Clinical and Genetic Determinants of Progression of Type 2 Diabetes: A DIRECT Study

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OBJECTIVE

To identify the clinical and genetic factors that explain why the rate of diabetes progression is highly variable between idividuals following diagnosis of type 2 diabetes.

RESEARCH DESIGN AND METHODS

We studied 5,250 patients with type 2 diabetes using comprehensive electronic medical records in Tayside, Scotland, from 1992 onward. We investigated the association of clinical, biochemical, and genetic factors with the risk of progression of type 2 diabetes from diagnosis to the requirement of insulin treatment (defined as insulin treatment or $HbA_{1c} \geq 8.5\%$ [69 mmol/mol] treated with two or more noninsulin therapies).

RESULTS

Risk of progression was associated with both low and high BMI. In an analysis stratified by BMI and HbA_{1c} at diagnosis, faster progression was independently associated with younger age at diagnosis, higher log triacylglyceride (TG) concentrations (hazard ratio [HR] 1.28 per mmol/L [95% CI 1.15–1.42]) and lower HDL concentrations (HR 0.70 per mmol/L [95% CI 0.55–0.87]). A high Genetic Risk Score derived from 61 diabetes risk variants was associated with a younger age at diagnosis and a younger age when starting insulin but was not associated with the progression rate from diabetes to the requirement of insulin treatment.

CONCLUSIONS

Increased TG and low HDL levels are independently associated with increased rate of progression of diabetes. The genetic factors that predispose to diabetes are different from those that cause rapid progression of diabetes, suggesting a difference in biological process that needs further investigation.

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The clinical course following a diagnosis of diabetes is highly variable. Some patients have a rapid deterioration in glycemia requiring early insulin treatment; others can be treated with oral agents for more than 20 years. It is important to gain insight into what factors are associated with progression of diabetes because understanding the biological mechanisms may aid in the development of therapies specifically aimed at

delaying diabetes progression, and understanding the characteristics of those who progress rapidly or slowly may aid in the management of patients with type 2 diabetes.

It is generally accepted that there is a physiological continuum between prediabetes and diabetes, with progression to diabetes being caused by progressive loss of β-cell secretory capacity (1) and glycemic deterioration in diabetes due to ongoing loss of function (2,3). This may suggest a common biological process for diabetes risk and diabetes progression.

Diabetes risk factors have been studied extensively (summarized by Nobel et al. [4]) and include clinical characteristics (e.g., age, sex, ethnicity, family history, BMI) and glucose and biochemical parameters associated with insulin resistance and inflammation (e.g., HDL levels, triacylglyceride (TG) concentrations, high-sensitivity C-reactive protein levels, and inflammatory cytokines [5,6]). In addition, studies of genetic associations have identified more than 65 diabetes risk variants (7); however, these provide little predictive utility over traditional clinical risk factors (8,9). Where the physiological effect of these variants is known the majority of the risk variants affect β-cell function (7).

A few previous studies have investigated factors associated with the rate of diabetes progression (3,10–15). The consensus of these studies is that a low BMI, young age at diagnosis, and low β-cell function are associated with faster progression of diabetes (either to failure of monotherapy or progression to insulin use). The UK Prospective Diabetes Study 25 reported that presence of "positive" GAD antibody concentrations also was associated with faster progression to insulin use (11). Beyond this, the mechanisms driving glycemic deterioration once diabetes is established remain unknown. No studies have investigated biomarkers of insulin resistance and inflammation and none have explored the effect of genetic variation on rates of diabetes progression.

Using a large, contemporary, population-based cohort in northeast Scotland with extensive longitudinal follow-up and biobanked DNA, we tested the hypothesis that clinical available insulin resistance biomarkers (low HDL, high LDL, low TG, high alanine transaminase [ALT], high BMI) were associated with rapid progression of diabetes. We further hypothesized that the genetic variants associated with diabetes risk were associated with increased rates of diabetes progression.

