Cardiovascular risk prediction in type 2 diabetes before and after widespread screening: a derivation and validation study

Romana Pylypchuk, Sue Wells, Andrew Kerr, Katrina Poppe, Matire Harwood, Suneela Mehta, Corina Grey, Billy P Wu, Vanessa Selak, Paul L Drury, Wing Cheuk Chan, Brandon Orr-Walker, Rinki Murphy, Jim Mann, Jeremy D Krebs, Jinfeng Zhao, Rod Jackson

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School of Population Health (R Pylypchuk PhD, S Wells PhD, A Kerr MD, K Poppe PhD, M Harwood PhD, B P Wu MPH, V Selak PhD, W C Chan MBChB, J Zhao PhD, Prof R Jackson PhD) **and School of Medicine** (R Murphy PhD), **Faculty of Medical and Health Sciences, University of Auckland, Auckland, New Zealand; Department of Cardiology** (A Kerr) **and Department of Endocrinology** (B Orr-Walker MBChB), **Middlemore Hospital, Auckland, New Zealand; Planning, Funding and Outcome Teams, Waitemata District Health Board, Auckland, New Zealand** (S Mehta MBChB); **Strategy and Performance Improvement Teams, Auckland District Health Board, Auckland, New Zealand** (C Grey PhD); **Ministry of Health, Wellington, New Zealand** (P L Drury MA); **Population Health, Counties Manukau District Health Board, Auckland, New Zealand** (W C Chan); **Department of Medicine, University of Otago, Dunedin, New Zealand** (Prof J Mann DM); **Department of Medicine, University of Otago, Wellington, New Zealand** (Prof J D Krebs PhD)

Correspondence to: Prof Rod Jackson, School of Population Health, Faculty of Medical and Health Sciences, University of Auckland, Auckland 1023, New Zealand **rt.jackson@auckland.ac.nz**

Summary

Background Until recently, most patients with diabetes worldwide have been diagnosed when symptomatic and have high cardiovascular risk, meaning most should be prescribed cardiovascular preventive medications. However, in New Zealand, a world-first national programme led to approximately 90% of eligible adults being screened for diabetes by 2016, up from 50% in 2012, identifying many asymptomatic patients with recent-onset diabetes. We hypothesised that cardiovascular risk prediction equations derived before widespread screening would now significantly overestimate risk in screen-detected patients.

Methods New Zealanders aged 30–74 years with type 2 diabetes and without known cardiovascular disease, heart failure, or substantial renal impairment were identified from the 400 000-person PREDICT primary care cohort study between Oct 27, 2004, and Dec 30, 2016, covering the period before and after widespread screening. Sex-specific equations estimating 5-year risk of cardiovascular disease were developed using Cox regression models, with 18 prespecified predictors, including diabetes-related and renal function measures. Equation performance was compared with an equivalent equation derived in the New Zealand Diabetes Cohort Study (NZDCS), which recruited between 2000 and 2006, before widespread screening.

Findings 46 652 participants were included in the PREDICT-1° Diabetes subcohort, of whom 4114 experienced first cardiovascular events during follow-up (median 5·2 years, IQR 3·3–7·4). 14 829 (31·8%) were not taking oral hypoglycaemic medications or insulin at baseline. Median 5-year cardiovascular risk estimated by the new equations was 4·0% (IQR 2·3–6·8) in women and 7·1% (4·5–11·2) in men. The older NZDCS equation overestimated median cardiovascular risk by three times in women (median 14·2% [9·7–20·0]) and two times in men (17·1% [4·5–20·0]). Model and discrimination performance measures for PREDICT-1° Diabetse equations were also significantly better than for the NZDCS equation (eg, for women: R^2=32% [95% CI 29–34], Harrell's *C*=0·73 [0·72–0·74], Royston's *D*=1·410 [1·330–1·490] *vs* R^2=24% [21–26], *C*=0·69 [0·67–0·70], and *D*=1·147 [1·107–1·187]).

Interpretation International treatment guidelines still consider most people with diabetes to be at high cardiovascular risk; however, we show that recent widespread diabetes screening has radically changed the cardiovascular risk profile of people with diabetes in New Zealand. Many of these patients have normal renal function, are not dispensed glucose-lowering medications, and have low cardiovascular risk. These findings have clear international implications as increased diabetes screening is inevitable due to increasing obesity, simpler screening tests, and the introduction of new-generation glucose-lowering medications that prevent cardiovascular events. Cardiovascular risk prediction equations derived from contemporary diabetes populations, with multiple diabetes-related and renal function predictors, will be required to better differentiate between low-risk and high-risk patients in this increasingly heterogeneous population and to inform appropriate non-pharmacological management and cost-effective targeting of expensive new medications.

