Genetic Predisposition to High Blood Pressure Associates With Cardiovascular Complications Among Patients With Type 2 Diabetes: Two Independent Studies

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(Article begins on next page)
Hypertension and type 2 diabetes (T2D) commonly coexist, and both conditions are major risk factors for cardiovascular disease (CVD). We aimed to examine the association between genetic predisposition to high blood pressure and risk of CVD in individuals with T2D. The current study included 1,005 men and 1,299 women with T2D from the Health Professionals Follow-up Study and Nurses’ Health Study, of whom 732 developed CVD. A genetic predisposition score was calculated on the basis of 29 established blood pressure–associated variants. The genetic predisposition score showed consistent associations with risk of CVD in men and women. In the combined results, each additional blood pressure–increasing allele was associated with a 6% increased risk of CVD (odds ratio [OR] 1.06 [95% CI 1.03–1.10]). The OR was 1.62 (1.22–2.14) for risk of CVD comparing the extreme quartiles of the genetic predisposition score. The genetic association for CVD risk was significantly stronger in patients with T2D than that estimated in the general populations by a meta-analysis (OR per SD of genetic score 1.22 [95% CI 1.10–1.35] vs. 1.10 [1.08–1.12]; $F^2$ = 71%). Our data indicate that genetic predisposition to high blood pressure is associated with an increased risk of CVD in individuals with T2D. Diabetes 61:3026–3032, 2012

**RESEARCH DESIGN AND METHODS**

The HPFS is a prospective cohort study of 51,529 U.S. male health professionals who were 40–75 years of age at study inception in 1986 (9). Between 1993 and 1999, 18,159 men provided blood samples. The NHS is a prospective cohort study of 121,700 female registered nurses who were 30–55 years of age at study inception in 1976 (10). A total of 32,826 women provided blood samples between 1989 and 1990. In the current analysis for the NHS, 1980 was defined as the baseline year because diet was first assessed since that year. In both cohorts, information about medical history, lifestyle, and disease has been collected biennially by self-administered questionnaires.

For the current study, NHS and HPFS participants were T2D case subjects who had genotype data from the NHS and HPFS T2D GWAS (11). T2D case subjects were defined according to self-reported T2D confirmed by a validated supplementary questionnaire. For case subjects before 1998, we used the National Diabetes Data Group criteria to define T2D (12), which included one of the following: one or more classic symptoms (excessive thirst, polyuria, weight loss, hunger, pruritus, or coma) plus fasting plasma glucose level of ≥7.8 mmol/L (140 mg/dL), random plasma glucose level of ≥11.1 mmol/L (200 mg/dL), or 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 (as described previously) on different occasions in the absence of symptoms; or treatment with hypoglycemic medication (insulin or oral hypoglycemic agent). The validity of this method has been confirmed (13). We used the American Diabetes Association diagnostic criteria for diabetes diagnosis from 1998 onward (14). 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). CVD cases were defined as coronary heart disease (CHD) (fatal or nonfatal myocardial infarction, coronary artery bypass grafting, or percutaneous transluminal coronary angioplasty) or stroke (fatal or nonfatal). Nonfatal
myocardial infarction was confirmed by review of medical records using
the criteria of the World Health Organization of symptoms plus either
electrocardiographic changes or elevated levels of cardiac enzymes. Nonfatal stroke
was confirmed by review of medical records using the criteria of the National
Survey of Stroke (15). Fatal myocardial infarction and fatal stroke cases were
confirmed by review of medical records or autopsy reports with the permission
of the next of kin. Physicians blinded to risk factor status reviewed the medical
records. Only diabetic patients who were diagnosed with CVD after the
diagnosis of T2D through 2008 were included as cardiovascular complication
case subjects. Control subjects were defined as those free of CVD after the
diagnosis of T2D through 2008. Finally, a total of 1,005 men and 1,299 women with
T2D of European ancestry were included: 380 men (551 CHD and 292 stroke) and
347 women (292 CHD and 55 stroke) with cardiovascular complications, and, 1,572 (625 men and 497 women) non-CVD control subjects. The study was
approved by the Human Research Committee at the Brigham and Women’s Hospital,
and all participants provided written informed consent.

