Received: 17 October 2020 | Revised: 13 January 2021 | Accepted: 1 March 2021

DOI: 10.1111/1753-0407.13175

ORIGINAL ARTICLE

Journal of Diabetes WILEY

Predicting the risk of developing type 2 diabetes in Chinese people who have coronary heart disease and impaired glucose tolerance

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Abstract

Aims: Robust diabetes risk estimates in Asian patients with impaired glucose tolerance (IGT) and coronary heart disease (CHD) are lacking. We developed a Chinese type 2 diabetes risk calculator using Acarbose Cardiovascular Evaluation (ACE) trial data.

Methods: There were 3105 placebo-treated ACE participants with requisite data for model development. Clinically relevant variables, and those showing nominal univariate association with new-onset diabetes ($P < .10$), were entered into BASIC (clinical variables only), EXTENDED (clinical variables plus routinely available laboratory results), and FULL (all candidate variables) logistic regression models. External validation was performed using the Luzhou prospective cohort of 1088 Chinese patients with IGT.

Results: Over median 5.0 years, 493 (15.9%) ACE participants developed diabetes. Lower age, higher body mass index, and use of corticosteroids or thiazide diuretics were associated with higher diabetes risk. C-statistics for the BASIC (using these variables), EXTENDED (adding male sex, fasting plasma glucose, 2-hour glucose, and HbA1c), and FULL models were 0.610, 0.757, and 0.761 respectively. The EXTENDED model predicted a lower 13.9% 5-year diabetes risk in the Luzhou cohort than observed (35.2%, 95% confidence interval 31.3%-39.5%, C-statistic 0.643).

Conclusion: A risk prediction model using routinely available clinical variables can be used to estimate diabetes risk in Chinese people with CHD and IGT.

KEYWORDS

coronary heart disease, impaired glucose tolerance, risk prediction, type 2 diabetes mellitus

Highlights

- We developed a 5-year diabetes risk calculator for Chinese people with CHD and IGT.

- Higher FPG, 2hPG, and HbA1c were major determinants of new-onset diabetes.
- It can inform decision-making when considering primary prevention measures.

1 | INTRODUCTION

Primary prevention of type 2 diabetes (T2D) has become a major challenge, particularly for China, which has the world's largest number of people with diabetes (116.4 million cases in 2019) equating to one in four of the world's adults with diabetes.[1] A major concern is that almost half of all adults in China - estimated to be 400 to 500 million people - have "prediabetes".[2,3] Identifying those individuals at highest risk of progressing to T2D to inform the need for early intervention is highly desirable, given that many trials have now shown that T2D can be delayed or prevented by lifestyle modification[4-6] or by pharmacological agents,[7-10] with dietary intervention in the Da Qing study also reducing cardiovascular and all-cause mortality in the longer term.[11]

To date, few diabetes risk prediction tools have been tailored specifically for people with impaired glucose tolerance (IGT). The two that were derived from large-scale IGT trials[12,13] used predominantly Caucasian cohorts and have not been evaluated in Chinese populations, which may well have different characteristics.[14,15] Patients with established coronary heart disease (CHD) are of particular concern as they are at greater risk of developing T2D than the general population. Indeed, over half of all patients with CHD have been shown to have T2D or "prediabetes" in Western[16] and Chinese[17] cohorts attending cardiology outpatient clinics or admitted to hospital cardiovascular wards.

We have used data from the Acarbose Cardiovascular Evaluation (ACE) trial, which randomized Chinese patients with CHD and IGT to acarbose or placebo with prospective ascertainment of new-onset diabetes,[10] to develop a T2D risk calculator for a Chinese population.

2 | METHODS

2.1 | Population

The ACE trial design, baseline population characteristics, and results have been published previously.[10,18,19] Briefly, ACE was a randomized, double-blind, placebo-controlled, event-driven, Phase IV superiority trial conducted in 176 outpatient clinics in tier 3 and tier 2 hospitals in China. Eligible participants were aged 50 years or older with established CHD (defined as previous myocardial infarction, previous unstable angina, or current stable angina), and IGT (confirmed by a 75 g oral glucose tolerance test [OGTT]). Between March 2009 and October 2015, 6522 patients were enrolled and included in the intention-to-treat population, with 3272 assigned at random to acarbose and 3250 to placebo. As acarbose has been shown to reduce the risk of T2D,[7,10] only the placebo group was considered in this analysis.