RESEARCH DESIGN AND METHODS

We performed an observational study using data from the Genetics of Diabetes Audit and Research (GoDARTS) database, which has been described previously (16,17). In brief, since October 1997, all patients with type 2 diabetes have been invited to give written informed consent to DNA collection as part of the Wellcome Trust United Kingdom type 2 diabetes case control collection. To date, nearly 10,000 patients with type 2 diabetes have participated in the GoDARTS study. All anonymous clinical information on these patients can be obtained from SCI-Diabetes (an electronic medical record of all patients with diabetes in Scotland) and linked to all biochemistry records and prescription encashments from 1992 onward, giving a comprehensive longitudinal record of diabetes therapy and glycemic control. The GoDARTS study was approved by the Tayside Committee on Medical Research Ethics, and informed consent was obtained from all patients (REC reference 053/04).

Study Population

To be eligible for the study, patients had to have been diagnosed with diabetes after 1 January 1994 to ensure sufficient prescribing information to accurately define time to insulin use. In addition, patients were required to have a baseline HbA$_{1c}$ and BMI measurement. To minimize inclusion of patients with type 1 diabetes, patients were included if they had a clinical diagnosis of type 2 diabetes after the age of 35 years with no progression onto insulin treatment within 1 year of diabetes diagnosis. Of a total of 9,636 patients with diabetes in the GoDARTS study, 5,250 (54%) met the criterion for inclusion in the study. All patients were white Europeans.

Detailed sample selection from this observational cohort can be found in Supplementary Fig. 1.

This cohort and research question were studied as part of the Diabetes Research on Patient Stratification (DIRECT) study, an EU FP7 Innovative Medicines Initiative (see www.direct-diabetes.org).

Measurement of Diabetes Progression (Time to Insulin Event)

To avoid bias due to insulin inertia (15,18), whereby there is a delay in commencing insulin after it is clinically indicated because of reluctance by the patient or the clinician, we used a composite end point for "requirement of insulin treatment." This time to insulin outcome was reached in 1,169 patients and was defined as the period from diagnosis to a clinical end point of the earlier of either 1) starting sustained (more than 6 months' duration) insulin treatment (339 patients) or 2) the clinical requirement of insulin treatment as indicated by two or more HbA$_{1c}$ measurements >8.5% (69 mmol/mol) more than 3 months apart when taking two or more noninsulin diabetes therapies (880 patients). Patients who did not go on to insulin treatment were right censored in the event of death, moving away from the study area, or reaching the study end on 31 December 2009. The mean (SD) follow-up was 8.5 (4.3) years.

Clinical Covariates

The following clinical variables were included as covariates: age at diagnosis of diabetes; calendar year of diagnosis; sex; BMI category (grouped by every 2 kg/m^2 between 22 and 44 kg/m^2); smoking status (ever vs. never); and social class (derived from the Scottish Index of Multiple Deprivation [SIMD], a lower score represents higher deprivation). In addition, the following baseline biochemistry parameters were included: HbA$_{1c}$, HDL, LDL, TG, and ALT. All biochemical baseline parameters were the closest measure to diagnosis within 12 months before diagnosis or the first measure after diagnosis. All biochemistry measurements except HDL were log transformed to fit a normal distribution.

Genetic Covariates

We used a weighted Genetic Risk Score (GRS) that covers 61 established type 2

diabetes risk variants to represent an individual's genetic susceptibility. The single nucleotide polymorphisms (SNPs) were selected from the latest DIAGRAM publication that reported 65 type 2 diabetes loci (7). Genotypes of the GoDARTS cohort were available from two sources: *1*) Affymetrix 6.0 SNP genotyping array data on 3,714 patients and *2*) CardioMetaboChip data on 3,064 patients and 4,114 controls. A proxy SNP with $r^2 > 0.6$ (according to the HapMap CEU panel, which consists of 30 trios of U.S. residents of Northern and Western European ancestry) was selected when the index SNP was not genotyped. Four SNPs with poor proxies were dropped. The remaining 61 SNPs passed routine genome-wide association study genotyping quality control (call rate $>98\%$; $P > 0.001$ in Hardy-Weinberg equilibrium), and their details are shown in Supplementary Table 1.