Genotyping and imputation. DNA was extracted from the buffy coat fraction
of centrifuged blood using a commercially available kit (QIAamp Blood kit; Qiagen,
Chatsworth, CA). We selected 29 single nucleotide polymorphisms (SNPs)
associated with systolic and/or diastolic blood pressure at a genomewide
significance level (Supplementary Table 1) (5). SNP genotyping and
imputation have previously been described in detail (11). Briefly, samples were
genotyped and analyzed using the Affymetrix Genome-Wide Human 6.0
array (Affymetrix; Santa Clara, CA) and the Birdseed calling algorithm. 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.
Most of the SNPs included in the genetic predisposition score were directly
genotyped (12 SNPs) or had a high imputation quality score (15 SNPs, MACH
r^2 ≥ 0.8), and 2 SNPs showed a moderate imputation quality score
(rs1310722, r^2 = 0.67 [HPFS] and 0.69 [NHS]; rs2521501, r^2 = 0.60 [both NHS
and HPFS]) (Supplementary Table 1).

Genetic predisposition score calculation. Genetic predisposition score was
calculated on the basis of the 29 SNPs by the previously reported weighted
method (5,16). Each SNP was weighted by the average effect size
(β-coefficient) for systolic and diastolic blood pressure obtained from the
reported GWAS (5). The genetic predisposition score was calculated by mul-
tiplying each β-coefficient by the number of corresponding risk alleles and
then summing the products. Because this produced a score out of 26,425
(twice the sum of the β-coefficients), the values were divided by 26,425 and
multiplied by 58 (the total number of the risk alleles) to make the genetic
predisposition score easier to interpret. Each point of the genetic pre-
disposition score corresponded to each blood pressure–increasing allele.

Assessment of dietary and lifestyle factors. Information about anthropo-
metric data, smoking status, physical activity, menopausal status, and post-
menopausal hormone therapy (women only); family history of myocardial
infarction; and medical and disease history was derived from the baseline
questionnaires (9,10). Participants were asked to report whether a clinician had
made a diagnosis of hypertension during the preceding 2 years and were also
asked whether they had undergone a physical examination or screening ex-
amination. Self-reported hypertension was shown to be highly reliable in the
NHS and HPFS (17,18). In a subset of women who reported hypertension,
medical record review confirmed a documented systolic and diastolic blood
pressure >140 and 90 mmHg, respectively, in 100% and >160 and 95 mmHg in
77%; additionally, self-reported hypertension was predictive of subsequent
cardiovascular events (17). BMI was calculated as weight in kilograms divided
by the square of height in meters. For men, physical activity was expressed as
METs per week by using the reported time spent on various activities, weighting
each activity by its intensity level. For women, physical activity was expressed
as hours per week because MET task hours were not measured at baseline in
the NHS. The validity of the self-reported body weight and physical activity data
has previously been described (19–21). Use of nonnarcotic analgesics (use of
aspirin in the NHS and use of aspirin and acetaminophen in the HPFS) was
reported on the baseline questionnaires. Alcohol intake and other detailed di-
etary information was collected from semiquantitative food-frequency ques-
tionnaires at baseline. The reproducibility and validity of the food-frequency
questionnaires have previously been reported (22,23). Based on the diet pre-
scribed in the DASH trial (24), a DASH score was constructed based on high
intake of fruits, vegetables, nuts and legumes, low-fat dairy products, and whole
grains and low intake of sodium, sweetened beverages, and red and processed
meats (25). The intake of supplemental folic acid in multivitamins or in isolated
form was determined by the brand, type, and frequency of reported use.

