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

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.
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vided written informed consent.

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 have 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 ≥ 7.8 mmol/L (140 mg/dL), a random plasma glucose level of ≥ 11.1 mmol/L (200 mg/dL), or a plasma glucose level 2 h after an oral glucose tolerance test of ≥ 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).

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 GWASs (7). We assumed that each SNP in the panel acts independently in
results were 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 ≤ 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).

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 were 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 were 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).
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 ($P_{\text{continuous}} = 0.01$) and the HPFS ($P_{\text{continuous}} = 0.02$) 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).
current findings provide consistent evidence 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, modest alcohol intake, and 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 GWASs 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 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
relationship between central obesity and T2D.

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