Effect of Diet Quality and Genetic Predisposition on Hemoglobin A_{1c} and Type 2 Diabetes Risk: Gene-Diet Interaction Analysis of 357,419 Individuals

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OBJECTIVE

To assess the interactions between diet quality and genetic predisposition to incident type 2 diabetes (T2D).

RESEARCH DESIGN AND METHODS

Between 2006 and 2010, 357,419 participants with genetic and complete dietary data from the UK Biobank were enrolled and prospectively followed up to 2017. The genetic risk score (GRS) was calculated on the basis of 424 variants associated with T2D risk, and a higher GRS indicates a higher genetic predisposition to T2D. The adherence to a healthy diet was assessed by a diet quality score comprising 10 important dietary components, with a higher score representing a higher overall diet quality.

RESULTS

There were 5,663 incident T2D cases documented during an average of 8.1 years of follow-up. A significant negative interaction was observed between the GRS and the diet quality score. After adjusting for major risk factors, per SD increment in the GRS and the diet quality score was associated with a 54% higher and a 9% lower risk of T2D, respectively. A simultaneous increment of 1 SD in both the diet quality score and GRS was additionally associated with a 3% lower T2D risk due to the antagonistic interaction. In categorical analyses, a sharp reduction of 23% in T2D risk associated with a 1-SD increment in the diet quality score was detected among participants in the extremely high GRS group (GRS >95%). We also observed a strong negative interaction between the GRS and the diet quality score on the blood HbA_{1c} level at baseline ($P < 0.001$).

CONCLUSIONS

The adherence to a healthy diet was associated with more reductions in blood HbA_{1c} levels and subsequent T2D risk among individuals with a higher genetic risk. Our findings support tailoring dietary recommendations to an individual's genetic makeup for T2D prevention.

Type 2 diabetes (T2D) has reached pandemic levels, affecting 463 million people worldwide (1). Studies have demonstrated that T2D originates from the complex

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interplay between both genetic and lifestyle factors, including diet (2,3). The so-called gene-diet interactions are defined as a joint effect of genetic and dietary exposures on the outcome, which is higher or lower than the sum of their individual effects (4). Previous evidence has shown considerable individuals' variability in response to dietary prevention or intervention for T2D, which may partly result from genetic variation and interactions between diet and genes (5). Therefore, elucidating the gene-diet interactions on T2D development could help us identify the susceptible populations and develop personalized nutrition guidance for more effective prevention of T2D. Although the interactions between specific dietary components and certain genetic variants on the risk of T2D have been indicated in some studies (6–8), limited findings have been replicated (9). Current dietary guidelines for T2D prevention and management have emphasized adopting an overall healthy eating pattern rather than focusing on individual nutrients or single food item (10–12). However, it remains unclear whether the importance of adhering to a healthy diet depends on an individual's genetic makeup.

In the past few years, successive waves of large-scale genome-wide association studies (GWAS) have established >500 loci associated with T2D risk (13–16). Superior to single nucleotide polymorphisms (SNPs), aggregating T2D-associated SNPs into genetic risk scores (GRS) can increase the predictability of incident T2D and enable a continuous measure of the genetic risk (16,17). Thus, generating GRS is more appropriate to examine gene-diet interactions on T2D and should be more intensively used (9).

Consistent evidence demonstrates that healthy dietary patterns, such as the Mediterranean diet and the Dietary Approach to Stop Hypertension (DASH) diet, could reduce the risk of developing T2D (18–20). These healthful dietary patterns are characterized by high consumption of whole grains, vegetables, fruits, legumes, and nuts and low consumption of refined grains, processed red meats, and sugar-sweetened beverages (21). Up to now, few studies have evaluated the interactions between overall diet quality and genetic predisposition to T2D. Although a nested case-control study showed that the genetic risk of developing T2D was enhanced by a Western dietary pattern in male health professionals (22), other studies failed to detect a significant interaction between the overall diet quality and the GRS (23–25). The major shortcoming of these previous studies is the inadequate sample size ($n < 30{,}000$), which may reduce statistical power to detect significant interactions (9). In addition, GRS constructed by fewer SNPs may provide a less accurate representation of the genetic risk for T2D. Overall, sparse scientific evidence supports tailoring dietary recommendations to individual genetic risk profiles for T2D prevention. A large sample size of population-wide biobanks is needed to identify the interactions between diet quality and genetic susceptibility to T2D (26).

In this study, we first created a diet quality score according to recent dietary and policy priorities for cardiometabolic health (27). Then, we examined the interaction between the diet quality score and the genetic predisposition to T2D, as captured by the GRS, on hemoglobin A_{1c} levels and T2D development in 357,419 adults from the UK Biobank study.

RESEARCH DESIGN AND METHODS

Study Population

The UK Biobank is a large prospective cohort consisting of ~0.5 million participants aged 40–69 years and recruited across the U.K. from 2006 to 2010 (28, 29). At baseline, participants were required to complete a series of touchscreen questionnaires, provide biological samples, and undergo various physical assessments. All participants gave informed consent at recruitment. The UK Biobank study was approved by the North West Multi-centre Research Ethics Committee (Manchester, U.K.).

The UK Biobank data set for this project included 502,505 participants. Exclusion criteria included the withdrawal of informed consent, patients with cardiovascular disease, cancer or diabetes at baseline, lack of genetic data or discordance between reported and genotype-inferred sex, not of White British descent, and those with incomplete data on important dietary components used for assessing the overall diet quality. Finally, 357,419 individuals were selected for the present analysis (Supplementary Fig. 1).

