PLOS ONE

A clinical diabetes risk prediction model for prediabetic women with prior gestational diabetes

Bernice Man[1]*, **Alan Schwartz**[2], **Oksana Pugach**[3], **Yinglin Xia**[4], **Ben Gerber**[1]

1 Division of Academic Internal Medicine and Geriatrics, Department of Medicine, University of Illinois at Chicago, Chicago, Illinois, United States of America, **2** Department of Medical Education, Department of Pediatrics, University of Illinois at Chicago, Chicago, Illinois, United States of America, **3** Institute for Health and Research Policy, University of Illinois at Chicago, Chicago, Illinois, United States of America, **4** Division of Gastroenterology and Hepatology, Department of Medicine, University of Illinois at Chicago, Chicago, Illinois, United States of America

* bernicem@uic.edu

Abstract

Introduction

Without treatment, prediabetic women with a history of gestational diabetes mellitus (GDM) are at greater risk for developing type 2 diabetes compared with women without a history of GDM. Both intensive lifestyle intervention and metformin can reduce risk. To predict risk and treatment response, we developed a risk prediction model specifically for women with prior GDM.

Methods

The Diabetes Prevention Program was a randomized controlled trial to evaluate the effectiveness of intensive lifestyle intervention, metformin (850mg twice daily), and placebo in preventing diabetes. Data from the Diabetes Prevention Program (DPP) was used to conduct a secondary analysis to evaluate 11 baseline clinical variables of 317 women with prediabetes and a self-reported history of GDM to develop a 3-year diabetes risk prediction model using Cox proportional hazards regression. Reduced models were explored and compared with the main model.

Results

Within three years, 82 (25.9%) women developed diabetes. In our parsimonious model using 4 of 11 clinical variables, higher fasting glucose and hemoglobin A1C were each associated with greater risk for diabetes (each hazard ratio approximately 1.4), and there was an interaction between treatment arm and BMI suggesting that metformin was more effective relative to no treatment for BMI $\geq$ 35kg/m^2 than BMI < 30kg/m^2. The model had fair discrimination (bias corrected C index = 0.68) and was not significantly different from our main model using 11 clinical variables. The estimated incidence of diabetes without treatment was 37.4%, compared to 20.0% with intensive lifestyle intervention or metformin treatment for women with a prior GDM.

Conclusions

A clinical prediction model was developed for individualized decision making for prediabetes treatment in women with prior GDM.

Introduction

Gestational diabetes mellitus (GDM) is a common medical complication of pregnancy with a prevalence of 7–9% [1–3]. Although GDM typically resolves after delivery, women remain at high risk of developing type 2 diabetes mellitus, with a cumulative incidence of 30–50% within 5–10 years of the index pregnancy [3, 4]. Women with a history of GDM are more likely to progress to diabetes compared to those without GDM despite the same degree of impaired glucose tolerance at baseline [5]. Thus, the American Diabetes Association (ADA) and American College of Obstetricians and Gynecologists recommend diabetes screening at 4–12 weeks postpartum and every 1–3 years thereafter [6, 7]. For those with prediabetes (with early evidence of abnormal glycemic parameters), screening is recommended annually.

For most adults with prediabetes, treatment involves intensive lifestyle intervention (ILI) and/or metformin. However, the expected treatment response differs based on individual clinical factors (e.g., beta cell function), including history of GDM. Specifically, among those with prior GDM, risk reduction with metformin is comparable to highly-effective ILI (both reducing 3-year risk of progression to diabetes by approximately 50%) [5]. In contrast, metformin is less effective than ILI in the general population, including parous women without a history of GDM [8]. Overall, evidence suggests there is heterogeneity in prediabetes treatment response when GDM history is considered [5, 9].

Individualized risk prediction with estimated treatment response may inform prediabetes treatment decisions [10, 11]. Women with prior GDM can become aware of their future risk of diabetes and potential benefit from metformin and/or ILI. Individualized risk/benefit assessment may improve diabetes risk perception and prediabetes treatment decisions in this high-risk population. Such an assessment may optimize the appropriate use of metformin and ILI, considering the risks and costs, personal preferences, and potential benefits. Individual risk estimation may improve clinical decision making and make diabetes prevention efforts more efficient, cost-effective and patient-centered [10, 11].

There are numerous models available to predict the risk of developing diabetes for the general population [10–15]. However, few use multivariable models to facilitate tailoring preventive interventions to individuals [10, 11, 16, 17]. Of the models specifically developed for women with prior GDM, predictors commonly include measures obtained during or soon after pregnancy (e.g., insulin use during pregnancy or breastfeeding history) [15]. In a multivariable analysis of 174 women with GDM in Sweden, predictors of diabetes within 5 years postpartum include parity, a first-degree family member with diabetes, fasting glucose and hemoglobin A1c (HbA1c) levels during pregnancy [18]. In another GDM-specific model, non-European origin, glucose concentration from the 75 gram, 2-hour oral glucose tolerance test (OGTT) at pregnancy, and body mass index (BMI) at 1–2 years post-partum were predictive of diabetes [19]. Use of models incorporating peripartum measures may be limited because such measures may not be consistently obtained and are not often readily available to different clinicians providing care years later. Additionally, these models do not consider prediabetes treatment response, and may not be generalizable to diverse ethnic minority populations in the U.S. or to women who have already developed prediabetes after pregnancy [18, 19].

Our objective was to develop a clinical diabetes risk prediction model specific for women with prior GDM. The model includes estimation of treatment response to metformin, ILI, or neither (placebo) and can be incorporated into a decision aid for clinicians to use in prediabetes treatment counseling.