The protocol of ACE trial was approved by the University of Oxford Tropical Research Ethics Committee, and by central or local ethics committees (as appropriate) at participating sites. All participants provided written informed consent. The ACE trial was registered with ClinicalTrials.gov, number NCT00829660, and the International Standard Randomized Controlled Trial Number registry, number ISRCTN91899513.

2.2 | Diagnosis of diabetes

During the ACE trial, fasting plasma glucose (FPG) values were measured every 4 months and a 75 g OGTT was performed annually. If either of these tests suggested diabetes, a confirmatory OGTT was done. Progression to diabetes was considered to have occurred if an elevated FPG (≥7.0 mmol/L) and/or 2-hour plasma glucose (2hPG) (≥11.1 mmol/L) value were recorded on two consecutive study visits, or if a diagnosis of diabetes was made by a nontrial physician and confirmed subsequently by an independent adjudication committee masked to study therapy allocation.[10]

2.3 | Risk factors for T2D

T2D risk factors considered included baseline demographic, clinical, and laboratory variables, which were selected for their availability in routine clinical practice for patients with CHD or were variables used commonly in previous diabetes risk scores. All values used were taken from the screening visit, (except for HbA1c which was captured only at the randomization visit), as the ACE trial encouraged optimization of CHD risk

reduction therapies during a 4-week run in the period before randomization.[18]

2.4 | Statistical analysis

ACE participants were categorized according to whether or not they had progressed to diabetes by their end of follow-up. Baseline characteristics for progressors and nonprogressors were summarized by median and interquartile range for continuous variables and numbers and percentages for categorical variables. Continuous variables were compared using Wilcoxon rank sum tests, and categorical variables were compared using Pearson chi-square tests. All statistical analyses were performed using SAS (version 9.4)[20] or R (version 3.4.3).[21]

2.5 | Development of 5-year T2D risk prediction models

Three risk prediction models using ACE baseline data were developed using methodology aligned to the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) statement[22]: (i) a BASIC model, limited to demographic and readily available clinical characteristics; (ii) an EXTENDED model, which added routinely available laboratory variables to the BASIC model; and (iii) a FULL model, using all prespecified ACE baseline variables.

The precise dates of diabetes onset are not available as ACE participants were assessed only every 4 months for possible development of diabetes. Accordingly, we used logistic regression rather than Cox models to build our risk calculator. Multivariable models were built with candidate variables included only if considered to be clinically relevan, or showing a nominally significant ($P < 0.10$) univariate relationship with new-onset diabetes. Both forward and backward selection methods were used to eliminate nonsignificant variables. The principal criteria for selecting models were an improvement in the C-statistic (increment ≥0.005) and goodness of fit ($P > 0.05$ indicating good fit). Interactions between sex and other covariates were also tested.

2.6 | Development of a 5-year T2D risk score

For ease of use in everyday clinical practice a risk scoring algorithm was developed, based on the optimal prediction model with routinely available variables. Continuous variables were categorized by tertiles, quartiles or clinically relevant cut-points. For example, body mass index (BMI) was categorized by the overweight (24 kg/m^2) and obesity (28 kg/m^2) threshold values recommended by the Chinese guidelines.[23] All variables were then entered into a logistic regression analysis to compute β coefficients so that each could be assigned an estimated risk score. The sum of these scores was used to derive an estimated 5-year risk of new-onset diabetes, which in turn could be classified as "Modest" (0%-25%), "Moderate" (25%-50%), or "High" (>50%), as described previously.[12]

2.7 | Internal validation

The performance of the three 5-year diabetes risk prediction models and the 5-year diabetes risk score in terms of discrimination (whether they distinguished between people who did/did not develop diabetes) and calibration (extent to which predicted probabilities agreed with the observed risk across groups of individuals) was evaluated in ACE placebo participants. The C-statistic was used to assess discrimination, which was classified as poor (0.5 to <0.6), acceptable (0.6 to 0.7), good (0.7 to <0.8), very good (0.8 to <0.9), or excellent (≥0.9). Calibration was estimated using the Hosmer-Lemeshow test, with a good fit indicated by a P value > 0.05, and graphically by comparing the predicted probability against the observed probability across deciles of predicted risk.