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Introduction

In 2003, the New Zealand Ministry of Health guidelines recommended that cardiovascular preventive treatment decisions should be informed by calculated cardiovascular risk, using a Framingham Heart Study-based cardiovascular risk prediction calculator that required clinicians to assess patients' diabetes status.[1,2] The majority of middle-aged New Zealanders met guideline eligibility criteria for 5-yearly cardiovascular risk assessments, effectively introducing almost universal diabetes screening.

Subsequently, a national More Heart and Diabetes Checks health target was introduced to increase cardiovascular risk assessments in the eligible population from 50% in 2012 to 90% by 2016.[3] The target included an assessment of diabetes status that was facilitated by the replacement of fasting blood glucose with the simpler non-fasting glycated haemoglobin (HbA_{1c}) as

Research in context

Evidence before this study

A 2019 systematic review identified and compared the performance of 15 cardiovascular disease risk prediction models developed in diabetes populations and 11 models developed in general populations but later validated in diabetes populations. The authors found that the discriminative performance of the prediction models was only modest and only half the studies had been externally validated. They concluded that improvements in performance through the identification of additional predictors, and further validation studies, were required before the models should be implemented in clinical practice. To our knowledge, none of these studies were either conducted or validated in populations with widespread diabetes screening.

Added value of this study

By September, 2016, approximately 90% of middle-aged New Zealanders had been screened for diabetes, up from about 15% in 2001 and 50% in 2012. This followed the establishment of a national funded More Heart and Diabetes Checks health target in 2012. We are currently unaware of any other country that has diabetes screening levels as high as New Zealand. In this unique study, we were able to validate the New Zealand Diabetes Cohort Study (NZDCS) cardiovascular risk prediction equation, which was derived from a representative New Zealand diabetes population between 2000 and 2006, before the introduction of widespread diabetes screening. The NZDCS equation overestimated median cardiovascular risk by three times in woman and two times in men in a more contemporary New Zealand diabetes population recruited between 2004 and 2016, with many participants diagnosed through screening following the establishment of the 2012 health target. We then developed the world's first cardiovascular risk prediction equations in a contemporary diabetes population with almost universal diabetes screening. The new equations were well calibrated, and had a significantly improved ability to differentiate between high-risk and low-risk patients compared with the NZDCS equation.

Implications of all the available evidence

Recent widespread diabetes screening has radically changed the cardiovascular risk profile of patients with diabetes in New Zealand. The combined effect of increasing obesity, increased use of cardiovascular risk prediction equations requiring diabetes assessments, the introduction of a simple non-fasting glycated haemoglobin as the international diabetes diagnostic standard, and the development of new-generation glucose-lowering medications will inevitably lead to increased diabetes screening worldwide. We have shown that cardiovascular risk prediction equations developed before widespread diabetes screening will significantly overestimate cardiovascular risk in many screen-detected patients. Therefore, new equations, derived from diabetes populations including screen-detected patients, and with additional predictors to help to differentiate between high-risk and low-risk patients, will be required to more accurately predict cardiovascular risk in people with diabetes. Without new equations, low-risk patients might be overtreated with new-generation glucose-lowering medications that have only been shown to reduce cardiovascular events in patients at high cardiovascular risk.

the recommended screening test.[4] The 90% target was achieved in September, 2016.[3]

In parallel with this timeline, between 2002 and 2016, approximately 400 000 primary care patients were recruited into the PREDICT cohort study when they completed cardiovascular risk assessments, with half of participants recruited after 2010.[5] New cardiovascular risk prediction equations were derived in this cohort after we showed that the previously recommended Framingham equation overestimated cardiovascular risk by approximately 50% in the PREDICT cohort.[6] These new general population equations, derived in people with and without diabetes, were incorporated into 2018 national risk management guidelines[7] and are now widely used.