Statistical analyses. χ^2 tests and t tests were used for comparison
of proportions and means of baseline characteristics between CVD case
and control subjects. We used logistic regression to estimate odd ratios (ORs)
and 95% CIs for CVD risk, adjusting for age and BMI. In multivariable analysis,
we further adjusted for family history of myocardial infarction (yes or no), smoking
(never, past, or current), menopausal status (pre- or postmenopausal [never,
past, or current hormone use] [women only]), physical activity (quartiles),
alcohol intake (0, 0.1–4.9, 5.0–9.9 10.0–14.9 or ≥ 15.0 g/day), DASH diet score
(quartiles), nonnarcotic analgesics use (yes or no), and supplemental folic acid
use (yes or no). Results in women and men were pooled by using inverse
variance weights under a fixed model, as there was no heterogeneity. Linear
relation analysis between the genetic predisposition score (as continuous
variables) and risk of CVD was performed by using a restricted cubic spline
regression model (26). In secondary analyses, we tested whether the association
between the genetic predisposition score and risk of CVD was modified by
self-reported hypertension status, BMI, physical activity, DASH diet score, alcohol
intake, use of nonnarcotic analgesic, and use of supplemental folic acid using
analyses stratified by these factors and by including the respective interaction
terms in the models. Similar analyses were repeated for the association between
the genetic predisposition score and CHD risk. In addition, we performed
a meta-analysis to compare the result in patients with T2D with that in general
populations (i.e., participant groups not restricted to patients with diabetes). All
reported P values are nominal and two sided. Statistical analyses were performed
in STATA version 10.0 (StataCorp, College Station, TX) or SAS 9.1 (SAS
Institute, Cary, NC).

RESULTS

Characteristics of study participants. Table 1 shows the characteristics of study participants. Among diabetic men and women, CVD case subjects were older, had

<table>
<thead>
<tr>
<th>Variables</th>
<th>Men</th>
<th>CVD case subjects</th>
<th>Women</th>
<th>CVD case subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control subjects</td>
<td></td>
<td>Control subjects</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>625</td>
<td>380</td>
<td>947</td>
<td>352</td>
</tr>
<tr>
<td>Age (years)</td>
<td>54 ± 8</td>
<td>58 ± 8</td>
<td>46 ± 7</td>
<td>52 ± 6</td>
</tr>
<tr>
<td>BMI (kg/m^2)</td>
<td>27.6 ± 4.0</td>
<td>28.1 ± 4.3</td>
<td>28.1 ± 5.1</td>
<td>29.7 ± 5.8</td>
</tr>
<tr>
<td>Family history of myocardial</td>
<td>34.1 ± 4.5</td>
<td>40.5</td>
<td>28.7 ± 5.3</td>
<td>31.0</td>
</tr>
<tr>
<td>infarction</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smokers</td>
<td>11.6 ± 6.0</td>
<td>11.1</td>
<td>22.9 ± 5.9</td>
<td>29.3</td>
</tr>
<tr>
<td>Hypertension</td>
<td>25.4 ± 5.9</td>
<td>45.8</td>
<td>10.8 ± 4.9</td>
<td>16.8</td>
</tr>
<tr>
<td>Alcohol (g/day)</td>
<td>11.4 ± 15.4</td>
<td>10.3 ± 16.2</td>
<td>4.8 ± 9.5</td>
<td>3.8 ± 8.7</td>
</tr>
<tr>
<td>Physical activity</td>
<td>14.8 ± 18.7</td>
<td>14.9 ± 20.1</td>
<td>3.9 ± 2.8</td>
<td>3.3 ± 2.6</td>
</tr>
<tr>
<td>DASH score</td>
<td>23.4 ± 5.2</td>
<td>24.3 ± 5.2</td>
<td>23.6 ± 4.4</td>
<td>24.0 ± 4.4</td>
</tr>
<tr>
<td>Supplemental folic acid intake</td>
<td>105 ± 203</td>
<td>139 ± 245</td>
<td>90 ± 193</td>
<td>108 ± 189</td>
</tr>
<tr>
<td>Use of nonnarcotic analgesics</td>
<td>36.8 ± 4.3</td>
<td>43.4</td>
<td>43.0 ± 4.3</td>
<td>50.8</td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>44.1 ± 9.4</td>
<td></td>
<td>69.9</td>
<td></td>
</tr>
<tr>
<td>Genetic predisposition score</td>
<td>30.7 ± 3.2</td>
<td>31.3 ± 3.2</td>
<td>30.9 ± 3.3</td>
<td>31.3 ± 3.1</td>
</tr>
</tbody>
</table>

Data are means ± SD or % unless otherwise indicated. *MET task hours per week for men and hours per week for women.
higher BMI, consumed less alcohol, and were more likely to have a family history of myocardial infarction, have self-reported hypertension, and use nonnarcotic analgesics than non-CVD control subjects.