Materials and methods

Study design

We conducted a secondary analysis of the Diabetes Prevention Program (DPP) data [8]. The analysis was conducted using the publicly-available data which included no participant identifying information. Our study findings can be replicated in its entirety from the DPP data available only upon request to the National Institute of Diabetes and Digestive and Kidney Diseases Central Repositories (https://repository.niddk.nih.gov/studies/dpp/). The DPP was a randomized, controlled clinical trial comparing the effectiveness of ILI, metformin (850 mg twice daily), and placebo for diabetes prevention over a mean follow-up period of 3.2 years. In addition, standard lifestyle recommendations were provided to all participants randomized to receive metformin or placebo. The ILI consisted of an individualized curriculum focusing on nutrition, exercise and behavioral modification. A weight reduction of at least 7 percent of initial body weight was the goal for participants assigned to ILI. The DPP was conducted from 1996–2001 at 27 sites in the U.S. Racial ethnic minorities and women with prior GDM were prespecified target groups in the DPP recruitment protocol [20]. The study design, rationale, and outcomes have been described previously [21]. The institutional review board of the University of Illinois at Chicago reviewed the study protocol and determined this study exempt from human subjects research oversight.

Study population

Diabetes Prevention Program participants were at least 25 years old, had a BMI $\geq$ 24 kg/m^2 ($\geq$ 22 kg/m^2 if Asian) and had prediabetes. Prediabetes was defined by a fasting glucose 95–125 mg/dL and a 2-hour 75-gram OGTT glucose 140–199 mg/dL. Participants were randomized to treatment with placebo, ILI, or metformin. Of note, women who were pregnant, less than 3 months postpartum, or currently nursing or within 6 weeks of completing nursing were excluded from the DPP trial. Women who answered the question, "Have you ever been told that you had a high sugar level or that you have diabetes?" and selected the answer "Only during pregnancy" were considered to have had GDM. The DPP study initially included a fourth intervention, troglitazone, which was discontinued in 1998 because of the drug's potential liver toxicity. Women with a history of GDM randomized to troglitazone were excluded from our analysis. Our study cohort included a subset of 317 women with prior GDM and prediabetes (Fig 1).

Candidate predictor variables

Candidate predictor variables for the model included 11 baseline clinical variables known to be associated with diabetes progression: age group, ethnicity, parental (either mother or father) history of diabetes (type not specified), BMI group, waist circumference, waist-to-hip ratio, fasting glucose and triglycerides, HbA1c, self-reported physical activity, and treatment arm (placebo, ILI, or metformin). For variables with multiple readings at baseline (waist circumference and hip girth), an average was used. BMI was grouped as < 30, 30 to < 35, and $\geq$ 35 kg/m^2. The age of participants was available in 5-year intervals and collapsed at both extremes: age <40 and age $\geq$ 65 years. A family history of diabetes was determined if either parent had
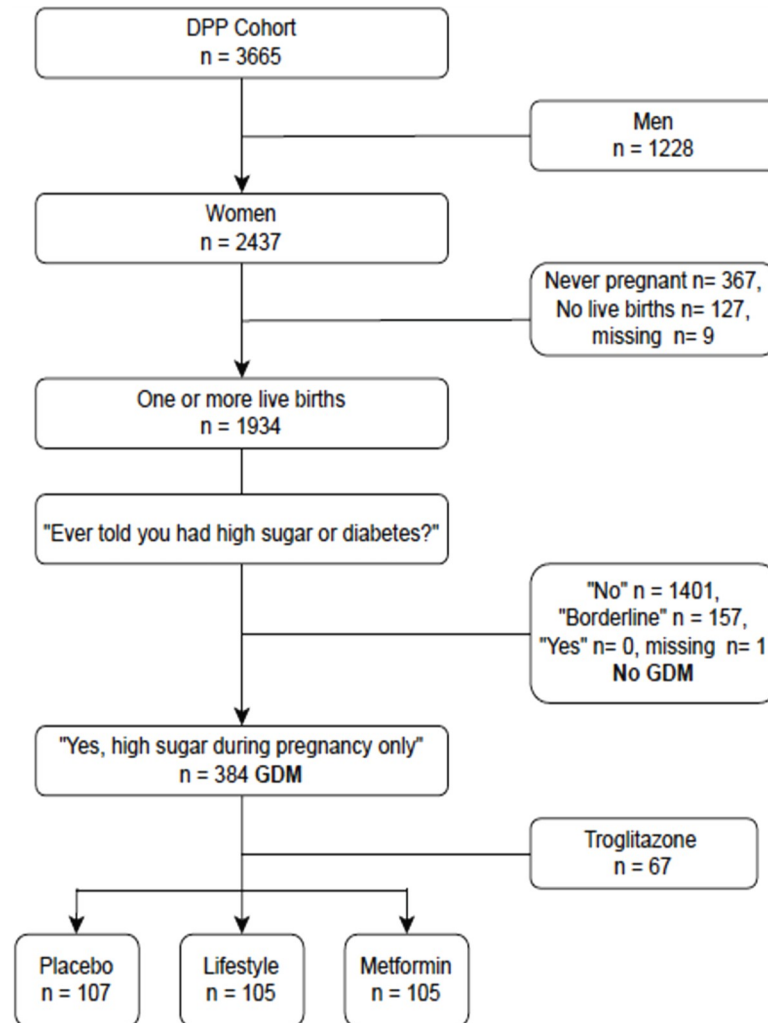
Fig 1. Flow diagram for selection of women with GDM in the DPP cohort.

diabetes. An unknown or negative parental history of diabetes was considered negative. Baseline leisure physical activity was assessed with a comprehensive list of activities in the DPP Modifiable Activity Questionnaire (MAQ), which estimated self-reported past-year activity by duration, frequency and relative intensity or metabolic equivalence task (MET) as expressed by MET-hours per week [22]. Physical activity estimates obtained from the MAQ correlated with measures of obesity and glucose tolerance in the DPP [23]. The 2011 Compendium of Physical Activity was used to determine the MET for each activity reported [24].