Genotyping and SNP Selection

A detailed description of the genotyping process, imputation, and quality control in the UK Biobank study has been published (30). Briefly, the SNPs were genotyped using the custom UK Biobank Lung Exome Variant Evaluation Axiom (807, 411 markers) or the UK Biobank Axiom array (825,927 markers) and then imputed using merged UK10K and 1000 Genomes Project phase 3 panels as the reference panel. We selected 424 SNPs representative of loci associated with T2D (Supplementary Table 1) based on the ancestry-specific analysis of Europeans in the largest genome-wide multiethnic meta-analysis (13). The SNPs missing in UK Biobank data were excluded, and no proxy SNPs were used.

Calculation of the GRS for T2D

A previously described weighting method (31) was used to calculate the GRS for T2D based on the 424 selected SNPs that passed quality control (13). Each SNP was weighted by its relative effect size (β-coefficient). We used β-coefficients derived from the European population in the latest genome-wide multiethnic meta-analysis (13) to obtain more precise effect sizes of these SNPs on T2D. The GRS was calculated by the following equation: $\text{GRS} = (\beta_1 \times \text{SNP}_1 + \beta_2 \times \text{SNP}_2 + \ldots + \beta_{424} \times \text{SNP}_{424}) \times (424/\text{sum of the } \beta\text{-coefficients})$, where SNP_i (i = 1, 2, ..., 424) is is the risk allele number of each SNP. The calculated GRS ranged from 358.4 to 469.8. A higher GRS indicates a higher genetic predisposition to T2D, and each a GRS point corresponds to one risk allele.

Assessment of Diet Quality and Covariates

In the assessment centers, participants completed a touch-screen short food frequency questionnaire (FFQ) that included 29 questions about diet over the past 12 months. Most of the questions inquired about the consumption frequency of major food groups, such as "How often do you eat processed meats (such as bacon, ham, sausages, meat pies, kebabs, burgers, chicken nuggets)?", followed by the options from "never" to "once or more daily." For vegetable and fruit consumption, participants were asked to directly enter the average number of servings consumed daily. In addition, a subsample of participants was invited for

a total of four times between 2011 and 2012 to complete an online 24-h dietary assessment. Detailed information on the dietary assessment has been reported elsewhere (32). In the present analysis, we only used data from the short FFQ, available on the full cohort, to maximize the sample size and better represent a long-term diet. The performance of the short FFQ has been validated by a repeated assessment 4 years after recruitment and by comparing the dietary touch-screen variables with the mean intakes from online 24-h dietary assessments, which demonstrated dietary variables from FFQ reliably rank individuals according to intakes of the main food groups (32).

According to the recent definition for ideal consumption of dietary components for cardiometabolic diseases, including T2D (27,33), we then created a diet quality score based on 10 foods predictive of T2D risk, emphasizing higher intake of vegetables, fruits, fish, dairy, whole grains, and vegetable oils and lower intake of refined grains, processed meats, unprocessed red meats, and sugar-sweetened beverages. Supplementary Table 2 summarizes the components and scaling methods of the diet quality score. Each dietary component was scored from 0 (unhealthiest) to 10 (healthiest) points, with intermediate values scored proportionally. The total diet quality score was the sum of all the diet component scores and ranged from 0 to 100, with a higher score representing a higher overall diet quality. The continuous scale and wide range of the diet quality score enable great sensitivity to differentiate dietary intakes.

Several potential confounders were also assessed through the touch-screen questionnaire, including age, sex, race, weight and height, education, Townsend deprivation index (34), household income, smoking, alcohol consumption, physical activity, history of diseases, dietary supplementation, and medication. MET was calculated according to the short form of International Physical Activity Questionnaire (35). Hypertension was defined as a self-reported history of hypertension, systolic blood pressure $\geq$140 mmHg, diastolic blood pressure $\geq$90 mmHg, or taking antihypertensive drugs. Blood samples were collected at baseline, and HbA_{1c} levels were measured. Detailed information on the measurement is available online at https://biobank.ctsu.ox.ac.uk/showcase.

Ascertainment of T2D

The definitions for prevalent and incident T2D cases are presented in Supplementary Table 3. Prevalent T2D was ascertained using the UK Biobank algorithms for the diagnosis of diabetes (36). Incident T2D cases were identified using cumulative hospital inpatient records with the code E11 from ICD-10. Hospital admission data were available for participants until 31 March 2017. Detailed information on T2D ascertainment can be found at https://biobank.ndph.ox.ac.uk/showcase/label.cgi?id=2000. Follow-up time was calculated from the date of attendance at the baseline assessment center to the time of T2D diagnosis, lost to follow-up, death, or the end of follow-up (31 March 2017), whichever occurred earlier.