The genetic predisposition score ranged from 18.1 to 40.8, and the mean ± SD was 31.0 ± 3.2 in both women and men. After adjustment for age and BMI, the genetic predisposition score was significantly associated with self-reported hypertension in both men and women. The ORs associated with each additional point of the score, which corresponds to one additional blood pressure-increasing allele, were 1.09 (95% CI 1.05–1.14) in men and 1.05 (1.01–1.09) in women.

**Genetic predisposition score and CVD risk.** As shown in Table 2, the ORs for CVD risk were 1.06 (95% CI 1.02–1.10) and 1.05 (1.01–1.09) with each additional point of the genetic predisposition score in diabetic men and women, respectively, adjusted for age and BMI. Multivariable adjustment did not change the associations. With no sex differences in ORs (all *P* for heterogeneity >0.26), we combined the results from men and women by using meta-analysis under a fixed-effects model. Each additional point of the genetic predisposition score was associated with a 6% increased risk of developing CVD (OR 1.06 [95% CI 1.03–1.10]), adjusted for age, BMI, and other dietary and lifestyle risk factors. The ORs for CVD risk significantly increased across the quartiles of the genetic predisposition score (*P* for trend = 0.0001). Compared with those in the lowest quartile, participants in the highest quartile of the genetic predisposition score had an OR of 1.62 (95% CI 1.22–2.14), adjusted for age, BMI, and other dietary and lifestyle risk factors. The association was attenuated but remained significant after further adjustment for self-reported hypertension (*P* for trend = 0.002). We further examined the association between the genetic predisposition score and CVD risk stratified by baseline hypertension status (Table 3). Although the association was more pronounced in patients with hypertension than in those without hypertension, there was no significant interaction (*P* for interaction = 0.19). In addition, we also used a restricted cubic spline regression model to investigate the association continuously (Fig. 1). The genetic predisposition score showed a linear relationship with increasing risk of CVD (*P* for linearity = 0.002, 0.028, and 0.0001 in men, women, and men and women combined, respectively).

Results were similar when the outcome was restricted to CHD. The ORs for CHD risk per blood pressure-increasing allele were 1.07 (95% CI 1.02–1.12) and 1.05 (1.00–1.10) in diabetic men and women, respectively, adjusted for age, BMI, and other dietary and lifestyle risk factors. In the combined results of men and women, the multivariable-adjusted OR was 1.55 (1.16–2.07) for CHD risk by comparing extreme quartiles of the genetic predisposition score (*P* for trend = 0.0002). Restricted cubic spline regression analysis also showed that there was a linear relationship between the genetic predisposition score and CHD risk (*P* for linearity = 0.0007).

**Stratified analyses by dietary and lifestyle risk factors.** We next examined whether the association between the genetic predisposition to high blood pressure and CVD risk varied across subgroups of the population stratified by dietary and lifestyle risk factors for hypertension. In combined results from men and women, we observed consistent associations across subgroups of the population stratified by BMI, physical activity, DASH diet score, alcohol intake, nonnarcotic analgesics use, and supplemental folic acid use (Table 3). There was no significant interaction between the genetic predisposition score and these dietary and lifestyle risk factors (all *P* for interaction >0.39). Results were similar in both sexes when we performed analyses in men and women separately (data not shown).

**Genetic effects in patients with diabetes compared with general populations.** We then compared our results in patients with T2D with data in general populations (i.e., participant groups that were not restricted to patients with diabetes) (Fig. 2). We used fixed-effects meta-analysis to combine the risk ratios for CVD (stroke or CHD) previously reported in such populations (5) and the risk ratios derived from a GWAS of CHD performed in nondiabetic participants of HPFS and NHS (Supplementary Data) (27).