Outcome measures

The outcome measure was the development of diabetes as defined by the ADA fasting glucose diagnostic cut off value, which in June 1997 was lowered to 126 mg/dL from 140 mg/dL [25]. Diagnostic criteria for diabetes was defined by a fasting plasma glucose $\geq$ 140 mg/dL (until June 23, 1997) or $\geq$ 126 mg/dL (on or after June 24, 1997), or a 2-hour 75-gram oral glucose tolerance test (OGTT) $\geq$ 200 mg/dL [21]. The diagnosis of diabetes was confirmed if consecutive testing with the same criteria, usually within 6 weeks, was met. The data was explored for

potential misclassification of diabetes due to the change in diagnostic criteria and we found the ultimate outcome of diabetes at three years was unaffected. All seventeen women who had two or more consecutive glucose readings between 126–140 mg/dL before June 23, 1997 were ultimately diagnosed with diabetes during the three-year follow-up period. Of the women who did not develop diabetes, none had two consecutive fasting glucoses $\geq$ 126 mg/dL. Clinical assessments were performed routinely every six months during the average three years of monitoring.

Statistical analyses

Bivariate analyses. Descriptive statistics for continuous variables were expressed as median with interquartile range (IQR) due to our small sample size. Categorical variables were described as frequency and proportion. All statistical tests were two-sided. Fisher's exact and Kruskal Wallis were used, as appropriate for categorical and continuous variables, respectively, to test differences.

Prediction risk model development and evaluation. All models were developed by using multivariable Cox proportional hazards regression and informed by clinical knowledge and previous research [26, 27]. Continuous variables were standardized. Given the extreme right skewness of the fasting triglyceride data, the values were log-transformed to prevent large values from influencing the results. We determined, a priori, that a single model instead of a separate model for each treatment arm would be developed to maximize use of the subsampled DPP data. Residual diagnostic was performed for all models. Proportional hazard assumption for all covariates in all models were checked and satisfied. The 11 candidate variables, including treatment arm (placebo, ILI, or metformin), as well as interactions between treatment arm and BMI group, were entered into an initial model (Model 1). The interaction of treatment arm with BMI group was included because of observed heterogeneity in treatment effects with different BMI groups in the DPP study [8, 28]. We explored reduced models which included known, highly sensitive screening clinical variables (i.e. fasting glucose and HbA1c) and additional commonly accepted predictors (i.e. BMI group, fasting triglycerides) [10, 11, 29–31]. Finally, a parsimonious model (Model 2) was developed that only included significant predictors at 0.05 significance level from the bivariate analysis. Model 2 included screening clinical variables (HbA1c, fasting glucose), BMI group, treatment arm, and the BMI group by treatment arm interaction. To measure the discriminatory performance of the final parsimonious risk model, Harrell's C-statistic was computed with bias correction [32]. Internal validation was performed with 10-fold cross validation by randomly separating the data into 10 subsets, and estimating the parameters after omitting one of the 10 subsets. The model was applied to the omitted subset and Harrell's C statistics were calculated for discrimination for each omitted subset. All statistical analyses were performed using R version 3.6.1 (Survival, rms, Survminer, Caret, and survivalROC packages) and can be accessed through https://github.com/bsgerber/dpp-dppos.

Results

Bivariate analyses

Among 3665 adults with prediabetes, 317 (8.6%) women reported a history of GDM with treatment of placebo, ILI, or metformin. Table 1 shows the baseline characteristics of women with prior GDM by treatment arm. Among women with prior GDM: 61.5% were of reproductive age (< 45 years old) and 40.7% self-identified as non-Caucasian. Baseline characteristics were similar among the three treatments with the exception of waist-to-hip ratio (p = 0.02). Three years after randomization, 82 (25.9%) women developed diabetes (Table 2). Diabetes free survival curves for each treatment are provided in S1 Fig. The estimated incidence of diabetes

Table 1. Baseline characteristics by treatment assignment.

	Lifestyle (N = 105)	Metformin (N = 105)	Placebo (N = 107)	p
Age Group, N (%)				0.13
<40	38 (36.2%)	38 (36.2%)	39 (36.4%)	
40–44	29 (27.6%)	28 (26.7%)	23 (21.5%)	
45–49	23 (21.9%)	21 (20.0%)	30 (28.0%)	
50–54	5 (4.8%)	11 (10.5%)	14 (13.1%)	
55–59	5 (4.8%)	2 (1.9%)	1 (0.9%)	
60+	5 (4.8%)	5 (4.8%)	0 (0.0%)	
Ethnicity, N (%)				0.77
Caucasian	64 (61.0%)	66 (62.9%)	58 (54.2%)	
African American	18 (17.1%)	19 (18.1%)	26 (24.3%)	
Hispanic, of any race	18 (17.1%)	16 (15.2%)	20 (18.7%)	
All other	5 (4.8%)	4 (3.8%)	3 (2.8%)	
Smoking Status, N (%)				0.28
Current	8 (7.6%)	4 (3.8%)	5 (4.7%)	
Former	27 (25.7%)	22 (21.0%)	34 (31.8%)	
≤ 100 cig lifetime	70 (66.7%)	79 (75.2%)	68 (63.6%)	
PCOS History, N (%)				0.37
Yes	2 (1.9%)	0 (0.0%)	2 (1.9%)	
No	103 (98.1%)	105 (100.0%)	105 (98.1%)	
BMI Group kg/m^2, N (%)				0.55
< 30	29 (27.6%)	30 (28.6%)	25 (23.4%)	
30 to < 35	33 (31.4%)	41 (39.0%)	37 (34.6%)	
35+	43 (41.0%)	34 (32.4%)	45 (42.1%)	
Family History of Diabetes, N (%)	57 (54.3%)	53 (50.5%)	71 (66.4%)	0.05
Live Births, Median (IQR)	2.0 (2.0, 3.0)	2.0 (2.0, 3.0)	2.0 (2.0, 3.0)	0.99
Waist Circumference (cm), Median (IQR)	102.8 (93.0, 111.5)	98.3 (91.8, 107.3)	102.5 (91.1, 108.9)	0.18
Waist to Hip Ratio, Median (SD)	0.881 ((0.842, 0.929)	0.867 ((0.823, 0.912)	0.872 (0.836, 0.920)	0.07
Fasting Glucose (mg/dL), Median (IQR)	105 (100, 110)	105 (100, 112)	106 (101, 112)	0.49
Hemoglobin A1c (%), Median (IQR)	5.9 (5.5, 6.1)	5.8 (5.6, 6.1)	5.9 (5.5, 6.2)	0.66
MET-hours/week, Median (IQR)	10.6 (4.2, 18.6)	8.9 (4.0, 20.0)	8.5 (4.1, 16.2)	0.58
Systolic BP (mmHg), Median (IQR)	118 (109, 126)	115 (108, 124)	117 (109, 126)	0.60
Diastolic BP (mmHg), Median (IQR)	75 (70, 80)	76 (70, 81)	75 (70, 82)	0.98
Triglyceride (mg/dL), Median (IQR)	136 (97, 204)	119 (94, 179)	130 (98, 193)	0.46

Column percentages are presented.

