

# A Risk Score for Type 1 Diabetes Derived From Autoantibody-Positive Participants in the Diabetes Prevention Trial-Type 1

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**OBJECTIVE** — The accurate prediction of type 1 diabetes is essential for appropriately identifying prevention trial participants. Thus, we have developed a risk score for the prediction of type 1 diabetes.

**RESEARCH DESIGN AND METHODS** — Diabetes Prevention Trial-Type 1 (DPT-1) participants, islet cell autoantibody (ICA)-positive relatives of type 1 diabetic patients ( $n = 670$ ), were randomly divided into development and validation samples. Risk score values were calculated for the validation sample from development sample model coefficients obtained through forward stepwise proportional hazards regression.

**RESULTS** — A risk score based on a model including log-BMI, age, log-fasting C-peptide, and postchallenge glucose and C-peptide sums from 2-h oral glucose tolerance tests (OGTTs) was derived from the development sample. The baseline risk score strongly predicted type 1 diabetes in the validation sample ( $\chi^2 = 82.3$ ,  $P < 0.001$ ). Its strength of prediction was almost the same ( $\chi^2 = 83.3$ ) as a risk score additionally dependent on a decreased first-phase insulin response variable from intravenous glucose tolerance tests (IVGTTs). Biochemical autoantibodies did not contribute significantly to the risk score model. A final type 1 diabetes risk score was then derived from all participants with the same variables as those in the development sample model. The change in the type 1 diabetes risk score from baseline to 1 year was in itself also highly predictive of type 1 diabetes ( $P < 0.001$ ).

**CONCLUSIONS** — A risk score based on age, BMI, and OGTT indexes, without dependence on IVGTTs or additional autoantibodies, appears to accurately predict type 1 diabetes in ICA-positive relatives.

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The increased understanding of the immune pathogenesis of type 1 diabetes has raised the possibility that interventions could delay or prevent its

occurrence. This has led to the performance of prevention trials (the European Nicotinamide Diabetes Intervention Trial and the Diabetes Prevention Trial-Type 1

[DPT-1]) to test interventions in individuals with autoimmune pre-diabetes (1–3). Although there was no overall treatment effect in these trials, they have shown that it is now possible to perform such studies using prediction methodologies. The recruitment of individuals with prespecified degrees of risk was successfully achieved through the assessment of relatives of type 1 diabetic patients with autoantibody determinations and metabolic testing.

Despite this measure of success, there is still a need to improve prediction methodology for type 1 diabetes. Efficiency could be enhanced by refining test selection and interpreting test results more meaningfully. Procedures for assessing risk have involved oral glucose tolerance tests (OGTTs) and intravenous glucose tolerance tests (IVGTTs); yet, it is not known whether both tests are necessary for prediction. Also, since the magnitude of glucose levels within the normal range has been shown to be indicative of type 1 diabetes risk (4), traditional definitions of hyperglycemia, such as impaired glucose tolerance, might not maximize the OGTT's value for prediction.

Besides improving accuracy and efficiency, a quantitative, standardized approach to prediction should also be helpful. Outcomes across trials could then be interpreted in the context of target populations with clearly defined risk. Although the European Nicotinamide Diabetes Intervention Trial and DPT-1 utilized similar methods for prediction, there were still substantial differences. Such an approach might also lead to improved monitoring of the progression to type 1 diabetes.

The most extensive information available for developing prediction strategies for type 1 diabetes resides in the data from the two insulin intervention trials that constituted DPT-1. Using the DPT-1 data, a risk score was developed to refine the prediction of type 1 diabetes in relatives of patients.

## RESEARCH DESIGN AND METHODS

Of 97,273 samples assessed for islet cell autoantibodies (ICAs),

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**Abbreviations:** DPT-1, Diabetes Prevention Trial-Type 1; FPIR, first-phase insulin response; GAD65; glutamic acid decarboxylase; HOMA-IR, homeostasis model assessment of insulin resistance; ICA, islet cell autoantibody; IVGTT, intravenous glucose tolerance test; mIAA, microinsulin antibodies; OGTT, oral glucose tolerance test.

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3.6% were positive. Of 711 individuals who participated in the DPT-1 insulin trials, data from 670 ( $n = 356$  for the parenteral insulin trial and  $n = 314$  for the oral insulin trial) were analyzed. Inclusion was based on data completeness for covariates used to develop predictive models. Most of the exclusions were due to absent BMI determinations ( $n = 26$ ).