However, while we showed that the recommended Framingham equation[1] significantly overestimated risk in the general PREDICT cohort,[6] this same Framingham equation had previously been shown to significantly underestimate cardiovascular risk in people with type 2 diabetes in the New Zealand Diabetes Cohort Study (NZDCS), recruited between 2000 and 2006, before widespread screening began.[8] The NZDCS investigators derived a cardiovascular risk prediction equation in this diabetes cohort and recommended that it replace the Framingham equation for assessing risk in New Zealanders with diabetes.[8]

We hypothesised that the NZDCS equation would now overestimate cardiovascular risk in a more contemporary New Zealand diabetes population, largely because many screen-detected patients would be identified much earlier in the course of their diabetes. Also, a recent systematic review examined the performance of both general population and diabetes-specific cardiovascular risk prediction equations in people with diabetes.[9] The authors concluded that improvements in performance through the identification of additional predictors and further validation studies were required before the models should be implemented in clinical practice. Here, we describe the external validation of the diabetes-specific NZDCS equation and the derivation of equivalent new equations, with additional diabetes-related and renal function-related predictors, in the subset of people with type 2 diabetes in the PREDICT study.

Methods

Study design and participants

PREDICT is an ongoing open cohort study that automatically recruits participants when New Zealand

primary health-care practitioners complete standardised cardiovascular risk assessments using PREDICT decision support software, as reported in detail elsewhere.[5,6] The software auto-populates PREDICT risk factor templates from patient records. Clinicians then complete missing fields before cardiovascular risk is calculated and recruitment finalised. Participant risk factor profiles captured by the software are linked to national databases documenting essentially all drug dispensing and International Classification of Diseases (ICD)-coded hospital admissions and deaths in New Zealand. The PREDICT study was approved by the Northern Region Ethics Committee Y in 2003 (AKY/03/12/314), with annual approval by the National Multi Region Ethics Committee since 2007 (MEC07/19/EXP).

Our study was restricted to the subcohort of PREDICT participants with type 2 diabetes, without known cardiovascular disease, heart failure, or substantial renal impairment, who had cardiovascular risk (baseline) assessments at primary care clinics using PREDICT software between Oct 27, 2004, and Dec 30, 2016. Some participants were known to have diabetes before recruitment while others were diagnosed at recruitment. As risk assessments are done opportunistically, it was not possible to differentiate between screen-detected cases and those who are risk assessed because of symptoms or signs suggestive of diabetes.

See Online for appendix

More than 95% of New Zealanders are enrolled in primary health organisations, which provide almost all primary health care.[10] About a third of the country's population is served by clinics using PREDICT software. During the study period, national guidelines recommended 5-yearly cardiovascular risk assessments using a Framingham Heart Study-based calculator,[1] for men aged 45–74 years and women aged 55–74 years, and 10 years earlier for Māori (the Indigenous population), Pacific, and South Asian peoples and those with known cardiovascular risk factors, including diabetes.[2] About 90% of New Zealanders meeting these eligibility criteria had cardiovascular risk assessments by September, 2016.[3]

Type 2 diabetes status was ascertained from one of the following: diagnosis recorded on PREDICT templates by primary care practitioners; ICD Tenth Revision (ICD-10) codes for type 2 diabetes from previous hospital discharge records; or dispensing of at least one diabetes medication within 6 months before baseline. People were excluded if they were younger than 30 years or older than 74 years; had a history of cardiovascular disease or congestive heart failure; had a history of renal dialysis, renal transplant, overt diabetic nephropathy, or non-diabetic nephropathy; had baseline estimated glomerular filtration rate (eGFR) less than 30 mL/min per 1·73 m²; or had body-mass index (BMI) less than 18·5 kg/m². Exclusions were based on a combination of diagnoses by general practitioners, hospital discharge records, and dispensing of anti-anginal drugs and loop diuretics (appendix p 1). Self-identified ethnicity is documented on all routine health records using a standard national classification system. Ethnic groups with fewer than 1000 participants were excluded, as well as participants whose ethnicity was not specified.

Participants' risk factor profiles, measured at baseline, were linked to national health databases using encrypted national health identifiers (NHIs). More than 95% of New Zealanders have a unique NHI that is attached to almost all interactions with publicly funded or subsidised health services and most private hospital services.[11] The national health databases used included all public hospitalisations, deaths, and subsidised drugs dispensed by community pharmacies. All commonly prescribed cardiovascular disease preventive and hypoglycaemic drugs are publicly subsidised.