Abbreviations: Cig cigarettes; PCOS Polycystic Ovarian Syndrome; BMI Body Mass Index; MET Metabolic Equivalent Task; IQR Interquartile Range; BP Blood Pressure.

without treatment (placebo group) was 37.4% for women with prior GDM, compared with 20% for either ILI or metformin (p < 0.01).

Risk models

Cox proportional hazard models for Models 1 and 2 are presented in Table 3. Using model 1, fasting glucose and HbA1C were always significant predictors of higher hazard. Women with

Table 2. Baseline characteristics by diabetes outcome.

	No Diabetes (N = 235)	Diabetes (N = 82)	p
Age Group, N (%)			0.44
<40	88 (37.4%)	27 (32.9%)	
40–44	59 (25.1%)	21 (25.6%)	
45–49	55 (23.4%)	19 (23.2%)	
50–54	18 (7.7%)	12 (14.6%)	
55–59	6 (2.6%)	2 (2.4%)	
60+	9 (3.8%)	1 (1.2%)	
Ethnicity, N (%)			0.14
Caucasian	148 (63.0%)	40 (48.8%)	
African American	44 (18.7%)	19 (23.2%)	
Hispanic, of any race	35 (14.9%)	19 (23.2%)	
All other	8 (3.4%)	4 (4.9%)	
Smoking Status, N (%)			0.97
Current	13 (5.5%)	4 (4.9%)	
Former	61 (26.0%)	22 (26.8%)	
≤100 cig lifetime	161 (68.5%)	56 (68.3%)	
PCOS History, N (%)			0.23
Yes	4 (1.7%)	0 (0.0%)	
No	231 (98.3%)	82 (100.0%)	
BMI Group (kg/m^2), N (%)			0.19
<30	59 (25.1%)	25 (30.5%)	
30 to <35	89 (37.9%)	22 (26.8%)	
35+	87 (37.0%)	35 (42.7%)	
Family History of Diabetes, N (%)	133 (56.6%)	48 (58.5%)	0.76
Live Births, Median (IQR)	2.0 (2.0, 3.0)	2.0 (2.0, 3.0)	0.88
Waist Circumference (cm), Median (IQR)	100.0 (92.0, 107.8)	103.9 (91.9, 112.6)	0.47
Waist to Hip Ratio, Median (SD)	0.876 (0.835, 0.914)	0.884 (0.837, 0.935)	0.43
Fasting Glucose (mg/dL), Median (IQR)	104 (100, 110)	111 (106, 118)	< 0.01
Hemoglobin A1c (%), Median (IQR)	5.8 (5.5, 6.1)	6.1 (5.7, 6.3)	< 0.01
MET-hours/week, Median (IQR)	9.0 (4.0, 18.5)	9.4 (4.8, 19.8)	0.58
Systolic BP (mmHg), Median (IQR)	116 (108, 126)	118 (111, 127)	0.20
Diastolic BP (mmHg), Median (IQR)	76 (70, 80)	74 (70, 83)	0.58
Triglyceride (mg/dL), Median (IQR)	129 (98, 186)	112 (91, 209)	0.70
Treatment Arm			<0.01
Placebo	67 (28.5%)	40 (48.8%)	
Lifestyle	84 (35.7%)	21 (25.6%)	
Metformin	84 (35.7%)	21 (25.6%)	

Column percentages are presented, row percentages are available in S1 Table.

Abbreviations: Cig cigarettes; PCOS Polycystic Ovarian Syndrome; BMI Body Mass Index; MET Metabolic Equivalent Task; IQR Interquartile Range; BP Blood Pressure.

https://doi.org/10.1371/journal.pone.0252501.t002

a BMI ≥ 35 kg/m^2 had the greatest risk of progressing to diabetes in the placebo arm (S2 Fig). Both models were evaluated and found to have fair discriminative performance corrected with ten-fold cross validation (Table 3). Using likelihood-ratio tests, we assessed the goodness of fit of Models 1 and 2 (rms package) and found no significant differences in discriminative performance. We include the diabetes prediction equation based on Model 2 in Table 4.

Table 3. Two models predicting progression to diabetes at three years for women with prior gestational diabetes.

Baseline Predictors[†]	Hazard Ratio (95% CI)	
	Model 1	Model 2
Treatment effect in normal BMI group		
Placebo		
Lifestyle	0.404 (0.121, 1.346)	0.527 (0.163, 1.709)
Metformin	1.108 (0.447, 2.751)	1.210 (0.510, 2.869)
Fasting glucose, mg/dL	1.537* (1.233, 1.914)	1.465* (1.198, 1.793)
Hemoglobin A1c, %	1.449* (1.096, 1.917)	1.379* (1.083, 1.755)
BMI group, kg/m^2, effect in placebo group		
< 30		
≥ 30 to < 35	0.678 (0.251, 1.829)	1.049 (0.442, 2.486)
≥ 35	0.537 (0.180, 1.605)	1.212 (0.564, 2.607)
Log triglycerides, mg/dL	0.953 (0.740, 1.228)	
Race/Ethnicity		
Caucasian		
African American	0.746 (0.372, 1.498)	
Hispanic	1.723 (0.934, 3.179)	
Other	1.647 (0.539, 5.031)	
Age group, years		
< 40		
40–44	1.022 (0.521, 2.005)	
45–49	1.370 (0.733, 2.560)	
50–54	1.483 (0.702, 3.133)	
55–59	1.144 (0.220, 5.938)	
60+	0.731 (0.093, 5.739)	
Family History	0.918 (0.575, 1.466)	
Waist circumference, cm	1.426 (0.955, 2.130)	
Waist-to-hip ratio	1.066 (0.820, 1.385)	
MET-hours/week	1.166 (0.931, 1.460	
BMI ≥ 30 to < 35 kg/m^2		
Lifestyle vs Placebo	1.627 (0.345, 7.676)	1.246 (0.274, 5.667)
Metformin vs Placebo	0.291 (0.066, 1.289)	0.257 (0.061, 1.083)
BMI ≥ 35 kg/m^2		
Lifestyle vs Placebo	1.175 (0.286, 4.830)	1.017 (0.251, 4.115)
Metformin vs Placebo	0.281 (0.072, 1.095)	0.247* (0.071, 0.858)
R^2	0.191	0.151
Bias corrected C	0.6577	0.6868