The risk algorithm in DPT-1 was described previously (2,3). The presence of ICAs was required for entry into both trials. If the first-phase insulin response (FPIR) of an IVGTT was below a defined threshold and/or an OGTT was abnormal, individuals were estimated to be at >50% 5-year risk and eligible for the parenteral insulin trial. If neither criterion was present, but insulin autoantibodies were positive, the estimated 5-year risk was 26–50% and individuals were eligible for the oral insulin trial.

DPT-1 participants were tested for ICAs at screening. Samples were also obtained for the subsequent testing of biochemical autoantibodies. ICA-positive individuals underwent IVGTTs followed by OGTTs. Median intervals from the initial screen, the IVGTT, and the OGTT to randomization were 1.18, 0.17, and 0.04 years, respectively. The parenteral insulin trial intervention included twice-daily injections of 0.125 units/kg of recombinant human ultralente insulin (Humulin U; Eli Lilly) with adjustments for weight and hypoglycemia, along with yearly 4-day intravenous insulin infusions at 0.015 units  $\cdot$  kg $^{-1}$   $\cdot$  h $^{-1}$  with adjustments for glucose. The oral insulin trial intervention included recombinant human insulin crystals at a dose of 7.5 mg/day. OGTTs were performed at 6-month ( $\pm 3$  months) intervals after randomization in both trials. The oral glucose dose was 1.75 g/kg (75-g maximum). Plasma glucose and C-peptide measurements were obtained after fasting and at 30, 60, 90, and 120 min. Most individuals were diagnosed with type 1 diabetes at routine visits. If glucose values were in the diabetes range (fasting glucose  $\geq 126$  mg/dl and/or 2-h glucose  $\geq 200$  mg/dl), a confirmation visit was arranged. If glucose values were not confirmed, participants continued to be followed at 6-month intervals.

### Laboratory measures

Methodologies for assessing autoantibody positivity have been described (5). ICAs were determined by indirect immunofluorescence; titers  $\geq 10$  JDF units were considered positive. Glutamic acid decar-

boxylase (GAD65) and ICA512 autoantibodies were measured simultaneously by a combined radioassay. Microinsulin autoantibodies (mIAA) were also measured by radioassay.

Plasma glucose levels were measured by the glucose oxidase method. Insulin and C-peptide levels were measured by radioimmunoassay. Interassay coefficients of variation for the insulin assay were 4.5% in the high reference pool and 6.9% in the low reference pool. Those for the C-peptide assay were 6.9 and 7.8% for the relatively high and low reference pools, respectively.

The FPIR was defined as the sum of insulin levels at the first and third minutes of the IVGTT. An FPIR less than the 10th percentile according to age norms was considered below threshold and was utilized for trial eligibility, except for parents, for whom a cutoff of less than the 1st percentile was used. An FPIR less than the 10th percentile according to age norms (FPIR less than the 10th percentile) was utilized for these analyses. C-peptide values in the undetectable range ( $< 0.2$  ng/ml) were assigned a value of 0.1 ng/ml. Fasting glucose measurements were obtained at  $-10$  min and at time 0; the latter were utilized for the analyses, except for three individuals with missing values at time 0. Initial heights and weights were considered as baseline. The homeostasis model assessment of insulin resistance (HOMA-IR) was defined as fasting glucose (mmol/l)  $\times$  fasting insulin (mU/l)/22.5 (6,7). For simplicity, the total glucose and total C-peptide, defined as the totals of OGTT postchallenge glucose and C-peptide values (computed for each as the 30-, 60-, 90-, and 120-min sum), were utilized; they correlated very well with the respective areas (trapezoidal rule) under the curve ( $r = 0.99$  for both).

### Data analysis

The  $t$  test and  $\chi^2$  test were utilized for simple comparisons, and the log-rank test was used to compare the distributions of event times between groups. Linear regression and Pearson correlations were used to describe linear relations among variables. The Cox proportional hazards regression model was used to examine covariate effects on the type 1 diabetes risk over time from randomization. The Kaplan-Meier estimate of the survival function was used to obtain an estimate of the cumulative incidence of type 1 diabetes over time. These results were used to estimate the 5-year type 1 diabetes risk for

each participant using the methods described in the APPENDIX. Prediction accuracy was assessed by computation of the cumulative incidence within subgroups defined according to the estimated 5-year risk. The accuracy of prediction was also assessed with receiver operator curves.