The weighted GRS was constructed by summing the number of risk-increasing alleles carried by each person at each SNP, weighted by the logarithm of the allelic odds ratio of the SNP as reported in published meta-analyses (7). Missing genotypes were imputed with twice the population allele frequency of the risk-increasing allele. As such, the GRS created from the 61 SNPs has a possible range of 0 to 10.543. Instead of reporting an "averaged allelic effect" that is specific to the composite SNPs for GRS construction (19), here we report a SNP-independent "per GRS unit effect." Results from analysis of the averaged allelic effect GRS are generally not comparable between studies because the type 2 diabetes genes initially discovered tend to have a larger allelic effect than those from the bigger, more recent studies. In contrast, our method of GRS construction can be readily extended to include any number of SNPs as the number of known type 2 diabetes variants increases, and the effect estimate of GRS defined as such are comparable regardless of the number of SNPs involved. This is particularly useful when comparing multiple scores derived from different subgroups of SNPs. Using this approach, each unit of the GRS corresponds to an expected type 2 diabetes genetic risk increase of 2.72. In keeping with this, the GRS score

showed a per-unit risk increase of 2.68 (95% CI 2.40–2.88) in 6,230 patients and 3,866 controls from the GoDARTS study (data not shown).

To further dissect the type 2 diabetes risk genes, we developed two subscores: a β-cell function GRS from 16 SNPs and an insulin resistance GRS from 7 SNPs, based on what is known about the effect of these SNPs on glucose/insulin traits from the latest Meta-Analyses of Glucose and Insulin-related traits Consortium (MAGIC) publication (SNPs are marked in Supplementary Table 1) (20).

Statistical Analysis

Our primary analysis used the Cox proportional hazards regression model (coxph in R; http://www.r-project.org/) for time to requirement of insulin treatment. When HbA$_{1c}$ at diagnosis was included as a continuous covariate, proportional hazard assumptions were not met. Baseline HbA$_{1c}$ was subsequently stratified into three groups to allow for a different hazard function in each group (HbA$_{1c}$ <7% [53 mmol/mol], 7–9% [53–75 mmol/mol], and >9% [75 mmol/mol]). The relationship between BMI and rate of progression to insulin treatment was nonlinear and was categorized into groups by an increment of 2 kg/m². Thus BMI and baseline HbA$_{1c}$ categories were included as strata variables to allow different baseline hazard functions for each BMI and baseline HbA$_{1c}$ subgroup, whereas the other covariates are

assumed to have the same effect across strata. A high level of missing data exist in baseline LDL and ALT measurements, and they were excluded from the phenotype model given the high collinearity between them and TG and HDL. The phenotypic model was stratified by the categorical groups for HbA$_{1c}$ and BMI, and it included all the other clinical covariates. To assess the effect of the diabetes GRS, we included the GRS as a covariate in the clinical phenotype model. For both models, $P < 0.05$ was considered significant.

RESULTS

Clinical Phenotype

The characteristics of the patients included in the study are shown in Table 1, along with the univariate association of each clinical variable with progression to requirement of insulin treatment. Year of diagnosis was an important predictor, showing a clear change in practice over time, with slower progression to insulin treatment in those diagnosed more recently. There was a univariately increased risk of progression to insulin treatment in those with a higher baseline TG, LDL, and ALT and a lower baseline HDL. The BMI distribution is presented in Fig. 1 and shows an increased rate of progression to insulin in those with a low and a high BMI relative to the lowest-risk group (with a BMI between 24 and 26 kg/m²). For example, compared with those with a BMI between 24 and 26 kg/m², those with a

Table 1—Characteristics of the patients and their univariate associations with diabetes progression

Covariate	Mean (SD) or *n*	HR (95% CI)	*P*	Total (*n*)
Females vs. males	2,877:2,373	1.09 (0.97–1.22)	0.15	5,250
Smokers vs. nonsmokers	3,999:1,251	1.06 (0.93–1.22)	0.38	5,250
Year of diagnosis	2002 (1999–2004)*	0.90 (0.88–0.92)	<0.001	5,250
Age at diagnosis (years)	61.8 (10.8)	0.96 (0.95–0.96)	<0.001	5,250
Social class†	2.84 (1.44)	0.93 (0.89–0.96)	<0.001	5,191
BMI (kg/m²)	31.3 (5.9)	NA‡	NA	5,250
Baseline HbA$_{1c}$ (%)	7.86 (2.05)/62	NA‡	NA	5,250
Baseline HDL (mmol/L)	1.2 (0.33)	0.39 (0.32–0.48)	<0.001	5,222
Baseline LDL (mmol/L)§	2.35 (0.85)	1.34 (1.06–1.71)	0.02	4,306
Baseline TG (mmol/L)§	2.77 (2.51)	1.77 (1.61–1.95)	<0.001	5,114
Baseline ALT (mmol/L)§	32.3 (17.0)	1.41 (1.24–1.61)	<0.001	4,504