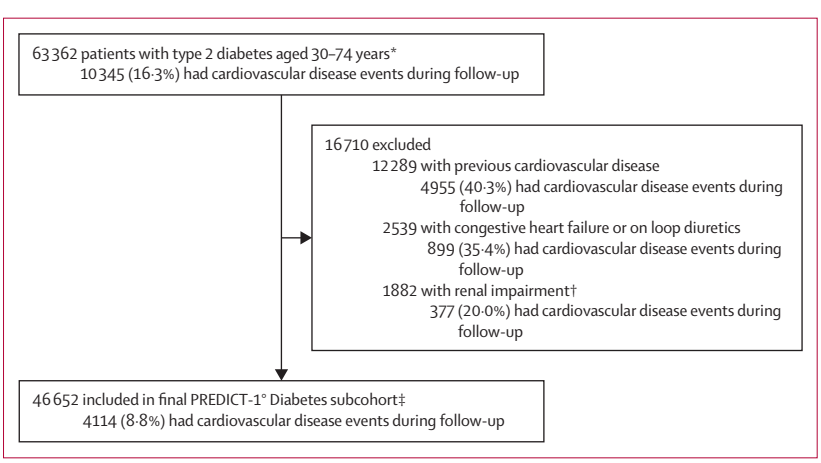

Figure 1: **PREDICT-1° Diabetes subcohort enrolment, exclusions, and incidence of cardiovascular disease events during follow-up**

eGFR=estimated glomerular filtration rate. *Excluding patients who classified themselves as Middle Eastern, Latin American, or African (because there were fewer than 1000 participants in these categories), those who did not specify their ethnicity, and those with body-mass index less than 18·5 kg/m². †Had a history of renal dialysis, renal transplant, overt diabetic nephropathy, or non-diabetic nephropathy, or had eGFR mL/min per 1·73 m². ‡Including those with missing values, which were replaced with imputed values.

Outcomes

The primary outcome was prespecified using the total cardiovascular disease outcome in the Framingham equations,[1] defined from ICD-10 Australian Modification codes as hospitalisations or deaths from ischaemic heart disease (including angina), ischaemic or haemorrhagic cerebrovascular events (including transient ischaemic attacks), peripheral vascular disease, congestive heart failure, or other ischaemic cardiovascular disease deaths (appendix p 2).

Predictors

We followed TRIPOD recommendations for developing and reporting prediction equations to ensure that all aspects of the analyses required to assess bias and potential usefulness were presented.[12]

The variables included in the new PREDICT-1° Diabetes models were all prespecified and were all kept in the final models to reduce the risk of overfitting (appendix p 3). They included all common cardiovascular

	Women (n=22 658)	Men (n=23 994)
Percentage of total cohort	48·6%	51·4%
Incident cardiovascular disease events	1627 (7·2%)	2487 (10·4%)
Total person-years observed	119 194	125 646
Crude incidence of cardiovascular disease per 1000 per year	13·7 (95% CI 13·0–14·3)	19·8 (95% CI 19·0–20·6)
Median follow-up, years*	5·2 (3·2–7·4)	5·2 (3·3–7·4)
Patients followed up for ≥5 years	12 093 (53·4%)	12 659 (52·8%)
Age, years	54·1 (10·8)	53·9 (10·7)
Years since diagnosis of type 2 diabetes†	5·3 (5·7)	5·0 (5·3)
Self-identified ethnicity		
European	6057 (26·7%)	8098 (33·8%)
Māori	3660 (16·2%)	3658 (15·2%)
Pacific	6632 (29·3%)	5175 (21·6%)
Indian	3481 (15·4%)	3834 (16·0%)
Chinese or other Asian	2828 (12·5%)	3229 (13·5%)
NZDep quintile		
1 (least deprived)	2475 (10·9%)	3520 (14·7%)
2	3059 (13·5%)	3673 (15·3%)
3	3560 (15·7%)	4067 (17·0%)
4	5019 (22·2%)	5184 (21·6%)
5 (most deprived)	8545 (37·7%)	7550 (31·5%)
Current smoker	3355 (14·8%)	4639 (19·3%)
Family history of premature cardiovascular disease	2350 (10·4%)	2231 (9·3%)
History of atrial fibrillation	265 (1·2%)	452 (1·9%)
SBP, mm Hg	132 (15·9)	132 (15·0)
TC:HDL†	4·0 (1·2)	4·4 (1·4)
eGFR, mL/min per 1·73 m²†	90 (18·1)	89 (16·8)
HbA_{1c}, mmol/mol†	62 (20·5)	63 (20·9)
ACR, mg/mmol†	9·9 (44·3)	10·8 (45·0)
BMI, kg/m²†	33·5 (8·1)	31·4 (6·8)
Microalbuminuria‡	5211 (23%)	7438 (31%)
Macroalbuminuria§	1359 (6%)	1680 (7%)
Medications at baseline assessment		
Oral hypoglycaemic agents	15 317 (67·6%)	15 830 (66·0%)
Insulin	1574 (6·9%)	1373 (5·7%)
Blood pressure-lowering medications	13 706 (60·5%)	13 760 (57·4%)
Lipid-lowering medications	11 937 (52·7%)	13 386 (55·8%)
Antithrombotic medications	7805 (34·5%)	9177 (38·2%)