[†]continuous variables are standardized.

*$p < 0.05$

Abbreviations: CI confidence intervals; BMI body mass index.

https://doi.org/10.1371/journal.pone.0252501.t003

Additionally, time dependent receiver operating characteristic (ROC) curves were produced for both models (S3 Fig).

Discussion

A diabetes risk prediction model using four commonly-available clinical measures was successfully developed for women with prior GDM. Our model performed with similar

Table 4. Model equation[†] to calculate probability of developing diabetes at 3 years.

Probability of progression to DM = $1-S0(t)^{\exp(f(x))}$
S0(3 years) = 0.656
F(X) =
- 0.640 x TREATMENT$_L$
+ 0.191 x TREATMENT$_M$
+ 0.047 x BMI$_1$
+ 0.193 x BMI$_2$
+ 0.382 x ((FASTING GLUCOSE– 107.1293) / 7.4786)
+ 0.321 x ((HEMOGLOBIN A1c- 5.8427) /0.4834)
+ 0.220 x TREATMENT$_L$ x BMI$_1$
+ 0.017 x TREATMENT$_L$ x BMI$_2$
- 1.358 x TREATMENT$_M$ x BMI$_1$
- 1.400 x TREATMENT$_M$ x BMI$_2$

[†]S0 = 3-year survival probability for a woman with the reference covariate pattern where the categorical covariates are set at their reference (placebo, BMI group < 30) and continuous variables are set at the mean (continuous variables are standardized).

TREATMENT$_L$ 1 if treatment is lifestyle, 0 otherwise

TREATMENT$_M$ 1 if treatment is metformin, 0 otherwise

BMI$_1$ 1 if BMI $\geq$ 30 to <35 kg/m^2, 0 otherwise

BMI$_2$ 1 if BMI $\geq$ 35 kg/m^2, 0 otherwise

discrimination as other diabetes prediction models developed from the DPP for the general population [10, 11]. Similar to other models derived from the general population, our parsimonious model includes fasting glucose, HbA1c, BMI, and treatment (ILI, metformin, or placebo) [33]. These commonly available measures offer great value to clinicians in evaluating diabetes risk. Measurement of HbA1c is a guideline-recommended, routinely-assessed screening test for diabetes, and is known to predict diabetes in the DPP cohort and in other large community-based cohorts [25, 34, 35]. In addition, a woman's BMI is a modifiable, strongly-predictive risk factor for diabetes after a GDM pregnancy [19]. Although measures of abdominal obesity, waist circumference and waist-to-hip ratio correlate with cardiometabolic risk, neither added predictive value in our models [33, 36]. Furthermore, the addition of the triglyceride level, a clinical marker of metabolic syndrome and insulin resistance, did not improve discrimination [29, 30, 37, 38].

Other models have identified similar risk factors for diabetes among women with GDM [18, 19, 39]. In a prospective case-control study of 150 Australian women with GDM and 72 overweight women with normal glucose tolerance, GDM women with a high risk profile (elevated BMI, blood pressure, glucose, insulin, triglyceride, and lower high-density lipoprotein levels) were more likely to develop diabetes compared to women with a low-risk profile in a cluster analysis [40]. Among 1,263 Chinese women with prior GDM, waist circumference, body fat and BMI were all associated with an increased risk of diabetes, with waist circumference and body fat better indicators for diabetes than BMI [41]. Women with previous GDM have a high-risk profile similar to metabolic syndrome where there may be greater benefit from risk reduction therapy [42].

Although a number of risk factors for diabetes are well known, risk estimation is not commonly used in clinical practice. Risk prediction models can facilitate medical decision making [43], and may be more accurate or, at least, less biased than subjective predictions. An

evidence-based GDM risk estimate can provide individualized health information to women and clinicians to guide prediabetes treatment discussion. Model equations (Table 4) may help clinicians estimate the risk of progression to diabetes and magnitude of risk reduction with different prediabetes treatment options (i.e., metformin and/or ILI). To realize the benefits of risk prediction, clinical implementation of decision-making activities including aids must be further investigated. Barriers to utilizing risk calculators have been described and may include concern for generalizability and lack of added value to clinical judgment [44, 45].

It is estimated that women with prior GDM have at least a seven-fold increased risk of developing type 2 diabetes compared with those with normoglycemic pregnancies.[46] The model's modifiable clinical measures appear most relevant to consider in diabetes risk assessment of women with prior GDM, particularly when incorporated into treatment decision making activities. We have developed a decision aid targeting women with prior GDM to assist in decisions regarding diabetes prevention therapy. Models such as those derived from the DPP may be incorporated into decision aids to provide users with calculated diabetes risk scores, if treated with ILI, metformin, or standard lifestyle recommendations.

We recognize our study has a number of limitations. First, this model was developed from DPP participants, and may not be representative of the general population of women with GDM. Adults with certain chronic medical diseases and those taking common chronic medications were excluded from the DPP trial. The diagnosis of GDM was based on self-reporting; however, studies show women recall their GDM diagnosis and treatment accurately [47, 48]. Pregnant women with undiagnosed, preexisting diabetes may be inadvertently diagnosed with GDM, if early first trimester screening is not performed [49]. However, women with prepregnancy diabetes will likely have diabetes after delivery and would have been excluded from the DPP. In addition, women with prior GDM with subsequent prediabetes may not have selected the answer "only during pregnancy" when asked about a history of hyperglycemia; these women were not in our sample.