*Year of diagnosis shows the median and quartile. †Per 1 SIMD unit, coded from 1 (most deprived) to 5 (most affluent). ‡Covariates treated as stratification factors. §Log transformed.
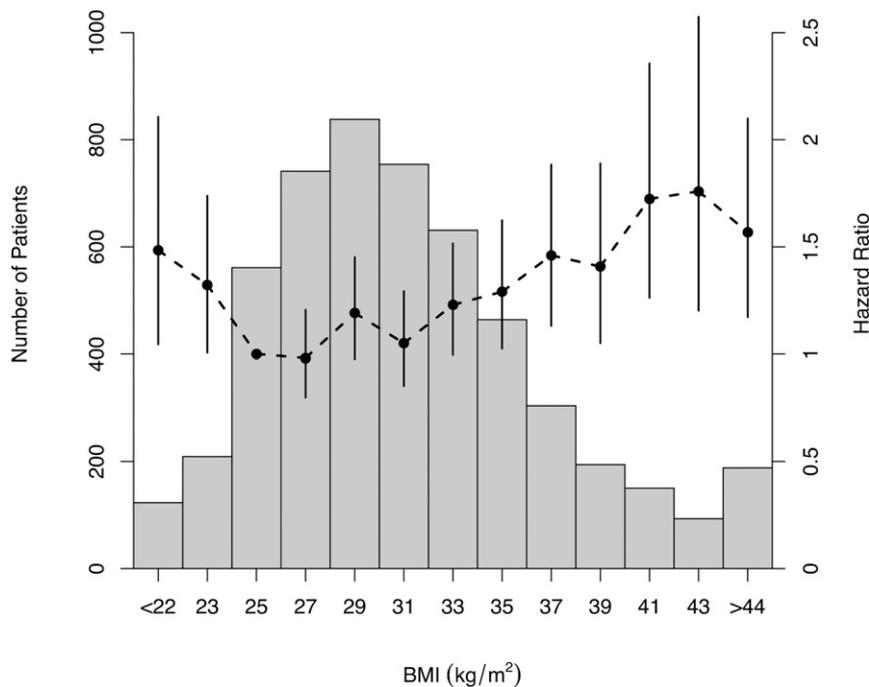
Figure 1—BMI distribution and its effect on progression to insulin requirement. Distribution of BMI in the population studied is shown on the *x*-axis. For each BMI band, the hazard rate ratio is shown relative to the BMI band of 24–26 kg/m^2; error bars are the 95% CIs for the hazard rate ratio.

BMI <24 kg/m^2 have a hazard ratio (HR) of 1.35 (95% CI 1.00–1.79), and those with a BMI >30 kg/m^2 have an HR of 1.30 (95% CI 1.06–1.58). As would be expected, HbA$_{1c}$ at diagnosis of diabetes is a major determinant of the risk of progression to insulin treatment, in particular when the composite end point relies on the HbA$_{1c}$ result. Compared with the group with baseline HbA$_{1c}$ <7% (53 mmol/mol), those with HbA$_{1c}$ between 7% (53 mmol/mol) and 9% (75 mmol/mol) had an HR of 1.98 (95% CI 1.71–2.3), and those with HbA$_{1c}$ >9% (75 mmol/mol) had an HR of 3.22 (95% CI 2.78–3.72) (data not shown).

Table 2 shows the full clinical phenotypic model. Within the BMI and HbA$_{1c}$ strata, a younger age at diagnosis of diabetes, an earlier year of diagnosis, lower HDL levels, and higher TG levels were independently associated with a faster rate of progression to insulin treatment.

Sensitivity Analysis
To assess the effect of using a combined end point rather than actual prescribed insulin use as the end point, we carried out the phenotypic modeling again using the single end point of sustained insulin treatment (Supplementary Table 2*A* and *B*); 723 patients eventually reached this end point. The results of this model were largely unchanged. The only additional significant effect was in the univariate analysis, where female

sex was associated with earlier insulin treatment. Since there was no detectable association when the composite end point was used, we infer that we successfully controlled for the insulin inertia effect by using the composite end point, which our data suggest is more commonly seen in men than women.