Statistical Analysis

We used Cox proportional hazards regression models to calculate hazard ratios (HRs) and 95% CIs for T2D according to the categories of the diet quality score or GRS. The interaction between the diet quality score and GRS on the subsequent incidence of T2D was tested by including a multiplicative interaction term in the Cox proportional hazards models. Continuous standardized values ([value − mean]/SD) of the GRS and diet quality score were used in these analyses for appropriate scaling for clinical interpretation. Proportional hazards assumption was checked by calculating the correlation between Schoenfeld residuals and ranked event times. Several potential confounders were included in our multivariable-adjusted models. Model 1 was adjusted for age and sex. Model 2 was further adjusted for assessment centers, BMI, education, Townsend deprivation index, household income, smoking, physical activity, alcohol consumption, history of hypertension, history of high cholesterol, vitamin supplement use, mineral supplement use, aspirin use, and lipid-lowering medication. Missing data were coded as a missing indicator category, if necessary. Similarly, general linear models were used to estimate HbA_{1c} levels at baseline according to the categories of the GRS and assess the interaction between the diet quality score and the GRS on HbA_{1c} levels by including a multiplicative interaction term.

The diet quality score or GRS was also divided into low, median, or high levels according to tertiles, and we estimated the HRs of T2D and HbA_{1c} levels according to joint categories of the diet quality score and GRS (9 categories). Given that the empirical risk of chronic diseases was evidenced to sharply increase in the extreme tails of the GRS distribution (37,38), we further estimated the changes in the HRs of T2D and HbA_{1c} levels associated with 1-SD increment in the diet quality score in percentile categories of the GRS to see whether the interactions existed among the individuals with extremely high genetic risk.

Sex-specific analyses were performed to investigate whether the interactions differed by sex. We also tested the potential interactions for specific diet components. Several sensitivity analyses were also conducted. We tested whether the association was affected by further adjusting for a sleep pattern (poor, intermediate, or healthy) (39), hormone replacement therapy and oral contraceptive use, glucosamine use, or fish oil use. We further excluded incident T2D cases that occurred within the first year to minimize the possibility of reverse causation. Finally, analyses were restricted to the participants with no missing covariate data.

Statistical analyses were performed with SAS 9.4 software (SAS Institute, Cary, NC). Tests were two-sided, and the significance was defined as $P < 0.05$.

RESULTS

Population Characteristics

Characteristics of participants in the current UK Biobank categorized by quartiles of diet quality score are summarized in Table 1. At baseline, participants with higher diet quality scores were generally older, more often women, highly educated, more physically active, and had lower BMIs. They were also more likely to have prevalent hypercholesteremia and use aspirin, vitamins, minerals, and lipid-lowering medications. The mean GRS of T2D for participants was 414 with a normal distribution (Supplementary Fig. 2). Besides, the GRS was not correlated with the diet quality score. As expected, the HRs of T2D were lower

Table 1—Baseline characteristics of participants across quartiles of the diet quality score in the UK Biobank cohort

	Quartiles of diet quality score				
Characteristics	Q1 *n* = 89,354	Q2 *n* = 89,276	Q3 *n* = 89,485	Q4 *n* = 89,304	*P**
Male	56.6	43.9	38.2	38.1	<0.001
Age (years)	54.6 ± 8.2	55.7 ± 8.1	56.3 ± 7.9	57.2 ± 7.7	<0.001
BMI (kg/m^2)	27.7 ± 4.7	27.3 ± 4.5	26.9 ± 4.5	26.4 ± 4.4	<0.001
Townsend deprivation index	−1.3 ± 3.1	−1.6 ± 2.9	−1.8 ± 2.8	−1.7 ± 2.8	<0.001
Household income (£)†					<0.001
<18,000	18.7	16.1	15.4	17.7	
18,000 to 30,999	21.6	21.3	21.3	22.5	
31,000 to 51,999	24.0	24.2	24.2	23.6	
52,000 to 100,000	18.7	20.5	20.8	18.7	
>100,000	4.7	5.7	5.9	4.9	
Education					<0.001
College or university degree	26.1	33.1	37.5	39.7	
Vocational qualifications	12.0	11.3	10.9	10.9	
Optional national exams at ages 17–18 years	11.2	12.2	12.4	11.5	
National exams at age 16 years	31.4	28.1	26.0	24.3	
Others	18.6	14.7	12.6	12.9	
Physical activity (MET-h/week)	42.3 ± 47.6	43.2 ± 44.5	44.3 ± 42.9	49.8 ± 45.9	<0.001
Smoking status					<0.001
Never	50.8	56.2	58.2	58.2	
Previous	31.7	33.7	34.4	35.7	
Current	17.3	9.9	7.2	5.9	
Alcohol consumption					<0.001
Never or special occasions only	16.3	15.3	14.9	17.0	
1 to 3 times/month	11.2	11.1	11.0	11.2	
1 or 2 times/week	26.0	26.7	26.8	26.7	
3 or 4 times/week	22.8	24.6	26.4	25.8	
Daily or almost daily	23.7	22.2	20.9	19.3	
History of hypertension	55.1	53.5	52.5	53.2	<0.001
History of high cholesterol	11.0	11.7	11.9	12.5	<0.001
Family history of diabetes	20.5	20.2	20.0	19.9	0.012
Aspirin use	8.4	8.4	8.5	8.8	0.015
Vitamin supplementation	24.7	30.4	33.7	37.5	<0.001
Mineral supplementation	8.0	11.2	13.1	16.0	<0.001
Lipid-lowering medication use	10.3	10.8	10.8	11.2	<0.001
Genetic risk score	414.0 ± 11.9	414.0 ± 11.9	414.0 ± 11.9	414.1 ± 11.9	0.350

Data are means ± SD or %. **P* values for differences were analyzed by χ^2 test for categorical variables or ANOVA for continuous variables. †£1.00 = $1.30, €1.20.

with the increasing quartiles of the diet quality score (Supplementary Fig. 3).