2.8 | External validation

External validation of the diabetes prediction models and the risk score algorithm were performed using data from the Luzhou survey, an independent prospective Chinese cohort followed between 2011 and 2016. This survey was part of the Risk Evaluation of cAncers in Chinese diabeTic Individuals: a lONgitudinal (REACTION) study, a multicenter prospective observational study investigating the association between diabetes and the risk of cancer among individuals with or without T2D in mainland China.[24] A total of 10 007 residents aged between 40 and 89 years were enrolled from five Luzhou communities using a multistage cluster random sampling method, of which 2565 had IGT (with or without CHD). In the Luzhou survey cohort, incident diabetes was defined as any one, or a combination, of FPG ≥7.0 mmol/L, 2hPG ≥11.1 mmol/L, or a self-report of a previous diagnosis of T2D made by a health care professional. In 2014 and 2016, 1155 of these IGT participants were reviewed to determine if they had developed

TABLE 1 Acarbose Cardiovascular Evaluation (ACE) participants baseline characteristics by progression or not to diabetes

	Overall	Nonprogressors	Progressors	*P* value
	3105 (100%)	2612 (84.1%)	493 (15.9%)	–
Age (years)	63.00 (57.00, 70.00)	63.00 (58.00, 70.00)	61.00 (56.00, 68.00)	<0.0001
Sex (Male)	2249 (72.4%)	1872 (71.7%)	377 (76.5%)	0.033
Ethnicity (Han)	3001 (96.7%)	2523 (96.6%)	478 (97.0%)	0.78
Smoking status				0.034
Never smoker	1364 (43.9%)	1167 (44.7%)	197 (40.0%)	–
Ex-smoker	1286 (41.4%)	1079 (41.3%)	207 (42.0%)	–
Current smoker	455 (14.7%)	366 (14.0%)	89 (18.1%)	–
Currently taking alcohol	368 (11.9%)	308 (11.8%)	60 (12.2%)	0.87
Weight (kg)	70.00 (63.00, 78.00)	70.00 (62.00, 77.00)	74.00 (65.00, 80.00)	<0.0001
Height (cm)	167.00 (160.00, 171.00)	167.00 (160.00, 170.00)	168.00 (161.00, 172.00)	0.0075
Waist circumference (cm)	91.00 (86.00, 97.00)	90.00 (85.00, 97.00)	93.00 (88.00, 100.00)	<0.0001
Hip circumference (cm)	100.00 (95.00, 105.00)	100.00 (94.00, 104.00)	100.00 (96.00, 106.00)	<0.0001
Body mass index (kg/m^2)	25.39 (23.44, 27.64)	25.20 (23.36, 27.41)	26.26 (24.44, 28.31)	<0.0001
Waist-to-hip ratio	0.92 (0.88, 0.95)	0.91 (0.88, 0.95)	0.92 (0.89, 0.96)	0.061
Waist to height ratio	0.55 (0.52, 0.59)	0.55 (0.51, 0.58)	0.56 (0.53, 0.59)	<0.0001
Systolic blood pressure (mm Hg)	130.00 (120.00, 140.00)	130.00 (120.00, 140.00)	130.00 (120.00, 140.00)	0.12
Diastolic blood pressure (mm Hg)	80.00 (70.00, 85.00)	80.00 (70.00, 85.00)	80.00 (70.00, 86.00)	0.060
Fasting plasma glucose (mmol/L)	5.42 (5.00, 5.90)	5.37 (4.97, 5.80)	5.82 (5.40, 6.30)	<0.0001
2-hour plasma glucose (mmol/L)	9.10 (8.36, 10.07)	9.00 (8.30, 9.92)	9.81 (8.86, 10.66)	<0.0001
HbA1c (%)	5.90 (5.60, 6.30)	5.90 (5.56, 6.20)	6.20 (5.80, 6.50)	<0.0001
HbA1c (mmol/mol)	41 (38, 45)	41 (37, 44)	44 (40, 48)	<0.0001
Total cholesterol (mmol/L)	4.05 (3.47, 4.79)	4.03 (3.47, 4.77)	4.16 (3.54, 4.86)	0.074
High-density lipoprotein cholesterol (mmol/L)	1.12 (0.96, 1.33)	1.13 (0.96, 1.34)	1.08 (0.94, 1.26)	<0.0001
Low-density lipoprotein cholesterol (mmol/L)	2.23 (1.77, 2.85)	2.21 (1.76, 2.84)	2.30 (1.80, 2.90)	0.10
Triglycerides (mmol/L)	1.43 (1.04, 1.97)	1.39 (1.02, 1.93)	1.60 (1.16, 2.19)	<0.0001
Estimated glomerular filtration rate (ml/min/1.73m^2)	88.57 (74.79, 103.26)	88.35 (74.40, 103.47)	89.19 (77.21, 102.95)	0.19
Alanine amino transferase (U/L)	22.00 (16.42, 31.00)	22.00 (16.00, 31.00)	24.00 (18.00, 33.00)	<0.0001
Hemoglobin (g/dL)	14.20 (13.20, 15.10)	14.20 (13.10, 15.10)	14.50 (13.60, 15.30)	<0.0001
Mean red cell corpuscular volume (fL)	91.70 (89.00, 94.80)	91.80 (88.90, 94.90)	91.40 (89.00, 94.40)	0.11
White blood cell count (x10^9/L)	6.12 (5.20, 7.30)	6.10 (5.18, 7.24)	6.30 (5.37, 7.58)	0.0021
Platelets (x10^9/L)	195.00 (163.00, 232.00)	195.00 (163.00, 230.00)	197.00 (164.00, 238.00)	0.37
Cardiovascular medical history				
Hypertension	2034 (65.5%)	1691 (64.7%)	343 (69.6%)	0.043
Myocardial infarction	1367 (44.0%)	1145 (43.8%)	222 (45.0%)	0.66
Unstable angina	1333 (42.9%)	1126 (43.1%)	207 (42.0%)	0.68
Stable angina	687 (22.1%)	579 (22.2%)	108 (21.9%)	0.95
Atrial fibrillation	122 (3.9%)	114 (4.4%)	8 (1.6%)	0.0060
Heart failure	116 (3.7%)	99 (3.8%)	17 (3.4%)	0.81