Women with GDM are at greatest risk of developing diabetes within the postpartum period and first five years of their index pregnancy; the mean time from the index pregnancy was 12 years for GDM women in the DPP [50]. Women who were in the immediate postpartum period and/or breastfeeding were excluded and the mean time from the index pregnancy was 12 years for GDM women in the DPP [50]. Thus, women enrolled in the DPP may not have represented women with the greatest risk for diabetes, and the model may underestimate the predicted risk of diabetes in women with GDM. Second, prediabetes and incident diabetes were defined by fasting blood glucose and 75-gram OGTT criteria in the DPP. In clinical practice, however, screening and diagnosis are more commonly performed with HbA1c. Interestingly, risk reduction by metformin and lifestyle were similar, 44% and 49% respectively, when diabetes incidence was defined by HbA1c $\geq$ 6.5% (48 mmol/mol) for the overall (men and women) DPP cohort [35]. Third, estimates of risk reduction with an ILI are based on the specific DPP intensive lifestyle program. The risk reduction benefit may not apply to other less-intensive lifestyle interventions. Fourth, our model does not account for treatment adherence (metformin or lifestyle), which would contribute to heterogeneity in treatment effects. Anticipated adherence to therapy is important in decision making, as lifestyle adherence is more effective than metformin in promoting regression to normal glucose regulation [11]. Lastly, our model does not account for peripartum related predictors (e.g. pregnancy OGTT levels or postpartum BMI) which may be more predictive of diabetes risk, though these measures are not always readily available at future medical encounters. Finally, the model was developed utilizing only GDM participants in the DPP. Given the relatively small sample meeting our criteria, external validation is necessary before clinical use.

Conclusion

We have developed and internally validated a clinically applicable prediction model which includes fasting glucose, HbA1c, BMI, treatment arm, and BMI by treatment arm interaction for women with prior GDM. Incorporating individualized diabetes risk prediction into prediabetes treatment decision making may improve understanding the potential benefit of ILI and/or metformin in diabetes prevention.

Supporting information

S1 Fig. Kaplan Meier curves for probability of diabetes free with follow up time of 3 years of women with prediabetes and a history of gestational diabetes in placebo, intensive lifestyle, and metformin arms.
(TIF)

S2 Fig. Predicted probability of not progressing to diabetes by BMI group and treatment.
(TIF)

S3 Fig. Time dependent receiver operating characteristic (ROC) curves for model 1 (full) and model 2 (parsimonious).
(TIF)

S1 Table. Baseline characteristics by diabetes outcomes with row percent.
(DOCX)

Acknowledgments

Author Contributions

Conceptualization: Bernice Man, Alan Schwartz, Ben Gerber.

Formal analysis: Bernice Man, Alan Schwartz, Oksana Pugach, Yinglin Xia, Ben Gerber.

Investigation: Bernice Man, Ben Gerber.

Methodology: Bernice Man, Alan Schwartz, Yinglin Xia, Ben Gerber.

Supervision: Alan Schwartz, Oksana Pugach, Ben Gerber.

Writing – original draft: Bernice Man, Ben Gerber.

Writing – review & editing: Bernice Man, Alan Schwartz, Oksana Pugach, Yinglin Xia, Ben Gerber.

References

1. DeSisto CL, Kim SY, Sharma AJ. Prevalence estimates of gestational diabetes mellitus in the United States, Pregnancy Risk Assessment Monitoring System (PRAMS), 2007–2010. Prev Chronic Dis. 2014; 11:E104. https://doi.org/10.5888/pcd11.130415 PMID: 24945238

2. Man B, Turyk ME, Kominiarek MA, Xia Y, Gerber BS. Diabetes Screening in US Women With a History of Gestational Diabetes, National Health and Nutrition Examination Survey, 2007–2012. Prev Chronic Dis. 2016; 13:E124. https://doi.org/10.5888/pcd13.160106 PMID: 27609302

3. Zhu Y, Zhang C. Prevalence of Gestational Diabetes and Risk of Progression to Type 2 Diabetes: a Global Perspective. Curr Diab Rep. 2016; 16(1):7. https://doi.org/10.1007/s11892-015-0699-x PMID: 26742932

4. Kim C, Berger DK, Chamany S. Recurrence of gestational diabetes mellitus: a systematic review. Diabetes Care. 2007; 30(5):1314–9. https://doi.org/10.2337/dc06-2517 PMID: 17290037

5. Ratner RE, Christophi CA, Metzger BE, Dabelea D, Bennett PH, Pi-Sunyer X, et al. Prevention of diabetes in women with a history of gestational diabetes: effects of metformin and lifestyle interventions. J Clin Endocrinol Metab. 2008; 93(12):4774–9. https://doi.org/10.1210/jc.2008-0772 PMID: 18826999

6. ACOG Practice Bulletin No. 190: Gestational Diabetes Mellitus. Obstet Gynecol. 2018; 131(2):e49–e64. https://doi.org/10.1097/AOG.0000000000002501 PMID: 29370047

7. Management of Diabetes in Pregnancy: Standards of Medical Care in Diabetes-2018. Diabetes Care. 2018; 41(Suppl 1):S137–s43. https://doi.org/10.2337/dc18-S013 PMID: 29222384

8. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med. 2002; 346(6):393–403. https://doi.org/10.1056/NEJMoa012512 PMID: 11832527

9. Aroda VR, Christophi CA, Edelstein SL, Zhang P, Herman WH, Barrett-Connor E, et al. The effect of lifestyle intervention and metformin on preventing or delaying diabetes among women with and without gestational diabetes: the diabetes prevention program outcomes study 10-year follow-up. J Clin Endocrinol Metab. 2015; 100(4):1646–53. https://doi.org/10.1210/jc.2014-3761 PMID: 25706240