### Table 2

<table>
<thead>
<tr>
<th></th>
<th>Quartile 1</th>
<th>Quartile 2</th>
<th>Quartile 3</th>
<th>Quartile 4</th>
<th><em>P</em> for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N (case/control subjects)</td>
<td>67/157</td>
<td>87/155</td>
<td>108/157</td>
<td>118/156</td>
<td></td>
</tr>
<tr>
<td>Score median (range)</td>
<td>27.0 (20.0–28.5)</td>
<td>29.7 (28.6–30.7)</td>
<td>31.8 (30.8–32.7)</td>
<td>34.2 (32.8–39.6)</td>
<td></td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age and BMI adjusted</td>
<td>1.06 (1.02–1.10)</td>
<td>1.00</td>
<td>1.32 (0.88–1.97)</td>
<td>1.61 (1.09–2.37)</td>
<td>1.74 (1.18–2.55)</td>
</tr>
<tr>
<td>Multivariable adjusted*</td>
<td>1.07 (1.02–1.11)</td>
<td>1.00</td>
<td>1.32 (0.88–1.99)</td>
<td>1.05 (1.11–2.46)</td>
<td>1.72 (1.17–2.55)</td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N (case/control subjects)</td>
<td>75/236</td>
<td>82/238</td>
<td>101/236</td>
<td>94/237</td>
<td></td>
</tr>
<tr>
<td>Score median (range)</td>
<td>27.2 (18.2–28.5)</td>
<td>29.8 (28.6–30.9)</td>
<td>31.9 (31.0–33.2)</td>
<td>34.9 (33.3–40.8)</td>
<td></td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age and BMI adjusted</td>
<td>1.05 (1.01–1.09)</td>
<td>1.00</td>
<td>1.02 (0.70–1.49)</td>
<td>1.50 (1.03–2.17)</td>
<td>1.37 (0.94–1.98)</td>
</tr>
<tr>
<td>Multivariable adjusted*</td>
<td>1.06 (1.01–1.11)</td>
<td>1.00</td>
<td>0.95 (0.62–1.44)</td>
<td>1.45 (0.97–2.19)</td>
<td>1.50 (1.00–2.26)</td>
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<tr>
<td>Combined OR (95% CI)†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age and BMI adjusted</td>
<td>1.05 (1.02–1.08)</td>
<td>1.00</td>
<td>1.15 (0.87–1.52)</td>
<td>1.55 (1.18–2.03)</td>
<td>1.53 (1.17–2.00)</td>
</tr>
<tr>
<td>Multivariable adjusted*</td>
<td>1.06 (1.03–1.10)</td>
<td>1.00</td>
<td>1.12 (0.84–1.51)</td>
<td>1.55 (1.17–2.07)</td>
<td>1.62 (1.22–2.14)</td>
</tr>
</tbody>
</table>

*Adjusted for age, BMI, family history of myocardial infarction, smoking, menopausal status (women only), physical activity, alcohol intake, DASH diet score, nonnarcotic analgesics use, and supplemental folic acid use. †Results were combined between women and men using inverse variance weights under a fixed model, as there was no heterogeneity between women and men (all *P* for heterogeneity >0.26).
Self-reported hypertension

In two independent studies of men and women with T2D, we examined the association between a genetic predisposition score and CVD risk. The risk ratios per SD of the genetic predisposition score were approximately 1.1 among these studies, with a combined risk ratio of 1.10 (95% CI 1.08–1.12) and no heterogeneity ($I^2 = 0\%$). We recalculated the CVD risk per SD of the genetic predisposition score in our T2D patients and observed a stronger effect of the genetic predisposition score on CVD risk (OR 1.22 [95% CI 1.10–1.35]) compared with that in the general populations. The associations between the genetic predisposition score and CVD risk showed significant heterogeneity between the diabetic and the general populations ($I^2 = 71\%$, $P$ for heterogeneity = 0.045).

**DISCUSSION**

In two independent studies of men and women with T2D, we examined the association between a genetic predisposition score, composed of 29 independent high blood pressure–predisposing variants, and risk of CVD. Our highly consistent results in men and women indicate that the genetic predisposition to high blood pressure may significantly increase risk of cardiovascular complications in diabetic patients, independent of dietary and lifestyle risk factors for hypertension.