TABLE 1 (Continued)

	Overall	Nonprogressors	Progressors	*P* value
Revascularization	1469 (47.3%)	1239 (47.4%)	230 (46.7%)	0.79
Stroke or transient ischemic attack	212 (6.8%)	182 (7.0%)	30 (6.1%)	0.54
Concomitant medications				
Statin	2843 (91.6%)	2393 (91.6%)	450 (91.3%)	0.87
Any other lipid-lowering therapy	26 (0.8%)	22 (0.8%)	4 (0.8%)	1.00
Beta-blockers	2110 (68.0%)	1767 (67.6%)	343 (69.6%)	0.43
Angiotensin receptor blocker	803 (25.9%)	683 (26.1%)	120 (24.3%)	0.43
Angiotensin-converting enzyme inhibitors	1080 (34.8%)	912 (34.9%)	168 (34.1%)	0.76
Aldosterone antagonist	105 (3.4%)	86 (3.3%)	19 (3.9%)	0.62
Calcium channel blocker	963 (31.0%)	792 (30.3%)	171 (34.7%)	0.062
Thiazide diuretic	104 (3.3%)	79 (3.0%)	25 (5.1%)	0.029
Nonthiazide diuretic	83 (2.7%)	75 (2.9%)	8 (1.6%)	0.15
Any other antihypertensive therapy	80 (2.6%)	70 (2.7%)	10 (2.0%)	0.50
Aspirin	2930 (94.4%)	2461 (94.2%)	469 (95.1%)	0.48
Clopidogrel	1981 (63.8%)	1668 (63.9%)	313 (63.5%)	0.92
Other antiplatelet therapy	44 (1.4%)	41 (1.6%)	3 (0.6%)	0.15
Nitrates	1270 (40.9%)	1067 (40.8%)	203 (41.2%)	0.93
Other antianginal drugs	214 (6.9%)	179 (6.9%)	35 (7.1%)	0.92
Digitalis	57 (1.8%)	49 (1.9%)	8 (1.6%)	0.84
Antiarrhythmics	62 (2.0%)	56 (2.1%)	6 (1.2%)	0.24
Corticosteroids	30 (1.0%)	20 (0.8%)	10 (2.0%)	0.017
New electrocardiogram abnormality	1856 (59.8%)	1584 (60.6%)	272 (55.2%)	0.026

Note: Data are shown as median and interquartile range or N (%).