The Interaction Between the Diet Quality Score and GRS on T2D Incidence and HbA_{1c}

A total of 5,663 participants with T2D were documented during an average of 8.1 years of follow-up (2,882,727 person-years). In the analysis of continuous standardized values (Table 2), we observed a significant interaction between the diet quality score and the GRS on the subsequent T2D risk (*P* for interaction = 0.038) in the age- and sex-adjusted model (model 1). The interaction was slightly enhanced after further adjusting for other demographic characteristics, lifestyle factors, and the use of other supplements and medications (model 2; *P* for interaction = 0.031). Relative to the mean values, each SD increment in GRS was associated with a 54% (95% CI 50–58%) higher risk ($P < 0.001$), and per SD increment in the diet quality score was related to a 9% (95% CI 7–12%) lower T2D risk ($P < 0.001$). Besides, a simultaneous increment of 1 SD in both the diet quality score and the GRS was additionally associated with a reduction of 3% in T2D risk ($P = 0.031$) due to the antagonistic interaction.

Similarly, we observed a strong interaction between the diet quality score and the GRS on blood HbA_{1c} levels (Table 2). In the multivariable-adjusted model, each SD increment in the GRS was associated with 0.544

Table 2—Interaction between the diet quality score and the GRS on the risk of type 2 diabetes and blood HbA_{1c} level*

	UK Biobank			
	β	SE	*P*	HR (95% CI)
Type 2 diabetes				
Model 1†				
GRS	0.438	0.014	<0.001	1.55 (1.51–1.59)
Diet quality score	−0.239	0.015	<0.001	0.79 (0.77–0.81)
GRS × diet quality score	−0.028	0.014	0.038	0.97 (0.95–0.998)
Model 2‡				
GRS	0.431	0.014	<0.001	1.54 (1.50–1.58)
Diet quality score	−0.098	0.015	<0.001	0.91 (0.88–0.93)
GRS × diet quality score	−0.029	0.014	0.031	0.97 (0.95–0.997)
HbA_{1c} (mmol/mol)				
Model 1†				
GRS	0.570	0.007	<0.001	—
Diet quality score	−0.276	0.007	<0.001	—
GRS × diet quality score	−0.051	0.007	<0.001	—
Model 2‡				
GRS	0.544	0.007	<0.001	—
Diet quality score	−0.146	0.007	<0.001	—
GRS × diet quality score	−0.050	0.007	<0.001	—

*Cox proportional hazards regression models for type 2 diabetes and generalized linear models for HbA_{1c} were performed using standardized values of the diet quality score and the GRS. †Model 1 was adjusted for age and sex. ‡Model 2 was further adjusted for centers (22 categories), BMI (in kg/m^2; <18.5, 18.5–25, 25–30, 30–35, ≥35, or missing), education (college or university degree, vocational qualifications, optional national exams at ages 17–18 years, national exams at age 16 years, others, or missing), Townsend deprivation index (quintiles), household income (<£18,000, £18,000–30,999, £31,000–51,999, £52,000–100,000, >£100,000, or missing), smoking (never, former, current, or missing), alcohol consumption (never or special occasions only, 1 to 3 times/month, 1 or 2 times/week, 3 or 4 times/week, or daily/almost daily), physical activity (in MET-h/week; quintiles), history of hypertension (yes or no), history of high cholesterol (yes or no), vitamin supplement use (yes or no), mineral supplement use (yes or no), aspirin use (yes or no), and lipid-lowering medication (yes or no).

mmol/mol higher HbA_{1c} level ($P < 0.001$). The per SD increment in the diet quality score was related to a 0.146 mmol/mol lower HbA_{1c} level ($P < 0.001$). Besides, 1-SD increment in the diet quality score plus 1-SD increment in the GRS was additionally associated with a reduction of 0.050 mmol/mol in HbA_{1c} level ($P < 0.001$).

In sex-specific analyses, we found a significant interaction between the diet quality score and the GRS on T2D risk in men (*P* for interaction = 0.029) but not in women (*P* for interaction = 0.459) (Supplementary Table 4). However, the strong interactions between the diet quality score and the GRS on HbA_{1c} were consistent in both men and women (both *P* for interaction < 0.001). For individual diet components, higher scores in refined grains, whole grains, processed meats, fish, fruits, and vegetables were significantly associated with reductions in T2D risk. Among these diet components, processed meats showed a significant interaction with the GRS on T2D risk (*P* for interaction = 0.005) (Supplementary Table 5).

T2D Risk and HbA_{1c} According to Joint Categories of the Diet Quality Score and the GRS

Results from the joint categories of the diet quality score and the GRS showed that a higher GRS was associated with a higher risk of T2D and that this association was more pronounced among participants who had a lower diet quality score (Fig. 1*A*). Viewed differently, the positive associations of poor diet quality with T2D risk were stronger among participants with a higher GRS. Compared with the individuals in the lowest tertile of GRS and the highest tertile of the diet quality score, those in the highest tertile of the GRS and the lowest tertile of the diet quality score had a 2.29-fold increase in T2D risk. Similar results were also detected for blood HbA_{1c} levels (Fig. 1*B*).