Because each individual SNP may have a moderate genetic effect and only explain a small proportion of the variation of blood pressure, we examined the collective contribution of the multiple genetic variants by computing a genetic predisposition score, which emphasized the overall genetic susceptibility to high blood pressure. As greater genetic variance was explained by multiple variants, the genetic predisposition might be estimated more accurately by using this approach. In diabetic patients, each additional blood pressure–increasing allele in the genetic predisposition score was associated with a 6% increased risk of CVD. By accumulation, individuals in the highest quartile of the score had a 60% greater risk of developing CVD than those in the lowest quartile. Therefore, this approach provides a broader characterization of the individual’s genetic risk profile, which may be useful for identifying a substantial proportion of people with a high genetic risk of CVD.

High blood pressure is one of the most important risk factors for CVD risk in patients with T2D (2–4). That the observed genetic associations should be unaffected by confounding from environmental factors and free of reverse causation (28) suggests that there is a causal relationship between the genetic predisposition to high blood pressure and increased risk of CVD. This is in line with the fact that hypertension plays a causal role in the development of CVD, which has been supported by several controlled clinical trials indicating that control of blood pressure significantly reduces the cardiovascular complications in patients with T2D (29–35), although it remains debatable whether tight control of blood pressure offers additional benefits in the reduction of cardiovascular risk compared with usual control of blood pressure (35–37).

One of our novel findings is that the association between the high blood pressure genetic predisposition score and risk of CVD was significantly stronger in patients with T2D...
than that previously reported in various general populations (5). In the general population, each additional SD of the genetic predisposition score may increase CVD risk by ~10%, while the increment of CVD risk per SD of the genetic predisposition score was 22% in patients with T2D. This finding is consistent with some previous data from clinical trials in which blood pressure–lowering reduced the rate of CVD events more in patients with T2D than in those without diabetes (31,33). Given a comparable amount in reduction of systolic blood pressure, the risk reduction in CVD mortality was 76% in diabetic patients versus 13% in those without diabetes (33). Moreover, the effect of the genetic predisposition score of high blood pressure on CVD risk was even stronger than our previously observed effect of the T2D genetic predisposition score (~3% increased CVD risk per diabetes risk allele) in the same diabetic populations. Consistently, in the UK Prospective Diabetes Study, blood pressure control was found to be more effective than glycemic control at reducing cardiovascular events in patients with T2D (29).

Our current genetic association study lends support to this notion and also suggests that diabetic patients with a higher hypertension genetic predisposition score may need more blood pressure management to reduce CVD risk, although the optimal blood pressure goal for diabetic patients remains unknown (35–37).

The major strengths of our study include the consistent findings in two independent studies of diabetic patients, high-quality data of multiple genetic variants, and minimal population stratification (11). Several limitations need to be acknowledged. Blood pressure levels were not measured in our study samples; thus, we did not test the association between the genetic predisposition score and blood pressure, but we confirmed the association with hypertension in patients with T2D. The associations of these genetic variants with hypertension and blood pressure have been well established in the previous GWAS (5). Although our genetic predisposition score captured the combined information from the established genetic variants for blood pressure thus far, it may account for only
a small amount of variation of blood pressure (5). Because of the relative small number of stroke case subjects, we did not perform the association analysis for stroke risk separately. However, we observed similar genetic effect on risk of CVD (stroke and CHD) and CHD. The previously reported results for risk of stroke and coronary artery disease were also similar in the general populations (5). In addition, our study only includes diabetic patients of European ancestry, and it remains to be examined whether the results are generalizable to other ethnic groups.

In conclusion, we found that the genetic predisposition to high blood pressure was significantly associated with an increased risk of cardiovascular complications among men and women with T2D, independent of dietary and lifestyle risk factors. The observed genetic association in diabetic patients was stronger than that in the general populations. These results improve our understanding of the genetic predisposition to high blood pressure and risk of CVD and also support the causal role of high blood pressure in the development of CVD. Treatment of high blood pressure is important and needs to be a therapeutic priority in patients with T2D, particularly in those with a high genetic risk.

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Q.Q. designed the study, researched data, and wrote the manuscript. J.P.F., M.K.J., A.F., G.C.C., E.B.R., and F.B.H. contributed to discussion and edited and reviewed the manuscript. L.Q. designed the study, reviewed data, contributed to discussion, and edited and reviewed 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.

The authors thank all the participants of the NHS and the HPFS for their continued cooperation.

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