
30. Diabetes Prevention Program Research Group. Relationship of body size and shape to the development of diabetes in the diabetes prevention program. Obesity (Silver Spring) 2006;14:2107–2117
31. Ibañez J, Izquierdo M, Argüelles I, et al. Twice-weekly progressive resistance training decreases abdominal fat and improves insulin sensitivity in older men with type 2 diabetes. Diabetes Care 2005;28:662–667
32. Miyazaki Y, Mahankali A, Matsuda M, et al. Effect of pioglitazone on abdominal fat distribution and insulin sensitivity in type 2 diabetic patients. J Clin Endocrinol Metab 2002;87:2784–2791
33. Klimentidis YC, Chen Z, Arora A, Hsu CH. Association of physical activity with lower type 2 diabetes incidence is weaker among individuals at high genetic risk. Diabetologia 2014;57:2530–2534