Diabetes Genetic Risk Factors
We added the type 2 diabetes GRS to the clinical phenotypic model reported in Table 2 and found no significant association with time to requirement of insulin treatment (HR 0.89 [95% CI 0.78–1.17]) (data for other covariates in the full model are not shown). A univariate analysis of the GRS also revealed no association (HR 1.02 per unit GRS [95% CI 0.88–1.18]) (data for other covariates in the full model are not shown).

We then examined the effect of the type 2 diabetes GRS on age at diagnosis of diabetes and age at requirement of insulin treatment. The results of a multiple linear regression with adjustment for BMI are shown in Fig. 2. Each unit of type 2 diabetes GRS was associated with being 2.43 years (95% CI 1.1–3.8) younger at diagnosis and 2.15 years (95% CI 0.71–3.19) younger at requirement of insulin treatment; as

Table 2—Adjusted Cox proportional hazards model for diabetes progression (from diagnosis of diabetes to requirement of insulin treatment)

Covariate	HR (95% CI)	*P*
Age at diagnosis (per 1 year)	0.96 (0.95–0.97)	<0.001
Year of diagnosis (per 1 year)	0.91 (0.89–0.94)	<0.001
Baseline TG (per 1 mmol/L)*	1.28 (1.15–1.42)	<0.001
Females vs. males	1.19 (1.05–1.36)	0.008
Baseline HDL (per 1 mmol/L)	0.70 (0.55–0.87)	0.002
Smokers vs. nonsmokers	1.11 (0.95–1.29)	0.20
Social class (per 1 SIMD unit from most deprived to most affluent)	0.96 (0.92–1.01)	0.09

Analysis was stratified by HbA1$_c$ at diagnosis and BMI category. *Log transformed.
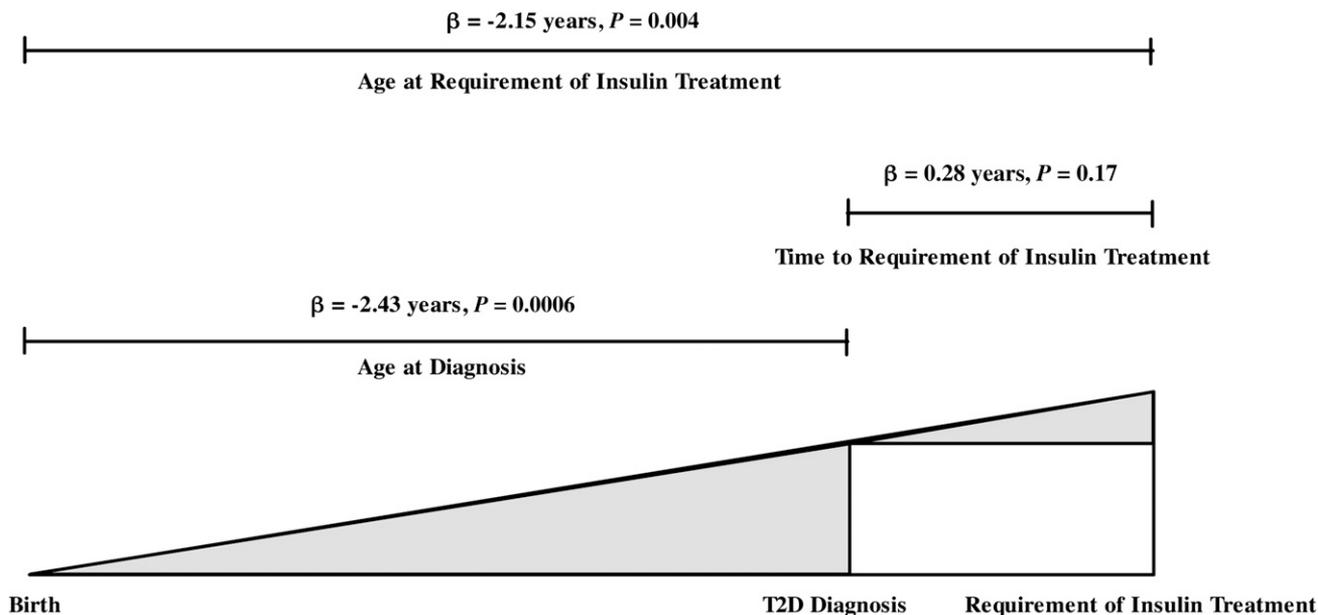
Figure 2—Type 2 diabetes (T2D) GRS association with different time spans in diabetes progression. The linear regressions were adjusted for BMI at diagnosis.