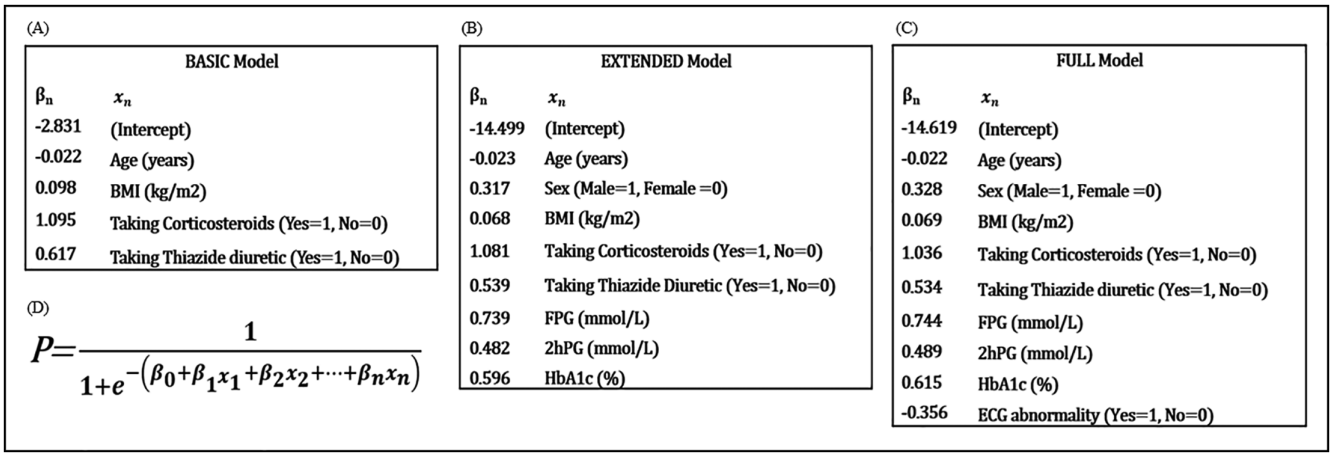

FIGURE 1 Intercepts and ß coefficients for the BASIC (A), EXTENDED (B), and FULL (C) models, and the model equation (D) using these values to estimate the probability of developing diabetes within 5 years. BMI, body mass index; ECG, electrocardiogram; FPG, fasting plasma glucose; 2hPG, 2-hour plasma glucose

diabetes, of whom 1088 had complete data for the variables required to perform external validation of our final 5-year diabetes risk prediction model and 5-year diabetes risk score algorithm.

3 | RESULTS

3.1 | Population

Of 3250 ACE placebo-assigned participants, 3105 (96%) had the requisite data for our analyses. Their baseline characteristics are listed in Table 1. Participants were predominantly Han (96.7%) and male (72.4%), with median age 63.0 years, BMI 25.4 kg/m^2, FPG 5.4 mmol/L, 2hPG 9.1 mmol/L, and HbA1c 5.9% (41 mmol/mol). CHD history was categorized (not mutually exclusively) as myocardial infarction (44.0%), unstable angina (42.9%), or stable angina (22.1%), with most participants having a prior history of hypertension (65.5%) and taking statins (91.6%), beta-blockers (68.0%), and aspirin (94.4%).

Over median 5.0 years follow-up, 493 (15.9%) ACE participants progressed to diabetes. Compared with non-progressors, progressors were more likely to be younger, male, and current smokers, with higher adiposity, glucose, and lipid measures, and to have a prior history of hypertension or atrial fibrillation and to be taking thiazide diuretics or corticosteroids (Table 1).

3.2 | Five-Year diabetes risk prediction model

The univariate associations with new-onset diabetes for 55 ACE candidate variables are summarized in Table S1. Of these, the 33 that were clinically relevant or had nominally significant associations with new-onset diabetes, were used for model development. Interactions between sex and other covariates did not achieve statistical significance (sex and age, $P = 0.055$; sex and BMI, $P = 0.056$) and were not included in the models.

In the BASIC model (Figure 1A), major risk factors for new-onset diabetes were lower age, higher BMI, and use of corticosteroids or thiazide diuretics. Modeling these variables yielded a C-statistic of 0.610 (Table 2) with a good fit ($P = 0.84$) (Figure S1A).

In the EXTENDED model (Figure 1B), the risk factors for new-onset diabetes added to the BASIC model were male sex and a higher baseline FPG, 2hPG, and HbA1c. Their inclusion increased the C-statistic from 0.610 to 0.757 (Table 2) and yielded a good fit ($P = 0.20$) (Figure S1B).

In the FULL model (Figure 1C), a new electrocardiographic abnormality was associated with a lower risk of diabetes incidence, but adding this variable only minimally improved the C-statistic from 0.757 to 0.761 (Table 2), also with a good fit ($P = 0.47$) (Figure S1C).