Data are %, n (%), mean (SD), or median (IQR), unless indicated otherwise. ACR=urinary albumin-to-creatinine ratio. BMI=body-mass index. eGFR=estimated glomerular filtration rate. HbA_{1c}=glycated haemoglobin. SBP=systolic blood pressure. TC:HDL=ratio of total cholesterol to HDL cholesterol. *Follow-up time ranged from 1 day to 12 years, in both men and women. †Missing values imputed, but means presented here are from complete cases. ‡ACR ≥2·5 mg/mmol in men or ≥3·5 mg/mmol in women, but <30 mg/mmol (both sexes). §ACR ≥30 mg/mmol.

Table 1: **Baseline characteristics of the PREDICT-1° Diabetes subcohort, by sex**

	Women	Men
Age, years	1·05 (1·04–1·05)	1·05 (1·04–1·06)
Years since diagnosis of type 2 diabetes	1·02 (1·01–1·03)	1·02 (1·01–1·03)
Self-identified ethnicity		
European	1 (ref)	1 (ref)
Māori	1·08 (0·92–1·27)	0·97 (0·85–1·11)
Pacific	0·78 (0·67–0·91)	0·82 (0·72–0·93)
Indian	1·16 (0·97–1·37)	1·15 (1·00–1·31)
Chinese or other Asian	0·70 (0·55–0·89)	0·68 (0·57–0·81)
NZDep, per quintile increase	1·07 (1·03–1·12)	1·05 (1·02–1·09)
Smoking		
Non-smoker	1 (ref)	1 (ref)
Current smoker	1·54 (1·34–1·77)	1·40 (1·27–1·55)
Family history of premature cardiovascular disease	1·10 (0·95–1·28)	1·22 (1·08–1·39)
History of atrial fibrillation	2·05 (1·53–2·75)	1·70 (1·38–2·08)
SBP, per 10 mm Hg increase	1·13 (1·10–1·16)	1·06 (1·03–1·09)
TC:HDL, per unit increase	1·12 (1·08–1·17)	1·08 (1·05–1·12)
eGFR, per 5 mL/min per 1·73 m² increase	0·96 (0·94–0·98)	0·99 (0·98–1·01)
ACR, per unit increase*	1·20 (1·16–1·24)	1·20 (1·16–1·23)
HbA_{1c}, per 5 mmol/mol increase	1·04 (1·02–1·05)	1·04 (1·03–1·05)
BMI, per 5 kg/m² increase	1·06 (1·02–1·10)	1·06 (1·03–1·10)
Medications at baseline assessment		
Oral hypoglycaemic medications	1·15 (1·01–1·30)	1·02 (0·93–1·13)
Insulin	1·37 (1·16–1·63)	1·21 (1·04–1·41)
Blood pressure-lowering medications	1·08 (0·95–1·24)	1·16 (1·04–1·29)
Lipid-lowering medications	0·84 (0·75–0·95)	0·95 (0·87–1·05)
Antithrombotic medications	1·06 (0·94–1·18)	1·07 (0·98–1·17)

Data are hazard ratios (95% CI) adjusted for all other variables included in the model. SBP=systolic blood pressure. TC:HDL=ratio of total cholesterol to HDL cholesterol. eGFR=estimated glomerular filtration rate. ACR=urinary albumin-to-creatinine ratio. HbA_{1c}=glycated haemoglobin. BMI=body-mass index. *Hazard ratios for ACR are per unit increase of the scaled (divided by 1000), log-transformed (natural log), and centred variable.