Associations of Diet Quality With T2D Risk and HbA_{1c} According to Percentile Categories of the GRS

In analyses according to the percentile categories of the GRS, a gradient of T2D risk was apparent across the 10 GRS groups (Fig. 2*A*), where participants with a higher GRS were at higher risk of developing T2D. This trend was especially visible for individuals in the right tail of the GRS distribution, where T2D risk increased sharply as the GRS increased. Compared with participants in the group with 40–60% GRS, the adjusted HRs (95% CIs) for those in the groups with 95–99% and >99% GRS groups were 2.14 (1.91–2.39) and 2.84 (2.37–3.39), respectively. We observed that the reduction of T2D risk associated with a 1-SD increment in the diet quality score was greater across the increasing categories of the GRS (*P* for interaction = 0.012) (Fig. 2*B*). Notably, sharp reductions in the risk of T2D were detected for individuals in the extremely high GRS groups (GRS >95%). Each SD increment in the diet quality score was related to a 23% (95% CI 15–30%) decreased T2D risk among individuals in the group with 95–99% GRS. A reduction of 23% (95% CI 7–36%) associated with a 1-SD increment in the diet quality score was also observed for those even in the group with >99% GRS. Similarly, the adjusted means of HbA_{1c} levels were higher across the genetic risk bins, with a sharp increase in the extremely high GRS group (GRS >99%) (Fig. 3*A*). Although the diet quality score was consistently associated with reduced HbA_{1c} levels in each genetic risk group, reductions were more prominent with the increasing GRS categories (*P* for interaction <0.001) (Fig. 3*B*). Specifically, participants with the top 1% GRS had 0.436 mmol/mol decreased HbA_{1c} associated with 1-SD increment of diet quality score.

Sensitivity Analyses

The documented significant interactions between the diet quality score and GRS on T2D risk and HbA_{1c} did not change substantially after further adjusting for sleep pattern, hormone replacement therapy and oral contraceptive use, glucosamine use, and fish oil use (Supplementary Table 6). Our results also remained similar when we further excluded incident T2D cases that occurred within the first year or those with missing covariate data (Supplementary Table 7).

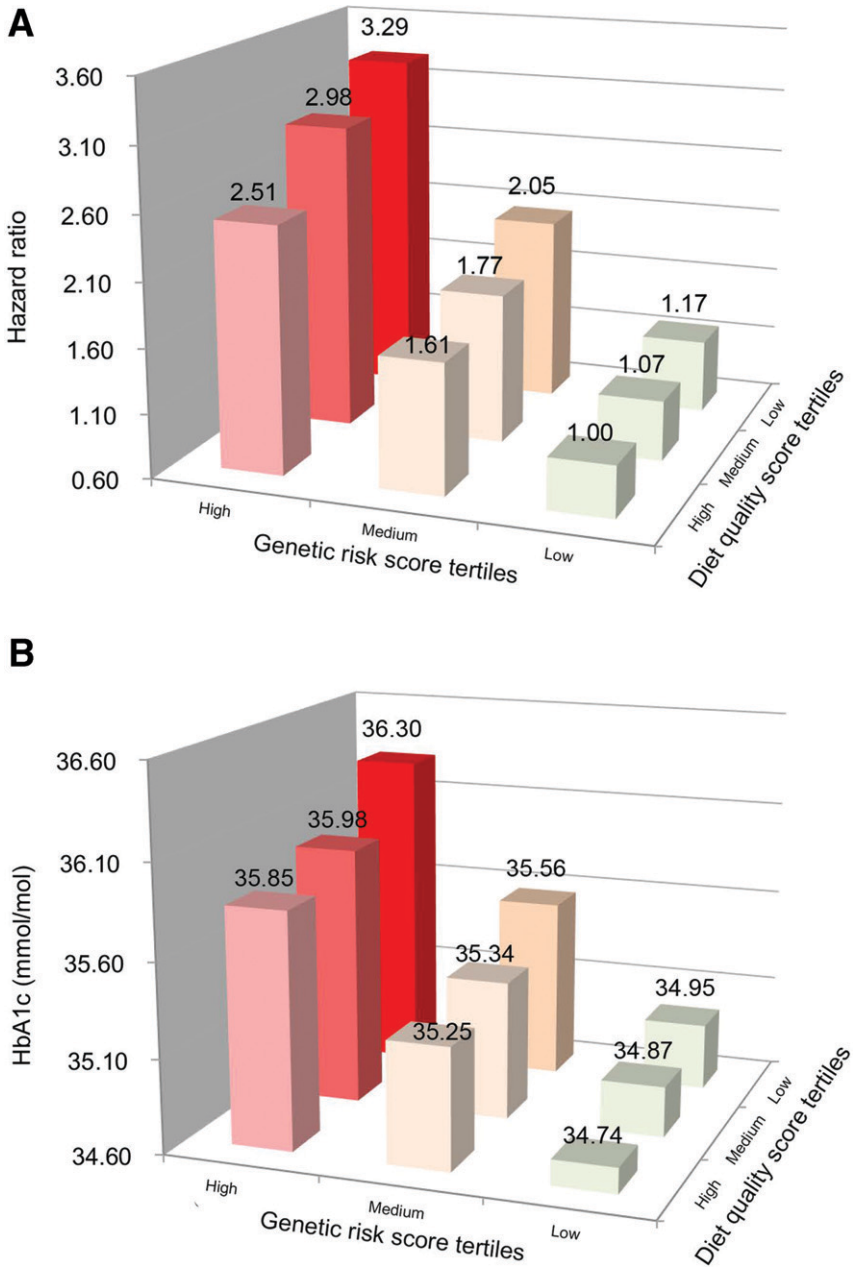

Figure 1—HRs of T2D and HbA_{1c} levels according to joint categories of the diet quality score and the GRS. Data are HRs of T2D (*A*) and HbA_{1c} levels (*B*) adjusted for age, sex, centers, BMI, education, Townsend deprivation index, household income, smoking, alcohol consumption, physical activity, history of hypertension, history of high cholesterol, vitamin supplement use, mineral supplement use, aspirin use, and lipid-lowering medication.