Accordingly, we elected to use the EXTENDED model as its performance was similar to the FULL model and because the variables required are more readily available.

3.3 | Five-year T2D risk score algorithm

We constructed a risk scoring algorithm using the EXTENDED model equations that produced risk scores ranging from 0 to 23 points (Figure 2). When the risk score was applied to ACE placebo participants it yielded a C-statistic of 0.754 with a good of fit ($P = 0.58$) (-Figure S1D). The proportions of the ACE placebo population classified by the risk scoring algorithm as high, moderate and modest risk were 2.9%, 16.2%, and 80.8%

TABLE 2 Five-year multivariable diabetes risk prediction models for Chinese people with CHD and IGT (N = 3105, 493 events)

	BASIC model		EXTENDED model		FULL model	
Model variables	**OR (95% CI)**	***P* value**	**OR (95% CI)**	***P* value**	**OR (95% CI)**	***P* value**
Age (per 10-year increase)	0.80 (0.70-0.91)	.00060	0.79 (0.69-0.91)	.00096	0.80 (0.70-0.92)	0.0017
Male (vs female)	–	–	1.37 (1.08-1.76)	.011	1.39 (1.09-1.78)	0.0085
Body mass index (per 1 kg/m^2)	1.10 (1.07-1.14)	<.0001	1.07 (1.03-1.11)	<.0001	1.07 (1.04-1.11)	<0.0001
Corticosteroid treatment (vs none)	3.00 (1.32-6.41)	.0057	2.95 (1.23-6.68)	.012	2.82 (1.17-6.43)	0.016
Thiazide diuretic treatment (vs none)	1.88 (1.15-2.95)	.0084	1.71 (1.02-2.80)	.036	1.71 (1.01-2.79)	0.039
Fasting plasma glucose (per 1 mmol/L)	–	–	2.09 (1.77-2.48)	<.0001	2.10 (1.78-2.49)	<0.0001
2-hour plasma glucose (per 1 mmol/L)	–	–	1.62 (1.46-1.80)	<.0001	1.63 (1.47-1.81)	<0.0001
HbA1c (per 1%)	–	–	1.81 (1.56-2.11)	<.0001	1.85 (1.59-2.15)	<0.0001
Electrocardiogram abnormality (vs normal)	–	–	–	–	0.70 (0.57-0.87)	0.00093
C-index (95% CI)	0.610 (0.583-0.637)		0.757 (0.735-0.780)		0.761 (0.738-0.784)	
Hosmer-Lemeshow goodness of fit *P*-value	0.84		0.20		0.47	

Abbreviations: 95% CI, 95% confidence interval; CHD, coronary heart disease; IGT, impaired glucose tolerance; OR, odds ratio.

Step 1. Sum scores for each risk factor	
Risk Factor	**Points**
Age (years)	
≤60	2
60-80	1
≥80	0
Sex	
Female	0
Male	1
Body mass index (kg/m^2)	
<24	0
≥24 to <28	1
≥28	2
Taking corticosteroids	
No	0
Yes	4
Taking thiazide diuretics	
No	0
Yes	2
Fasting plasma glucose (mmol/L)	
<5.6	0
≥5.6 to <6.1	2
≥6.1 to 7.0	4
2-hour plasma glucose (mmol/L)	
7.8 to <8.6	0
≥8.6 to <9.4	1
≥9.4 to <10.2	3
≥10.2 to 11.1	4
HbA_{1c} (%) (mmol/mol)	
<5.7 (<39)	0
≥5.7 to <6.5 (≥39 to <48)	2
≥6.5 (≥48)	4

Step 2. Read off five-year diabetes risk corresponding to the total score	
Total Score	**Five-year risk of diabetes**
0	1%
1	2%
2	3%
3	4%
4	5%
5	6%
6	8%
7	11%
8	14%
9	18%
10	23%
11	29%
12	35%
13	42%
14	50%
15	57%
16	65%
17	71%
18	77%
19	82%
20	86%
21	89%
22	92%
23	94%

FIGURE 2 Risk scoring algorithm based on EXTENDED model equations for estimating 5-year diabetes risk

respectively, with 52.7%, 35.5%, and 10.6% respectively developing diabetes (Figure 3).