Table 2: **Adjusted hazard ratios for total cardiovascular disease events in the PREDICT-1° Diabetes equations**

predictors that were available for most participants, and were informed by the published literature and advice from the five authors who are diabetologists (PLD, BO-W, JM, RM, and JDK). These included the variables required for calculating cardiovascular risk using published PREDICT-1° equations[5] derived in the whole PREDICT cohort without a history of cardiovascular disease (ie, sex; age; self-identified ethnicity; NZDep, an area-based socioeconomic deprivation index; family history of premature cardiovascular disease; smoking status; systolic blood pressure [SBP]; ratio of total cholesterol to HDL cholesterol [TC:HDL], atrial fibrillation confirmed by electrocardiograph; and use

	Value
Input data	
Patient description	The patient is a European woman, aged 55 years, with type 2 diabetes diagnosed 10 years ago; she does not smoke, has no history of atrial fibrillation and no family history of premature cardiovascular disease, and is categorised as NZDep quintile 3; her SBP is 135 mm Hg, TC:HDL cholesterol is 5 units, eGFR is 90 mL/min per 1·73 m^2, ACR is 2·5 mg/mmol, HbA_{1c} is 64 mmol/mol, and BMI is 30 kg/m^2; she is taking metformin and blood pressure-lowering treatment
β coefficient × variable	
Age	0·0424465 × c.Age*=0·0595096
NZDep	0·0699105 × c.NZDep*=–0·0459316
Years since diagnosis of type 2 diabetes	0·0163962 × c.Years since diagnosis*=0·07531816
SBP	0·0127053 × c.SBP*=0·0459885
TC:HDL	0·1139678 × c.TC:HDL*=0·1173072
eGFR	–0·0090784 × c.eGFR*=–0·0040048
ACR	0·1842885 × ln(c.ACR*)=–0·30834602
HbA_{1c}	0·0076733 × c.HbA1c*=0·00292642
BMI	0·0073966 × c.BMI*=–0·02600328
Taking blood pressure-lowering medication	0·0988141 × 1=0·0988141†
Taking oral hypoglycaemic medication	0·1248604 × 1=0·1248604†
Sum of coefficients × variables	0·14043868
Centred variables used in calculations	
c.Age	55 – 53·59800973=1·40199027
c.NZDep	3 – 3·657006944=–0·657006944
c.SBP	135 – 131·3803652=3·6196348
c.TC:HDL	5 – 3·970698781=1·029301219
c.eGFR	90 – 89·55886653=0·44113347
$c.HbA_{1c}$	64 – 63·61862222=0·38137778
c.Years since diagnosis	10 – 5·406364481=4·593635519
c.BMI	30 – 33·5155722=–3·5155722
ln(c.ACR)	ln[(2·5 + 0·009999997764826)/1000] + 4·314302355=–1·6731702
Risk calculation	
5-year risk of cardiovascular disease	$[1-\text{baseline survival}^{\exp(\text{sum of coefficients} \times \text{variables})}] \times 100 = [1-0{\cdot}945571^{\exp(0{\cdot}14043868)}] \times 100 = 6{\cdot}2\%$

ACR=urinary albumin-to-creatinine ratio. BMI=body-mass index. eGFR=estimated glomerular filtration rate. HbA_{1c}=glycated haemoglobin. SBP=systolic blood pressure. TC:HDL=ratio of total cholesterol to HDL cholesterol. *Centred variables. †Binary variable where reference value (ie, 0) corresponds to not taking medication.

Table 3: **Example calculation of 5-year risk of cardiovascular disease using the PREDICT-1° Diabetes equations**

of blood pressure-lowering, lipid-lowering, and antithrombotic drugs, including aspirin). The new models also included variables either used in the NZDCS equation (ie, HbA_{1c}, time since diagnosis of type 2 diabetes), or similar to those used in the NZDCS equation (ie, urinary albumin-to-creatinine ratio [ACR] in place of microalbuminuria or macroalbuminuria). Additional variables were eGFR, BMI, and use of oral hypoglycaemic drugs or insulin in the 6 months before baseline.

Data were substantially complete on most predictors; however, 4199 (9·0%) participants had missing eGFR. No other single predictor variable was missing for more than 5% of participants. Multiple imputation by chained equations was used to impute missing values, by sex.[13] Ten new datasets with imputed data were created, and model development assessment and validation were done identically in each dataset. Performance characteristics and model estimates from each iteration were combined using Rubin's rules.[14]