A split-sample cross-validation procedure was utilized to develop and assess a risk score. A randomly selected development sample of half the participants was used for risk score development. The other half of the participants constituted the validation sample. Risk scores from the development sample were formulated according to coefficients of variables remaining from forward stepwise proportional hazards modeling. A univariate  $P$  value  $< 0.05$  was required for entry into stepwise modeling, and a  $P$  value  $< 0.05$  was required for final selection into the model. SAS version 9.1.3 was used for the analyses. All  $P$  values are two sided.

**RESULTS** — The mean  $\pm$  SD age and BMI for the 670 participants (56% male) were  $13.8 \pm 9.6$  years (range 3.0–46.0) and  $19.8 \pm 5.0$  kg/m $^2$  (12.5–52.1), respectively. On average, type 1 diabetes occurred after  $2.5 \pm 1.5$  years of follow-up ( $n = 241$ ). Those who did not develop type 1 diabetes were followed for  $3.6 \pm 1.7$  years ( $n = 429$ ).

By a random process, the full cohort was divided equally into development and validation samples ( $n = 335$  for both). There were no significant differences between the two samples with regard to age, BMI, sex, or the occurrence of type 1 diabetes (37% in the development sample and 35% in the validation sample). As shown in Table 1, there were also no significant differences for any of the metabolic or autoantibody variables examined.

In univariate analyses that utilized proportional hazards models, there were statistically significant, positive associations of type 1 diabetes with the 2-h glucose and total glucose ( $P < 0.001$  for both) but not with the fasting glucose or log-HOMA-IR. Type 1 diabetes was inversely related to the C-peptide indexes ( $P = 0.003$  for log-fasting C-peptide;  $P < 0.001$  for total C-peptide). Type 1 diabetes was also significantly associated with ICA512 ( $P = 0.003$ ) but not with GAD65 or mIAA ( $n = 257$  for the latter due to missing values). There were also positive associations of type 1 diabetes with FPIR less than the 10th percentile ( $P = 0.034$ ), log-(HOMA-IR/FPIR) ( $P < 0.001$ ), and the number of biochemical autoantibodies

Table 1—Characteristics of the development and validation samples

	Development	Validation†
<i>n</i>	335	335
Fasting glucose (mg/dl)	86.2 ± 9.3	86.2 ± 9.1
2-h glucose (mg/dl)	114 ± 28	113 ± 27
Total glucose (mg/dl)/100	5.26 ± 1.06	5.25 ± 1.07
Fasting C-peptide (ng/ml)	1.03 ± 0.66	1.06 ± 0.70
Total C-peptide (ng/ml)/10	1.70 ± 0.75	1.65 ± 0.68
Biochemical autoantibodies (number)*	1.36 ± 0.99	1.45 ± 0.99
ICA512 (%)	43	47
GAD65 (%)	67	69
mIAA (%)*	48	52
FPIR less than the 10th percentile (%)	42	43

Data are means ± SD or percent. \**n* = 257 for development sample and *n* = 258 for validation sample. †*P* > 0.05 for all comparisons.

(*P* = 0.029; *n* = 257); there were inverse associations with height (*P* < 0.001), log-BMI (*P* = 0.049), and age (*P* < 0.001).

To obtain a risk score from the development cohort, forward stepwise modeling was performed in which all variables with univariate *P* values <0.05 (and *n* = 335) were included. Type 1 diabetes remained significantly associated with the total glucose (*P* < 0.001), total C-peptide (*P* < 0.001) and log-fasting C-peptide (now positively associated at *P* = 0.039), FPIR less than the 10th percentile (*P* = 0.021), log-BMI (now positively associated at *P* < 0.001), and age (*P* < 0.001). When each of the autoantibody variables was added back to the model, none were significantly associated with type 1 diabetes. (The backward elimination procedure yielded the same subset of predictors.)

Risk scores were determined from a model that included all variables remaining from the stepwise regression and a model that excluded FPIR less than the

10th percentile (Table 2). The performance of each risk score was examined in the validation sample cohort. The degree of association of type 1 diabetes with the risk scores was almost the same (proportional hazards model  $\chi^2 = 83.3$  with and 82.3 without the inclusion of FPIR less than the 10th percentile, both *P* < 0.001 on 1 d.f.). The area under the receiver operator curve for the risk score with FPIR less than the 10th percentile excluded was almost identical to that for the risk score with it included (0.81 for both, *P* < 0.001). In the subsequent analyses shown, only the model without FPIR less than the 10th percentile is utilized.