3.4 | External validation

Baseline characteristics for the 1088 Luzhou survey participants with IGT are listed in Table S2. They were all of Han ethnicity, more often female (66.8%), with a median age of 60.0 years, and the majority (96.3%) had no history of CHD. Overall, 230 (21.1%, 95% conference interval [CI] 18.8% - 23.7%) participants progressed to T2D over a median of 3.0 years, with a higher incidence in those with a history of CHD (13 of 40, 32.5%). To obtain an estimated 5-year diabetes incidence for the Luzhou survey cohort we applied a linear extrapolation, multiplying the observed incidence by 5/3 to give 383 progressors (35.2%, 95% CI 31.3% - 39.5%).

The EXTENDED model predicted a 5-year diabetes incidence of 13.9% for the Luzhou survey cohort,

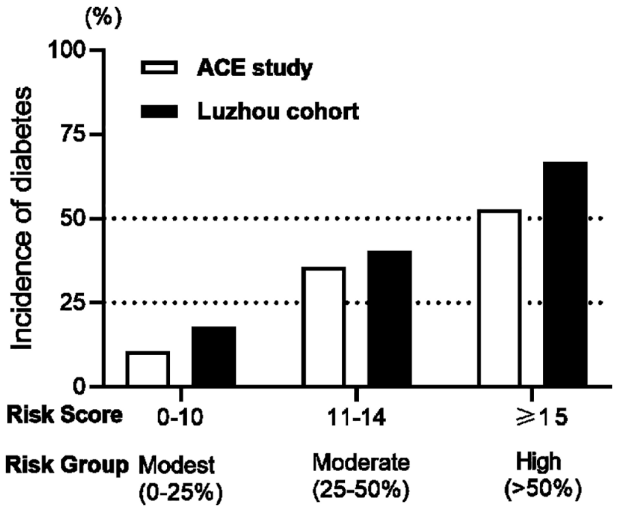

FIGURE 3 Diabetes progression in three risk classes (using risk score algorithm) in Acarbose Cardiovascular Evaluation (ACE) study and Luzhou survey cohort

substantially less than the projected proportion, with a C-statistic of 0.643 (0.602-0.685). The risk scoring algorithm predicted a 5-year diabetes incidence of 13.7%, with a C-statistic of 0.638 (0.595-0.680). The risk scoring algorithm classified 0.8%, 13.0%, and 86.2% of Luzhou survey cohort participants as high, moderate, and modest risk respectively, with 66.7%, 40.4%, and 17.8% respectively progressing to diabetes (Figure 3).

4 | DISCUSSION

We have developed a risk calculator, in compliance with the TRIPOD statement,[22] that predicts the 5-year likelihood that Chinese people with CHD and IGT will develop diabetes. This calculator uses variables that are readily available in an outpatient setting and can be used either in the form of equations or as a risk scoring algorithm.

The BASIC model, which just required information on age, BMI, and whether or not a patient was taking corticosteroids or a thiazide diuretics, had only moderate discrimination. The EXTENDED model, which added sex, baseline FPG, 2hPG, and HbA1c, showed good discrimination and a good fit. In the FULL model the only additional variable to be included was a new electrocardiographic abnormality but this did not materially alter the C-statistic or goodness of fit. Accordingly, we recommend using the EXTENDED model equations or the risk scoring algorithm derived from it which performed equally well.

Baseline variables shown here to be significantly associated with diabetes incidence are largely consistent with those in other diabetes prediction models. Higher BMI, male sex, use of corticosteroids, or thiazide diuretics and higher glucose levels are strongly associated with increased diabetes risk.[25-31] Among all variables, the three glucose measures (FPG, 2hPG, and HbA1c) were the most powerful predictors for future diabetes incidence. Our study found that lower age was associated with higher risk of diabetes, contrary to the trend in normal glucose tolerance populations but consistent with previous IGT population findings.[12] Developing IGT at earlier age may indicate that this population carries a stronger genetic background related to diabetes, or more unfavorable environmental and lifestyle factors, and may therefore be associated with a more rapid progression to diabetes. We have no explanation for the finding that a new electrocardiogram abnormality (including clinically insignificant and significant abnormality) at baseline was significantly associated with a reduced risk of diabetes.

External validation of the EXTENDED model and the risk scoring algorithm in the Luzhou survey cohort of Chinese individuals with IGT[24] showed acceptable discrimination but substantially underestimated diabetes incidence in this population. This may be because only 3.7% of the Luzhou survey cohort had CHD as well as IGT. Also, compared with the ACE study population, the Luzhou survey cohort population were younger and had a lower proportion of males, current smokers, current alcohol users, prior hypertension, with very few taking statins, a lower BMI, and a higher low-density lipoprotein cholesterol. These differences between the two populations are largely consistent with the differences between people with and without CHD. Further external validation, and possibly calibration, will be required to maximize the model's predictive ability.