10. Sussman JB, Kent DM, Nelson JP, Hayward RA. Improving diabetes prevention with benefit based tailored treatment: risk based reanalysis of Diabetes Prevention Program. BMJ. 2015; 350:h454. https://doi.org/10.1136/bmj.h454 PMID: 25697494

11. Herman WH, Pan Q, Edelstein SL, Mather KJ, Perreault L, Barrett-Connor E, et al. Impact of Lifestyle and Metformin Interventions on the Risk of Progression to Diabetes and Regression to Normal Glucose Regulation in Overweight or Obese People With Impaired Glucose Regulation. Diabetes Care. 2017. https://doi.org/10.2337/dc17-1116 PMID: 29021207

12. Noble D, Mathur R, Dent T, Meads C, Greenhalgh T. Risk models and scores for type 2 diabetes: systematic review. BMJ. 2011; 343:d7163. https://doi.org/10.1136/bmj.d7163 PMID: 22123912

13. Bang H, Edwards AM, Bomback AS, Ballantyne CM, Brillon D, Callahan MA, et al. Development and validation of a patient self-assessment score for diabetes risk. Ann Intern Med. 2009; 151(11):775–83. https://doi.org/10.7326/0003-4819-151-11-200912010-00005 PMID: 19949143

14. Lindström J, Tuomilehto J. The diabetes risk score: a practical tool to predict type 2 diabetes risk. Diabetes Care. 2003; 26(3):725–31. https://doi.org/10.2337/diacare.26.3.725 PMID: 12610029

15. Köhler M, Ziegler AG, Beyerlein A. Development of a simple tool to predict the risk of postpartum diabetes in women with gestational diabetes mellitus. Acta Diabetol. 2016; 53(3):433–7. https://doi.org/10.1007/s00592-015-0814-0 PMID: 26482741

16. Lindstrom J, Peltonen M, Eriksson JG, Aunola S, Hamalainen H, Ilanne-Parikka P, et al. Determinants for the effectiveness of lifestyle intervention in the Finnish Diabetes Prevention Study. Diabetes Care. 2008; 31(5):857–62. https://doi.org/10.2337/dc07-2162 PMID: 18252900

17. Costa B, Barrio F, Cabre JJ, Pinol JL, Cos X, Sole C, et al. Delaying progression to type 2 diabetes among high-risk Spanish individuals is feasible in real-life primary healthcare settings using intensive lifestyle intervention. Diabetologia. 2012; 55(5):1319–28. https://doi.org/10.1007/s00125-012-2492-6 PMID: 22322921

18. Ekelund M, Shaat N, Almgren P, Groop L, Berntorp K. Prediction of postpartum diabetes in women with gestational diabetes mellitus. Diabetologia. 2010; 53(3):452–7. https://doi.org/10.1007/s00125-009-1621-3 PMID: 19957074

19. Ignell C, Ekelund M, Anderberg E, Berntorp K. Model for individual prediction of diabetes up to 5 years after gestational diabetes mellitus. Springerplus. 2016; 5:318. https://doi.org/10.1186/s40064-016-1953-7 PMID: 27065426

20. Rubin RR, Fujimoto WY, Marrero DG, Brenneman T, Charleston JB, Edelstein SL, et al. The Diabetes Prevention Program: recruitment methods and results. Control Clin Trials. 2002; 23(2):157–71. https://doi.org/10.1016/s0197-2456(01)00184-2 PMID: 11943442

21. The Diabetes Prevention Program. Design and methods for a clinical trial in the prevention of type 2 diabetes. Diabetes Care. 1999; 22(4):623–34. https://doi.org/10.2337/diacare.22.4.623 PMID: 10189543

22. Kriska AM, Knowler WC, LaPorte RE, Drash AL, Wing RR, Blair SN, et al. Development of questionnaire to examine relationship of physical activity and diabetes in Pima Indians. Diabetes Care. 1990; 13 (4):401–11. https://doi.org/10.2337/diacare.13.4.401 PMID: 2318100

23. Kriska AM, Edelstein SL, Hamman RF, Otto A, Bray GA, Mayer-Davis EJ, et al. Physical activity in individuals at risk for diabetes: Diabetes Prevention Program. Med Sci Sports Exerc. 2006; 38(5):826–32. https://doi.org/10.1249/01.mss.0000218138.91812.f9 PMID: 16672833

24. Compendium of Physical Activities 2018. Available from: https://sites.google.com/site/compendiumofphysicalactivities/home.

25. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2018. Diabetes Care. 2018; 41(Suppl 1):S13–s27. https://doi.org/10.2337/dc18-S002 PMID: 29222373

26. Sauerbrei W, Perperoglou A, Schmid M, Abrahamowicz M, Becher H, Binder H, et al. State of the art in selection of variables and functional forms in multivariable analysis—outstanding issues. Diagnostic and Prognostic Research. 2020; 4.

27. Heinze G, Wallisch C, Dunkler D. Variable selection—A review and recommendations for the practicing statistician. Biom J. 2018; 60(3):431–49. https://doi.org/10.1002/bimj.201700067 PMID: 29292533

28. Aroda VR, Knowler WC, Crandall JP, Perreault L, Edelstein SL, Jeffries SL, et al. Metformin for diabetes prevention: insights gained from the Diabetes Prevention Program/Diabetes Prevention Program Outcomes Study. Diabetologia. 2017.