before, the GRS had no effect on the interval between diagnosis of diabetes and insulin requirement (0.28 years per GRS unit [95% CI −0.12 to 0.69]). Thus a greater genetic risk of diabetes is associated with a younger age at diagnosis of diabetes and subsequent younger age at insulin treatment, but not the time between diagnosis and insulin treatment, when compared with those with a lower genetic risk of diabetes.

In a secondary analysis we defined two GRS subscores: a β-cell function GRS (β-cell GRS) and an insulin resistance GRS. When included in the phenotypic model, we found no association of either the β-cell GRS (HR 1.10 per unit GRS [95% CI 0.90–1.34]) or insulin resistance GRS (HR 1.16 per unit GRS [95% CI 0.77–1.73]) with progression to insulin treatment after diabetes diagnosis (data for other covariates in the full model are not shown). Each unit increase of the β-cell GRS was associated with being 1.23 years (95% CI −0.66 to 3.12) younger at diagnosis and 1.0 years (95% CI −0.97 to 2.97) younger at requirement of insulin treatment; each unit increase of the insulin resistance GRS was associated with being 4.62 years (95% CI 0.7–8.5) younger at diagnosis and 3.69 years (95% CI −0.37 to 7.74) younger at

requirement of insulin treatment. In an exploratory analysis we assessed the effect of each variant on time to insulin treatment (Supplementary Fig. 2, Supplementary Table 1). No individual variants achieved significance for progression from diagnosis to requirement of insulin treatment after correction for multiple testing.

CONCLUSIONS

In this large, population-based study spanning the past 15 years, we have identified a number of clinical parameters that are associated with progression of diabetes through to insulin requirement. First, we show for the first time that high TG and low HDL levels are independently associated with progression beyond diabetes through to requirement of insulin treatment. Second, we confirm the finding of previous studies that young age, poor glycemic control, and low BMI at diagnosis are associated with rapid progression to requirement of insulin treatment (5,6). However, we report a U-shaped curve for BMI, with the lowest rate of progression at a BMI between 24 and 26 kg/m^2. Third, we show that established genetic variants associated with type 2 diabetes are associated with a younger onset of diabetes and a younger age at insulin treatment but are

not associated with diabetes progression.

Low HDL and high TG levels in the phenotypic model (and high ALT and high BMI when analyzed univariately) are associated with more rapid progression of diabetes. These results are consistent with our hypothesis that these parameters that drive progression to diabetes are associated with progression of diabetes after diagnosis. Because measures of insulin at diagnosis are not routinely collected, it is not possible to determine whether the changes in lipid and ALT levels are simply a marker of insulin resistance, with "insulin resistance" being the driver of progression, or whether these have a primary effect (e.g., lipotoxicity) on β-cell decline. It would be interesting to assess the effect of insulin sensitivity at diagnosis of diabetes on progression in a prospective collection because our data suggest that progression is associated with a more insulin-resistant phenotype (low HDL, high TG, high BMI).

The clinical phenotypic model that we have developed is largely consistent with previous publications. While some studies report that low BMI is associated with progression (12), others do not (14). Indeed, when we consider only a linear relationship between BMI and progression, the data do not show an

association of BMI with progression to insulin requirement. The U-shaped curve fits with our understanding of the biology of diabetes. Those who are normal weight at diagnosis (i.e., slim for someone with type 2 diabetes) are likely to be β-cell deficient and progress rapidly to insulin requirement, as shown in the UK Prospective Diabetes Study 26 (12). In contrast, those who are particularly adipose are likely to be markedly insulin resistant and have other factors that drive progression (e.g., lipotoxicity).

Surprisingly, we did not find a significant effect of type 2 diabetes risk variants on progression of diabetes. This lack of an association suggests that the biological factors captured by the diabetes risk variants do not play a large part in the biological mechanisms that result in progression of diabetes after diagnosis, and there certainly are biological mechanisms that may explain this difference, for example, glucotoxicity or lipotoxicity driving progression after the development of hyperglycemia (21).