Previous European and Chinese surveys have shown a high prevalence of IGT among CHD patients, approximately 32% to 33% respectively.[16,17] Those patients who progressed to diabetes have been reported to be at higher risk of adverse clinical outcomes with a greater mortality rate than those who do not develop diabetes.[32,33] Using our T2D risk calculator could provide individualized risk estimates for Chinese patients with CHD and IGT, which in turn could enhance their awareness of T2D risk and prompt interventions that may prevent or delay the onset of T2D in this population.

Categorizing estimated 5-year diabetes risk as "modest risk" (0%-25%), "moderate" (>25%-50%), or "high" (>50%) provides a simple stratification that could help select an appropriate intensity of intervention. Possible recommendations might be routine lifestyle advice for those at modest risk, intensive lifestyle intervention for those at moderate risk and intensive lifestyle plus pharmacologic intervention for those at high risk of

developing diabetes. Thus in clinical practice personalized diabetes risk estimates and risk classification could assist clinicians and patients when discussing the need to initiate primary prevention measures and the intensity required. External validation in Luzhou survey cohort showed that our model may have acceptable risk stratification ability in other IGT populations, which may help inform decision-making when considering primary prevention in this population.

Our study has several strengths. The ACE trial was a well-designed, large-scale, long-term secondary cardiovascular prevention study for which OGTT-confirmed new-onset diabetes was a prespecified secondary outcome, making it an excellent resource to evaluate baseline predictors of the development of new-onset diabetes. Also, as it was a multicenter study recruiting subjects from 176 sites across mainland China and Hong Kong, participants were likely to be representative of the Chinese population as whole with CHD and IGT.

The study also has several limitations. First, the ACE trial did not collect previously well-recognized predictors of diabetes such as a family history of diabetes and lifestyle and dietary factors (physical activity, fruit and vegetable consumption). Second, as the overwhelming majority of ACE population were taking the guideline recommend drugs for CHD management, it was not possible to test whether any of them individually had an impact on T2D risk, for example, aspirin or statins. Third, we could validate our model at this time only in a Chinese IGT population most of whom did not have CHD. Fourth, ACE trial participants were recruited from top-level Chinese hospitals (tier 2 and tier 3) meaning there was likely a selection bias to the population studied. Fifth, all ACE trial subjects received appropriate lifestyle advice with respect to diet, exercise, and smoking and their cardiovascular therapy was optimized, which may have led to a lower diabetes incidence than might otherwise have been expected.

In conclusion, in Chinese people with CHD and IGT, lower age, male sex, obesity, use of corticosteroids, or thiazide diuretics as well as higher FPG, 2hPG, and HbA1c were major determinants of new-onset diabetes. A risk prediction model, using routinely available clinical variables and glycemic measures, can estimate T2D risk in Chinese people with CHD and IGT. With further calibration our simple risk calculator could inform decision-making when considering primary prevention T2D measures in this population.

ACKNOWLEDGEMENTS

The ACE trial was conducted by the University of Oxford Diabetes Trial Unit as an academically independent study with funding from Bayer AG. R.R.H. is an Emeritus National Institute for Health Research Senior Investigator. We thank Qin Wan for access to data from the Luzhou survey cohort.

DISCLOSURE

S.X., C.S., and R.L.C have no disclosures. J.T. reports research grants and fees for consultancy, advisory board membership, or lectures from AstraZeneca, Bayer AG (related to the present study), Boehringer Ingelheim, Eli Lilly, Impeto Medical, Merck (Germany), Merck Sharp & Dohme, Sanofi Aventis, Novartis, Novo Nordisk, and Servier. R.R.H. reports research support from AstraZeneca, Bayer, and Merck Sharp & Dohme and personal fees from Bayer, Intarcia, Merck Sharp & Dohme, Novartis, and Novo Nordisk.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Xu S, Scott CAB, Coleman RL, Tuomilehto J, Holman RR. Predicting the risk of developing type 2 diabetes in Chinese people who have coronary heart disease and impaired glucose tolerance. *Journal of Diabetes*. 2021;13:817–826. https://doi.org/10.1111/1753-0407.13175