Model development

Cox regression modelling[15] was used to develop new sex-specific prediction equations for time to first event, including all prespecified variables (appendix p 3). Follow-up time was defined from baseline to the first of the following: hospital admission or death from cardiovascular disease, death from other causes, or end of the study (Dec 31, 2016). Reference groups for categorical variables are specified in the appendix (p 3). Model diagnostics included testing the proportionality assumption with the global Schoenfeld test[16] and plotting –ln[–ln(survival)] versus ln(time). Checks were made for influential observations using delta-beta (DFBETA) plots.[17] Non-linearity of continuous variables and first-order interactions between continuous and categorical variables were initially assessed using fractional polynomials.[18] Linearity was then assessed by visual inspection of LOWESS (locally weighted scatterplot smoothing) smoothed plots of Martingale residuals versus continuous covariates.[19] In the final models, all continuous variables were fitted as linear terms, except for a logarithmic transformation applied to ACR. Interaction terms were considered for inclusion if they met a predetermined threshold statistical significance of $p<0{\cdot}001$, were clinically plausible, and if the plotted data suggested effect modification. Continuous predictors were centred at their mean values. Adjusted hazard ratios were obtained from the sex-specific Cox regression models including all prespecified predictors. The 5-year baseline survival probabilities of each model were obtained by the smoothed kernel estimator feature of the Stata stcox command that was used to fit the models. Stata (version 13.0) was used for all analyses.

Internal validation of PREDICT-1° Diabetes equations

Calibration performance was assessed graphically by categorising participants into deciles of predicted 5-year cardiovascular risk and plotting mean 5-year predicted risk against observed 5-year risk. Observed 5-year risk was obtained by the Kaplan-Meier method.[20] Standard statistical metrics of model performance and discrimination (R^2, Harrell's *C* statistic, Royston's *D* statistic) were calculated. A description of these performance metrics is provided in the appendix (p 5). The whole diabetes subcohort was used to develop the new equations, as recommended by Steyerberg for large studies.[21] Sensitivity analyses were done by developing models using complete-case data.

External validation of the NZDCS equation in the PREDICT-1° Diabetes subcohort

The same calibration, model, and discrimination performance measures described above were used for the external validation of the NZDCS equation.[8] Calibration plots were constructed for both the original NZDCS models and models recalibrated to the PREDICT-1° Diabetes subcohort. To recalibrate the NZDCS model, we updated baseline survival values estimated by fitting Cox models with the prognostic index from the NZDCS model (offset term) in the PREDICT-1° Diabetes subcohort.[22] Then, to determine whether the additional variables included in the PREDICT-1° Diabetes equations were also independent predictors, over and above the NZDCS predictors, we derived Cox models with the sex-specific prognostic indices from the NZDCS equation plus the additional variables in the new equations (ie, NZDep, family history of premature cardiovascular disease, atrial fibrillation, BMI, eGFR, and lipid-lowering, antithrombotic, oral hypoglycaemic, and insulin drug treatment). We had previously used an identical approach to assess the value of additional predictors when developing the general population PREDICT-1° equations.[5]

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

63 362 people aged 30–74 years with type 2 diabetes were recruited between Oct 27, 2004, and Dec 30, 2016 (figure 1), with 33 582 (53·0%) recruited after 2010. We excluded 12 289 people with previous cardiovascular disease, 2539 with heart failure, and 1882 with significant renal impairment. The remaining 46 652 people constituted the PREDICT-1° Diabetes subcohort used in all analyses presented here (table 1). They experienced 4114 first cardiovascular disease events during 244 840 person-years of follow-up (median 5·2 years, IQR 3·3–7·4) to Dec 31, 2016. At baseline, 14 829 (31·8%) patients were not dispensed any oral hypoglycaemic drugs or insulin; 336 (1·4%) of 23 994 men and 340 (1·5%) of 22 658 women were on insulin only.

Cardiovascular outcome event numbers and types are shown in the appendix (p 6). Non-fatal myocardial infarction was the most common outcome, comprising 1213 (29·5%) of 4114 events, and 2123 (51·6%) of all events were coronary related. 963 (23·4%) events were strokes or transient ischaemic attacks, 666 (16·2%) were congestive heart failure, and 362 (8·8%) were peripheral vascular disease. Only 369 (9·0%) events were fatal.

Adjusted hazard ratios for total cardiovascular disease in the new equations are presented for women and men (table 2). Each additional year of age was associated with an increased estimated 5-year cardiovascular disease risk of approximately 5%, in relative terms, and every year since diabetes diagnosis was independently associated with a further 2% increased risk. Adjusted risk for Māori was similar to Europeans, while Pacific peoples had about a 20% lower risk. Indian people had a 15% higher risk than Europeans, whereas Chinese and other Asian peoples had a 30% lower risk. Risk increased monotonically in women and men per quintile of the socioeconomic deprivation index. Smoking, atrial