The model derived from the development sample was assessed further in the validation sample cohort. Using the development sample coefficients, a risk score was calculated for each validation sample participant that was then used to obtain an estimate of that participant's 5-year risk of type 1 diabetes (see APPEN-

DIX). Validation sample participants were then divided into subgroups according to the estimated 5-year risk (<25, 26–49, 50–74, and ≥75%). Figure 1 shows the cumulative incidence of type 1 diabetes within these 5-year risk subgroups. The curves were progressively steeper as the predicted risk increased (log-rank: *P* < 0.001). Within these subgroups, the respective estimated 5-year risks were 13, 29, 55, and 87%.

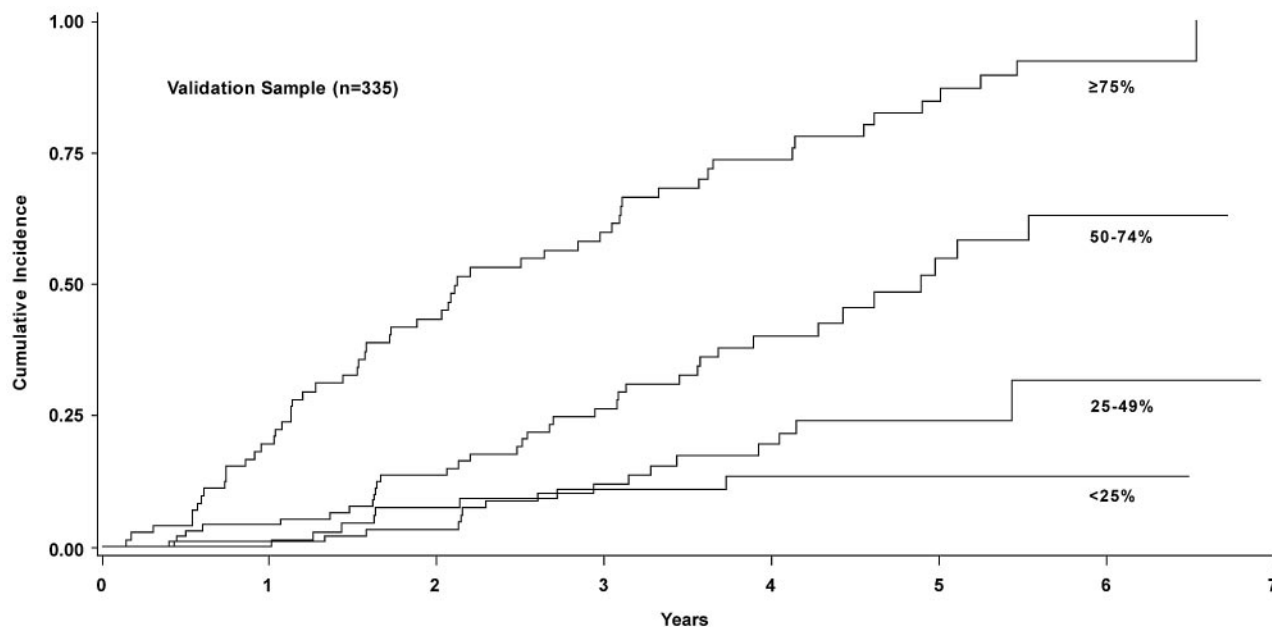
A type 1 diabetes risk score ([mean ± SD] 6.64 ± 1.00) was derived from all 670 participants with the same variables as those in the development sample model in order to maximize available information (see APPENDIX). As expected, type 1 diabetes was significantly associated with all variables that were included in the development sample risk score model (*P* < 0.001), and the type 1 diabetes risk score was highly correlated with the development sample risk score (*r* = 0.98). When FPIR less than the 10th percentile and each of the autoantibody variables were added back individually to the model, none was significantly associated with type 1 diabetes. The remaining analyses utilize the type 1 diabetes risk score.

Prediction by the type 1 diabetes risk score was assessed separately in the parenteral and oral insulin trial cohorts. Although these cohorts differed in that the parenteral trial cohort had a much higher occurrence rate (47 vs. 27%; hazard ratio 2.06 [95% confidence limit 1.59–2.67], *P* < 0.001), the type 1 diabetes risk score was strongly predictive of type 1 diabetes in each cohort (proportional hazards model  $\chi^2$  for the parenteral and oral trial cohorts were 119.2 and 55.8, respectively) (both *P* < 0.001 on 1 d.f.).