We used the GRS to maximize our power for this analysis and to test the hypothesis that, when considered together, the diabetes genetic risk factors are associated with progression of diabetes. Given the effect sizes of these variants on prediabetes risk, we would not anticipate a large clinical effect on diabetes progression. However, for a GRS element that confers diabetes risk of an odds ratio of 1.5, which is similar to the effect size of rs7903146 in *TCF7L2*, this study has 80% statistical power to detect an increased diabetes progression rate of an HR of 1.09 at the $\alpha = 0.05$ level. As such we were well powered to detect even a modest effect of the GRS. It is important to acknowledge that the use of the GRS makes an assumption that all gene variants that contribute to diabetes risk also contribute to progression. To explore heterogeneity in the effect of the diabetes risk variants on the rate of diabetes progression, we carried out a single-variant analysis. This analysis was underpowered and should only be considered exploratory, but it did not reveal any one diabetes risk variant that was associated with the progression of diabetes. A much larger multicenter

analysis would be required to explore the effect of individual diabetes risk variants on diabetes progression.

We used an observational data set to identify a large number of patients followed up for a sufficient length of time to enable a study of progression from diagnosis to the requirement of insulin treatment. There are no prospective studies available that are in any way comparable in size and duration of follow-up. However, the use of observational data does restrict analysis to biomarkers collected during routine clinical care. Therefore, pancreatic autoantibody titers and insulin or homeostasis model assessment–derived measures could not be included in the analysis. To avoid inclusion of patients with type 1 diabetes, we excluded patients who were diagnosed at an age younger than 35 years or who progressed to insulin treatment within 1 year; however, patients with slower onset late autoimmune diabetes in adults could have been included, and this may account for the more rapid progression in the nonobese patients. There are further limitations to this study that should be acknowledged. First, because this is a consented biobank, there is potential for bias in those included in the study; however, approximately half of the population with type 2 diabetes in the region are included, so the study cohort should be reasonably representative. Second, the use of clinical data relies on patients engaging in clinical care and remaining in the region; however, because of the free health care system, the comprehensive coverage of all patients by the primary care system, and the static population, this should add minimal bias. Finally, only 56% of the available population were included in the study, largely because of incomplete data for those who were excluded, and thus the study cohort may not be completely representative of the population.

Another important consideration that we cannot include in this analysis is the behavioral factors that may affect the rate of progression. Unlike prospective studies in which activity, diet, and adherence can be assessed, these data are not available in routine health

records and so cannot be incorporated into the model. The inclusion of the covariates of social deprivation score, smoking status, and baseline BMI may partly capture the effect of diet and lifestyle on progression, but it is possible that the lack of contribution of the type 2 diabetes GRS reflects masking of the biological effect by these and other unmeasured variables.

The lack of an association of the total type 2 diabetes GRS and in particular a GRS derived from known β-cell genes needs some consideration because low β-cell function at diagnosis is strongly associated with progression to insulin treatment (12). These variants are well established as affecting β-cell function when assessed in normal individuals without diabetes (9,20). If β-cell function could be measured at exactly the point at which diabetes develops, it would be the same for all individuals for a given level of insulin resistance. Therefore, a genetic defect in insulin secretion would result in diabetes developing at an earlier age, as we see in our data, but insulin secretion, if measured when diabetes develops, should not differ between individuals with different genotypes and should therefore not affect the progression rate of diabetes. This is also consistent with cross-sectional analyses that report that diabetes risk variants are associated with earlier use of insulin treatment (22,23); this should not be misinterpreted as a greater progression to insulin from diagnosis of diabetes.

In summary, we report that genetic variants of type 2 diabetes risk result in a younger age at diagnosis of diabetes and, as a result, a younger age at which insulin is required; however, in a well-powered analysis these are not associated with the rate at which diabetes progresses following diagnosis of diabetes. Our results suggest that the genetic factors that predispose to diabetes are different from those that cause progression of diabetes, which may be mediated by other mechanisms such as glucolipotoxicity, endoplasmic reticulum, and oxidative stress (21). Our findings that an increased rate of progression of diabetes is associated with obesity, low HDL levels, and high TG levels would certainly support this

conjecture. Further genetic studies such as a sufficiently powered genome-wide association study may help elucidate these mechanisms.

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