CONCLUSIONS

In this large study, including 357,419 participants of European descent, we examined the interplay between diet quality and genetic predisposition related to T2D and blood HbA_{1c}. Higher diet quality was significantly associated with reductions in HbA_{1c} and T2D risk among individuals at higher genetic risk for T2D but not among those at lower genetic risk. Besides, individuals at an extremely high genetic risk (GRS >95%) had a sharp reduction in T2D risk related to improved diet quality. From another perspective, improved diet quality might attenuate the genetic influences on T2D.

Comparison With Other Studies and Possible Explanations

Although it is widely hypothesized that genetic predisposition interacts with an unhealthy lifestyle on the epidemic of T2D, previous evidence suggests that lifestyle and genetic factors contribute independently to the susceptibility to T2D (33,40–43). Regarding the dietary factors, only few studies have tested the potential interaction between overall diet quality and genetic susceptibility to T2D. In the Health Professionals Follow-Up Study (HPFS) of 1,196 patients with diabetes and 1,337 control subjects without diabetes, higher adherence to a Western diet was associated with increased T2D risk only among participants with a high GRS (≥12 risk alleles) but not among those with a lower GRS (<12 risk alleles) (*P* for interaction = 0.02) (22).

However, two other larger studies did not find any significant interactions between diet quality and the GRS on T2D risk. The InterAct case-cohort study including 16,154 individuals reported no interactions between the T2D GRS calculated using 49 SNPs and the diet quality assessed by a Mediterranean diet score (23). Likewise, the Malmö Diet and Cancer cohort study of 25,069 participants showed that the GRS computed using 49 SNPs and the diet risk score derived from four important foods independently added to the T2D risk (24). Recently, a cross-sectional study of 3,733 White British participants found that a diet quality index according to the U.K. dietary reference values and guidelines was inversely associated with HbA_{1c} and that such protective associations were similar across tertiles of the GRS calculated by 87 SNPs (25).

Potential interactions were likely to be obscured due to the limited statistical power in these studies. First, the GRS constructed using a limited number of SNPs did not accurately represent the genetic risk. In our study, we used 424 T2D associated SNPs from the largest-to-date GWAS study, which explained 19% of T2D risk on a liability scale (13). The GRS integrating such a large number of loci dramatically enhanced the prediction of an individual's genetic risk for T2D.

Second, previous studies were subject to limited sample size ($n < 30,000$), which may attenuate statistical power to detect significant interactions. Importantly, evidence revealed that the empirical risk of diseases, including T2D, elevated sharply in the extreme tails of