Table 2—Models for prediction scores from stepwise proportional hazards regression in the development sample (*n* = 335)\*

	Coefficient ± SE	$\chi^2$	Hazard ratio (95% CI)
Model 1			
Log-BMI (kg/m <sup>2</sup> )	2.85 ± 0.58	24.2	17.2 (5.5–53.5)†
Age (years)	−0.11 ± 0.02	22.5	0.89 (0.85–0.94)†
Total glucose (mg/dl)/100	0.84 ± 0.08	103	2.33 (1.98–2.74)†
Log-fasting C-peptide (ng/ml)	0.39 ± 0.19	4.3	1.48 (1.02–2.13)‡
Total C-peptide (ng/ml)/10	−0.79 ± 0.22	12.8	0.45 (0.29–0.70)†
FPIR less than the 10th percentile	0.49 ± 0.21	5.4	1.63 (1.08–2.47)‡
Model 2			
Log-BMI (kg/m <sup>2</sup> )	2.41 ± 0.55	19.5	11.2 (3.8–32.8)†
Age (years)	−0.09 ± 0.02	19.1	0.91 (0.88–0.95)†
Total glucose (mg/dl)/100	0.85 ± 0.08	111	2.34 (2.00–2.74)†
Log-fasting C-peptide (ng/ml)	0.41 ± 0.19	4.8	1.51 (1.05–2.19)‡
Total C-peptide (ng/ml)/10	−0.93 ± 0.22	17.9	0.40 (0.26–0.61)†

\*A total of 124 of the participants developed type 1 diabetes; †*P* < 0.001; ‡*P* < 0.05.



**Figure 1**—Cumulative incidence curves in the validation sample ( $n = 335$ ) according to estimated 5-year type 1 diabetes risk categories (25% intervals) from the development sample risk score. The curves were progressively steeper as the predicted risk category increased (log rank:  $P < 0.001$ ).

We assessed whether a change in the risk score was in itself predictive of type 1 diabetes. There was an overall increase ( $0.16 \pm 0.92$ ,  $P < 0.001$ ,  $n = 490$ ) in the type 1 diabetes risk score from baseline to the 1-year visit that was greater ( $0.37 \pm 1.20$  vs.  $0.07 \pm 0.78$ ,  $P = 0.004$ ) in those who developed type 1 diabetes ( $n = 157$ ) than in those who remained nondiabetic ( $n = 333$ ). In proportional hazards regression, change in the type 1 diabetes risk score from baseline to the 1-year visit (adjusted for the baseline risk score) was highly predictive of type 1 diabetes ( $\chi^2 = 62.9$ ,  $P < 0.001$ ). The impact of change in the type 1 diabetes risk score is evident among participants in the 50–74% 5-year risk category at baseline who were seen at the 1-year visit. Type 1 diabetes occurred more frequently in those progressing to the  $\geq 75\%$  5-year risk category at the 1-year visit than in those remaining in the 50–74% risk category (28 of 40 vs. 17 of 41,  $P = 0.002$ ).

**CONCLUSIONS**— The comprehensive baseline data from DPT-1 has provided the opportunity to develop and validate a risk score for type 1 diabetes among relatives with autoimmune prediabetes. Using a split-sample validation procedure, a model was fit in a development sample and its performance was examined in a validation sample. The

development sample risk score was highly predictive of type 1 diabetes in the validation sample.

The change in the type 1 diabetes risk score from baseline to the 1-year visit was also highly predictive of type 1 diabetes. This finding further verifies the type 1 diabetes risk score and suggests that it can be used to monitor type 1 diabetes progression. With such monitoring, individuals initially deemed ineligible for prevention studies could subsequently be enrolled. Also, monitoring with a risk score could have clinical utility as interventions for pre-diabetes become available. The increase in the risk score from baseline to the 1-year visit in those who subsequently developed type 1 diabetes is consistent with DPT-1 findings (8) of a gradual progression to type 1 diabetes.

The type 1 diabetes risk score was strongly predictive of type 1 diabetes in both the parenteral and oral insulin trial cohorts, despite substantially different type 1 diabetes occurrence rates. Although these findings should not be viewed as part of the validation procedure, they suggest that the type 1 diabetes risk score could have applicability over a range of risk levels and occurrence rates.

Since the findings are contingent upon the presence of ICAs in a selected cohort, one cannot say to what extent the type 1 diabetes risk score and its derived

risk estimates apply to relatives identified through autoantibodies other than ICAs or to ICA-negative relatives. Also, other selection criteria for the DPT-1 trials besides ICAs could affect the type 1 diabetes risk score's applicability. Moreover, if methodologies for glucose and C-peptide measurements differ from those utilized in DPT-1, the risk estimates derived from the type 1 diabetes risk score might not be fully applicable. Finally, the type 1 diabetes risk score is not a definitive disease indicator; rather, it provides a probability.