29. Navarro-Gonzalez D, Sanchez-Inigo L, Pastrana-Delgado J, Fernandez-Montero A, Martinez JA. Triglyceride-glucose index (TyG index) in comparison with fasting plasma glucose improved diabetes prediction in patients with normal fasting glucose: The Vascular-Metabolic CUN cohort. Prev Med. 2016; 86:99–105. https://doi.org/10.1016/j.ypmed.2016.01.022 PMID: 26854766

30. Hjellvik V, Sakshaug S, Strom H. Body mass index, triglycerides, glucose, and blood pressure as predictors of type 2 diabetes in a middle-aged Norwegian cohort of men and women. Clin Epidemiol. 2012; 4:213–24. https://doi.org/10.2147/CLEP.S31830 PMID: 22936857

31. Stern MP, Williams K, Haffner SM. Identification of persons at high risk for type 2 diabetes mellitus: do we need the oral glucose tolerance test? Ann Intern Med. 2002; 136(8):575–81. https://doi.org/10.7326/0003-4819-136-8-200204160-00006 PMID: 11955025

32. Harrell FE Jr., Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Stat Med. 1996; 15(4):361–87. https://doi.org/10.1002/(SICI)1097-0258(19960229)15:4<361::AID-SIM168>3.0.CO;2-4 PMID: 8668867

33. Edelstein SL, Knowler WC, Bain RP, Andres R, Barrett-Connor EL, Dowse GK, et al. Predictors of progression from impaired glucose tolerance to NIDDM: an analysis of six prospective studies. Diabetes. 1997; 46(4):701–10. https://doi.org/10.2337/diab.46.4.701 PMID: 9075814

34. Leong A, Daya N, Porneala B, Devlin JJ, Shiffman D, McPhaul MJ, et al. Prediction of Type 2 Diabetes by Hemoglobin A1c in Two Community-Based Cohorts. Diabetes Care. 2018; 41(1):60–8. https://doi.org/10.2337/dc17-0607 PMID: 29074816

35. Diabetes Prevention Program Research Group. HbA1c as a predictor of diabetes and as an outcome in the diabetes prevention program: a randomized clinical trial. Diabetes Care. 2015; 38(1):51–8. https://doi.org/10.2337/dc14-0886 PMID: 25336746

36. Vazquez G, Duval S, Jacobs DR Jr., Silventoinen K. Comparison of body mass index, waist circumference, and waist/hip ratio in predicting incident diabetes: a meta-analysis. Epidemiol Rev. 2007; 29:115–28. https://doi.org/10.1093/epirev/mxm008 PMID: 17494056

37. Grundy SM. Hypertriglyceridemia, insulin resistance, and the metabolic syndrome. Am J Cardiol. 1999; 83(9b):25f–9f. https://doi.org/10.1016/s0002-9149(99)00211-8 PMID: 10357572

38. Boursier G, Sultan A, Molinari N, Maimoun L, Boegner C, Picandet M, et al. Triglycerides and glycated hemoglobin for screening insulin resistance in obese patients. Clin Biochem. 2018; 53:8–12. https://doi.org/10.1016/j.clinbiochem.2017.12.002 PMID: 29225096

39. Göbl CS, Bozkurt L, Prikoszovich T, Winzer C, Pacini G, Kautzky-Willer A. Early possible risk factors for overt diabetes after gestational diabetes mellitus. Obstet Gynecol. 2011; 118(1):71–8. https://doi.org/10.1097/AOG.0b013e318220e18f PMID: 21691165

40. Barden A, Singh R, Walters B, Phillips M, Beilin LJ. A simple scoring method using cardiometabolic risk measurements in pregnancy to determine 10-year risk of type 2 diabetes in women with gestational diabetes. Nutr Diabetes. 2013; 3:e72. https://doi.org/10.1038/nutd.2013.15 PMID: 23732679

41. Wang L, Liu H, Zhang S, Leng J, Liu G, Zhang C, et al. Obesity index and the risk of diabetes among Chinese women with prior gestational diabetes. Diabet Med. 2014; 31(11):1368–77. https://doi.org/10. 1111/dme.12532 PMID: 24961948

42. Akinci B, Celtik A, Yener S, Yesil S. Prediction of developing metabolic syndrome after gestational diabetes mellitus. Fertil Steril. 2010; 93(4):1248–54. https://doi.org/10.1016/j.fertnstert.2008.12.007 PMID: 19147138

43. Edwards AG, Naik G, Ahmed H, Elwyn GJ, Pickles T, Hood K, et al. Personalised risk communication for informed decision making about taking screening tests. Cochrane Database Syst Rev. 2013; 2: CD001865. https://doi.org/10.1002/14651858.CD001865.pub3 PMID: 23450534

44. Muller-Riemenschneider F, Holmberg C, Rieckmann N, Kliems H, Rufer V, Muller-Nordhorn J, et al. Barriers to routine risk-score use for healthy primary care patients: survey and qualitative study. Arch Intern Med. 2010; 170(8):719–24. https://doi.org/10.1001/archinternmed.2010.66 PMID: 20421559

45. Collins GS, Mallett S, Omar O, Yu LM. Developing risk prediction models for type 2 diabetes: a systematic review of methodology and reporting. BMC Med. 2011; 9:103. https://doi.org/10.1186/1741-7015-9-103 PMID: 21902820

46. Bellamy L, Casas JP, Hingorani AD, Williams D. Type 2 diabetes mellitus after gestational diabetes: a systematic review and meta-analysis. Lancet. 2009; 373(9677):1773–9. https://doi.org/10.1016/S0140-6736(09)60731-5 PMID: 19465232

47. Hinkle SN, Rawal S, Zhu Y, Grewal J, Albert PS, Zhang C. Validation of Self-reported Diagnosis of Gestational Diabetes at 6-weeks Postpartum. Epidemiology. 2017; 28(5):747–52. https://doi.org/10.1097/ EDE.0000000000000695 PMID: 28570385

48. Hosler AS, Nayak SG, Radigan AM. Agreement between self-report and birth certificate for gestational diabetes mellitus: New York State PRAMS. Matern Child Health J. 2010; 14(5):786–9. https://doi.org/ 10.1007/s10995-009-0529-3 PMID: 19838778

49. Battarbee AN, Cavallini M, Keller C, Boggess KA. Missed Opportunities for Early Diabetes Screening in Pregnancy. Am J Perinatol. 2021; 38(1):23–7. https://doi.org/10.1055/s-0039-1694727 PMID: 31421638

50. Kim C, Newton KM, Knopp RH. Gestational diabetes and the incidence of type 2 diabetes: a systematic review. Diabetes Care. 2002; 25(10):1862–8. https://doi.org/10.2337/diacare.25.10.1862 PMID: 12351492