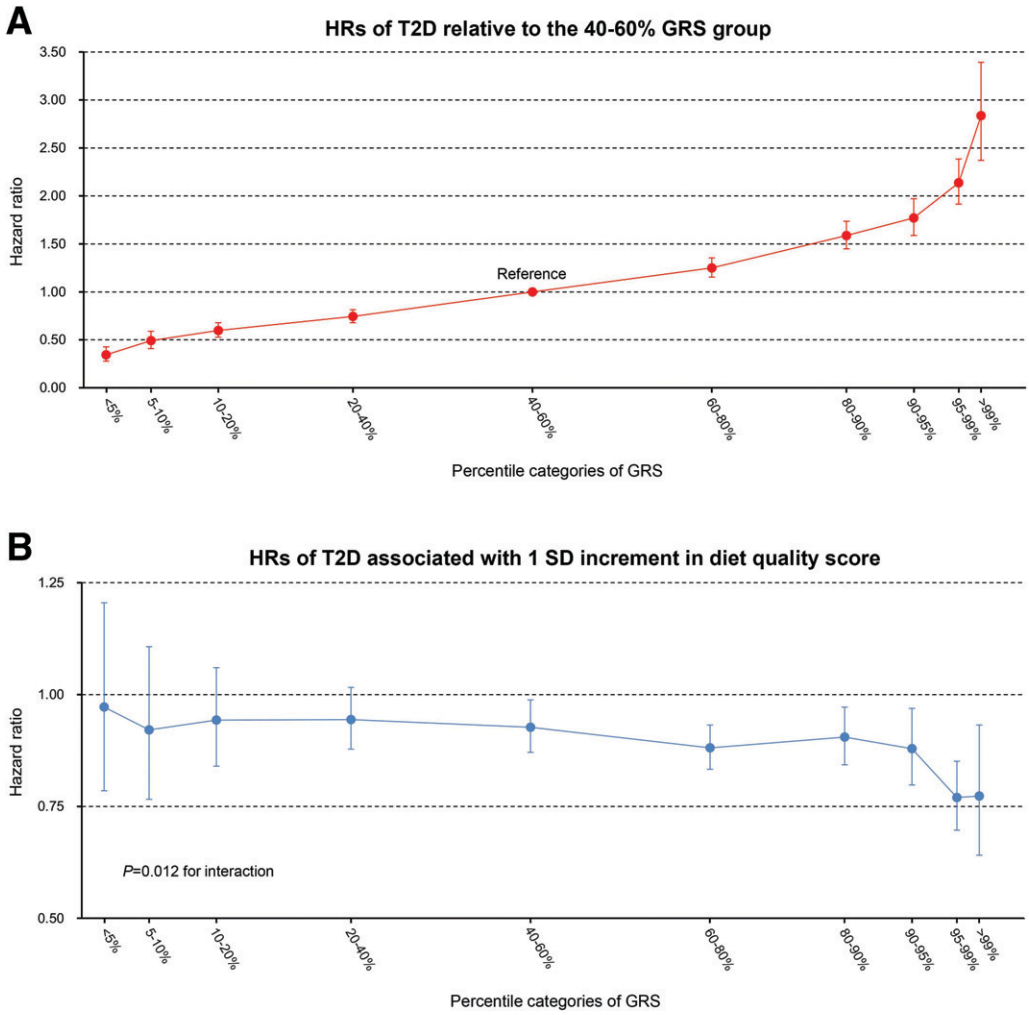

Figure 2—HRs of T2D according to percentile categories of the GRS. HRs of T2D relative to the 40–60% GRS group (*A*) and HRs of T2D associated with a 1-SD increment in the diet quality score (*B*) were adjusted for age, sex, centers, BMI, education, Townsend deprivation index, household income, smoking, alcohol consumption, physical activity, history of hypertension, history of high cholesterol, vitamin supplement use, mineral supplement use, aspirin use, and lipid-lowering medication. The vertical lines represent 95% CIs.

the GRS distribution (37,38), which was validated in our study. Previous studies roughly stratified the participants into a small number of risk groups, such as tertiles and quartiles of the GRS, and therefore, could not catch the effect of diet among those with extremely high genetic risk. In the current study, we novelly observed that individuals in the extremely high genetic categories (>95% GRS) had a sharp reduction in T2D risk related to improved diet quality, which largely explained the significant interaction between the diet quality score and the GRS in the analysis using continuous variables. We also detected that the protective associations of the diet quality score with T2D risk were not significant among those with a GRS <40%, which implied that for individuals with relatively low genetic risk, the effect of a high-quality diet might be weak and that modifications of other lifestyle factors, such as physical activity and smoking, may be considered. Similarly, the HPFS found that higher adherence to a Western dietary pattern was not associated with higher T2D risk among those with a lower GRS (56% of participants) (22). Together, our finding of a significant interaction between diet and genetic predisposition to T2D highlights the importance of sample size and T2D risk prediction accuracy by the GRS in the gene-diet analysis. More large-scale studies covering a sufficient sample of people with extremely high genetic risk are needed to replicate our findings.

The documented strong interaction between a healthy diet and HbA_{1c} may have public health significance because a small reduction in HbA_{1c} would lead to a population reduction in risk of T2D (44). The Prevención con Dieta Mediterránea (PREDIMED) study of 2,993 men and 4,025 women demonstrated an interaction between the Mediterranean diet and variants at the *TCF7L2* gene (rs7903146) on fasting glucose after a 4.8-year follow-up (45). They observed that the genetic effect of the rs7903146 SNP on fasting glucose was attenuated by high adherence to the Mediterranean diet. Moreover, they also found that the reductions in T2D incidence for rs4580704 G-allele carriers compared with the CC homozygotes were more evident in the Mediterranean diet intervention group than in the control group (46). These data collaborate with our finding to support the