The biochemical autoantibodies added little to the strength of the type 1 diabetes risk score model. Those autoantibodies are known predictors of type 1 diabetes (9–12). However, it is possible that once autoantibody positivity is established and other information is available, the presence or absence of other autoantibodies adds relatively little to prediction.

Even though FPIR less than the 10th percentile was predictive of type 1 diabetes, it contributed little additional prediction accuracy when it was included in the risk score model. This was evident in the similar  $\chi^2$  values for the risk scores and their almost identical areas under the receiver operator curves with and without FPIR less than the 10th percentile included as a variable in the risk score model. Thus, IVGTTs may not contribute

much prediction information beyond that of OGTTs.

Risk factors for type 1 diabetes have been examined, but little information is available regarding risk scores for type 1 diabetes. A prognostic risk index was developed in a recent study (11). In a sub-cohort that was followed in that study, HOMA-IR/FPIR was predictive of type 1 diabetes. This finding is consistent with that of an earlier study (10) and another study from DPT-1 (13). Although type 1 diabetes was related to HOMA-IR/FPIR in the present study, it was not among the variables retained for the risk score model.

Type 1 diabetes occurrence has been found to be associated with autoantibodies (9–17), FPIR (10–13,16,18), glucose intolerance (19,20), and an elevated proinsulin-to-C-peptide ratio (17). In addition, we have recently shown that glucose and C-peptide data from OGTTs can be strongly predictive (4), even in relatives with normal glucose tolerance. BMI has been reported to be predictive of type 1 diabetes in DPT-1 (18). Also, indirect evidence suggests an association between type 1 diabetes occurrence and BMI (21,22).

Since the analyses were performed solely for developing a predictive model, associations in the multivariate analyses should be interpreted cautiously. Certain variables that added relatively little to prediction, such as biochemical autoantibodies and IVGTT indexes, are certainly still important for understanding the development of type 1 diabetes.

DPT-1 used a two-stage approach for assessing risk in relatives of type 1 diabetic patients. The first stage identified autoantibody-positive relatives through screening, whereas the second stage further characterized risk according to the presence of abnormal glucose tolerance and IVGTT abnormalities. It appears that for future prevention trials, a first stage that includes autoantibody testing should be maintained. However, with the judicious selection of available information and with more quantitative methodology, risk characterization in the second stage can now be accomplished more efficiently and accurately.

In conclusion, a risk score that utilizes age and adiposity together with measures of oral glucose tolerance and  $\beta$ -cell function from OGTTs appears to accurately quantify the risk of developing type 1 diabetes among relatives with autoimmunity as characterized by ICA positivity.

## APPENDIX

### Calculation of 5-year risk from a proportional hazards model

Methodology regarding the calculation can be found in ref. 23. The Cox proportional hazards model expresses the hazard function and corresponding survival probability for a subject with a covariate vector  $x$  as a linear function of a set of regression coefficients  $\beta$  using the linear predictor  $x' \beta$ . Let  $\bar{x}$  designate the mean of the covariates in the sample and let  $\bar{S}(t)$  designate the Kaplan-Meier estimate of the survival function in the complete cohort as of time  $t$ . Then, from the proportional hazards model, this implies that the survival function from an individual with covariate vector  $x$  is obtained as the following:

$$S(t/x) = \bar{S}(t)^{\exp[(x-\bar{x})'\beta]} = \bar{S}(t)^{\exp[x'\beta - \bar{x}'\beta]}$$

The corresponding  $t$ -year risk of the event is then obtained as  $1 - S(t/x)$ .

From the final model based on all DPT-1 subjects, the type 1 diabetes risk score (linear predictor  $x' \beta$ ) was calculated according to the following formula:

$$\begin{aligned} \text{Type 1 diabetes risk score} = x' \beta = & 1.569 \times [\log\text{-BMI (kg/m}^2)] - 0.056 \times [\text{age (years)}] \\ & + 0.813 \times [\text{total glucose (mg/dl)/100}] \\ & + 0.476 \times [\log\text{-fasting C-peptide (ng/ml)}] \\ & - 0.848 \times [\text{total C-peptide (ng/ml)/10}] \end{aligned}$$

This type 1 diabetes risk score is then converted to the estimated 5-year risk according to the following formula:

$$5\text{-year risk} = 1 - 0.543^{\exp(x'\beta - 6.638)}$$

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