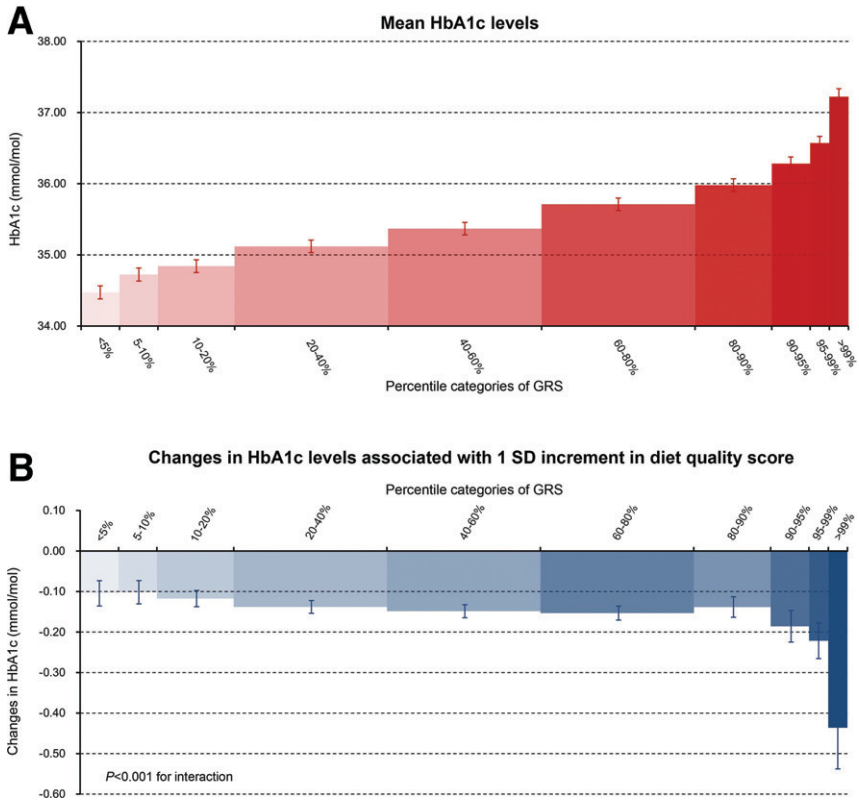

Figure 3—Blood HbA_{1c} levels according to percentile categories of the GRS. Mean HbA_{1c} levels (*A*) and changes in HbA_{1c} levels associated with a 1-SD increment in the diet quality score (*B*) were adjusted for age, sex, centers, BMI, education, Townsend deprivation index, household income, smoking, alcohol consumption, physical activity, history of hypertension, history of high cholesterol, vitamin supplement use, mineral supplement use, aspirin use, and lipid-lowering medication. The vertical lines represent SEs.

suggestion that maintaining a high-quality diet would benefit glycemic control and that such protection is more prominent for individuals at high genetic risk of T2D. Consistent with the interaction for T2D risk, the substantial reduction in HbA_{1c} associated with improved diet quality was found for participants with an extremely high GRS in our study, indicating the importance of identifying individuals with extremely high genetic risk and implementing early diet modification before the onset of T2D.

The biological mechanisms underlying the documented interactions between diet quality and genetic predisposition on HbA_{1c} and T2D risk remain unclear. The modifying effect could be partly explained by the beneficial bioactivities of a healthy diet, such as regulating lipid and glucose metabolism, enhancing insulin sensitivity, and balancing energy intake (10,21). Notably, a previous study suggested adhering to healthy dietary patterns significantly attenuated the genetic susceptibility to obesity and weight gain (47), which is a major risk factor for T2D. Interactions between important nutritional components of a healthy diet and genetic variants could also play a part. Our results suggest that processed meats may be the major food item driving the interaction between diet quality and genetic risk. Components of processed meats, including saturated fat, advanced glycation end products, heme iron, nitrosamine, sodium nitrite, and nitrose compounds, may have toxic effects on pancreatic β-cells or impair insulin sensitivity (48). It is possible that genetic variants associated with insulin secretion or insulin resistance strengthen this detrimental effect on T2D risk. In addition, variants of *TCF7L2* result in impaired glucagon-like peptide 1–induced insulin secretion, while a fiber-rich diet could stimulate glucagon-like peptide 1 and thus counteract the genetic effects (25,49). More experimental research is required to give biological insights into the gene-diet interactions on glucose intake and T2D risk.

In the sex-specific analysis, we showed that the interactions between the diet quality score and the GRS on HbA_{1c} were consistently strong among both men and women, but the interactions on T2D risk were detected in men but not in women, which may be due to the higher incidence of T2D in men than in women (50). Consistently, the previous HPFS showed a significant interaction between a Western diet and the GRS in male health professionals (22). The possible mechanisms explaining this difference may include the moderating effects of sex hormones on glucose and lipid metabolism (51). Studies have shown that men were more sensitive to diet-induced obesity or insulin resistance compared with women due to the lack of the protective effect of estrogen (51). It is possible that estrogen regulated the expressions of genes involved in glucose metabolism and thus attenuated the interaction between these genes and diet.

Strengths and Limitations

The major strength of the current study is the large population size, which provides sufficient statistical power to detect significant interactions and allows for analyses in individuals with extremely high genetic risk. In addition, we constructed a comprehensive diet quality score and took advantage of a large number of SNPs identified to be associated with T2D, which provided an accurate prediction of genetic risk. Other strengths include the wealth of data on covariates, including socioeconomic characteristics and lifestyle factors.

Some limitations should also be noted. First, residual confounding due to measurement errors or unmeasured factors is still possible, although we have carefully controlled for various nondietary factors in our models.

Second, consumption of dietary components of the diet quality score was assessed at baseline, which may not capture potential changes in dietary habits during the follow-up. The weaker interaction observed for T2D risk than HbA_{1c} at baseline implied that the precise measurement of diet was important for detecting significant interactions. Besides, information on covariates was also collected at baseline, and thus, changes during the follow-up could not be adjusted.

Therefore, studies using repeated measurements of diet and covariates should be encouraged.

Third, new cases of T2D were confirmed by hospital inpatient records or self-report in our study, which may not be precise. The lack of laboratory tests, such as fasting glucose or HbA_{1c} might underestimate the incident cases of T2D. However, this misclassification would occur virtually independent of the diet quality score and GRS and thus might not cause serious bias.

Fourth, although the diet quality score comprises important food items that are also included in many healthy dietary patterns, such as the Mediterranean Diet and Dietary Approach to Stop Hypertension, further studies are needed to test whether these specific dietary patterns also interact with the genetic risk of T2D.

Fifth, our study population was restricted to White European descent, and thus our findings may not immediately be generalized to other ethnic groups of populations. Finally, a causal relationship may not be implied due to the observational nature.

Conclusion and Implications

In summary, we showed that the protective associations of diet quality with T2D and blood HbA_{1c} were modified by the genetic risk. These results indicate that individuals with higher genetic risk, especially extremely high genetic risk, may benefit more from adherence to a healthy diet in T2D prevention. Our findings provide important evidence to support tailoring dietary recommendations to an individual's genetic makeup for T2D prevention. More studies with a large sample size of population-wide biobanks and precisely measured dietary exposures are needed to corroborate our results.

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