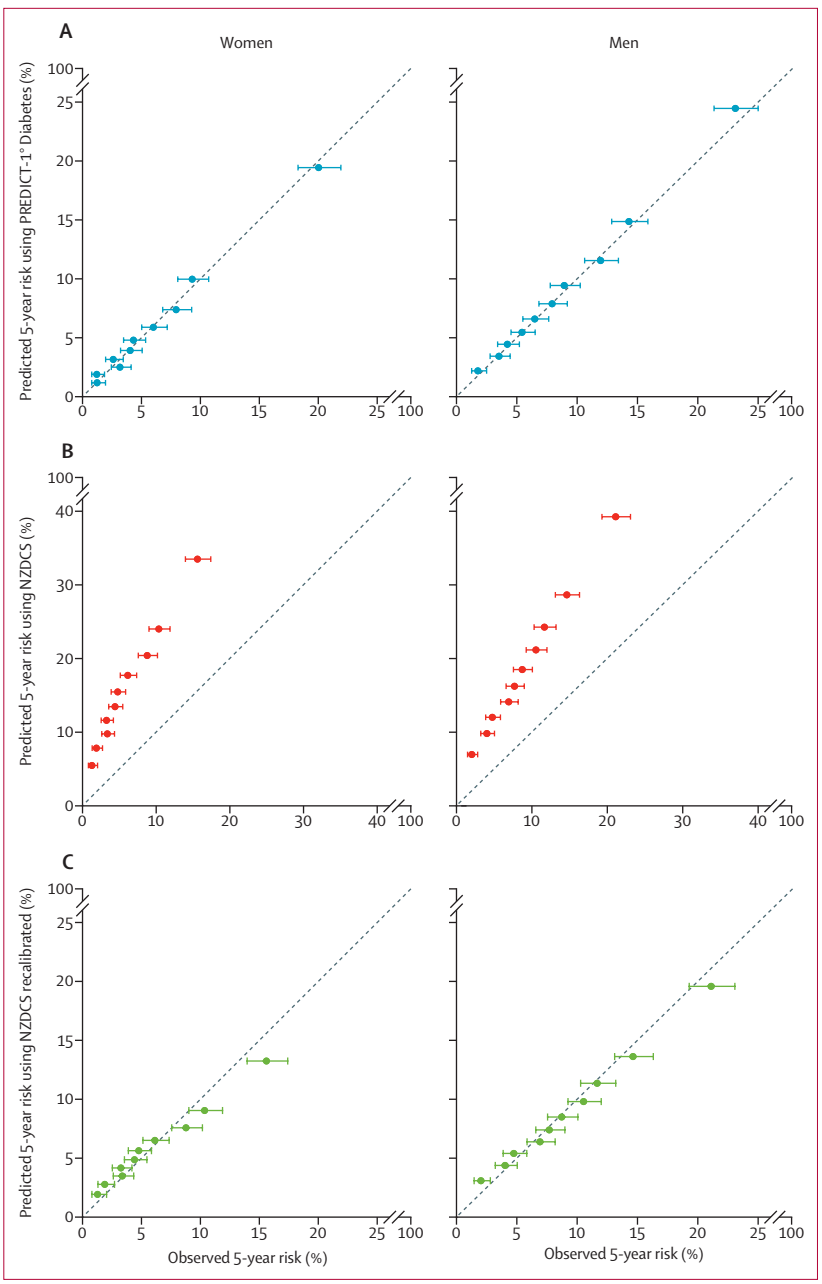

Figure 2: **Calibration plots for predicted versus observed 5-year risk of cardiovascular disease**
Predictions are made using PREDICT-1° Diabetes equations (A), the original NZDCS equation (B), and recalibrated NZDSC equations (C) with estimates shown for each risk decile. NZDCS=New Zealand Diabetes Cohort Study.

	PREDICT-1° Diabetes	NZDCS
Women		
R^2	32% (29–34)	24% (21–26)
Harrell's *C* statistic	0·73 (0·72–0·74)	0·69 (0·67–0·70)
Royston's *D* statistic	1·410 (1·330–1·490)	1·147 (1·107–1·187)
Men		
R^2	25% (22–27)	19% (17–21)
Harrell's *C* statistic	0·69 (0·68–0·70)	0·67 (0·66–0·68)
Royston's *D* statistic	1·169 (1·104–1·233)	0·997 (0·932–1·062)

Data in parentheses are 95% CIs. See appendix (p 5) for a description of these performance metrics. NZDCS=New Zealand Diabetes Cohort Study.

Table 4: **Performance metrics for PREDICT-1° Diabetes equations compared with the NZDCS equation**

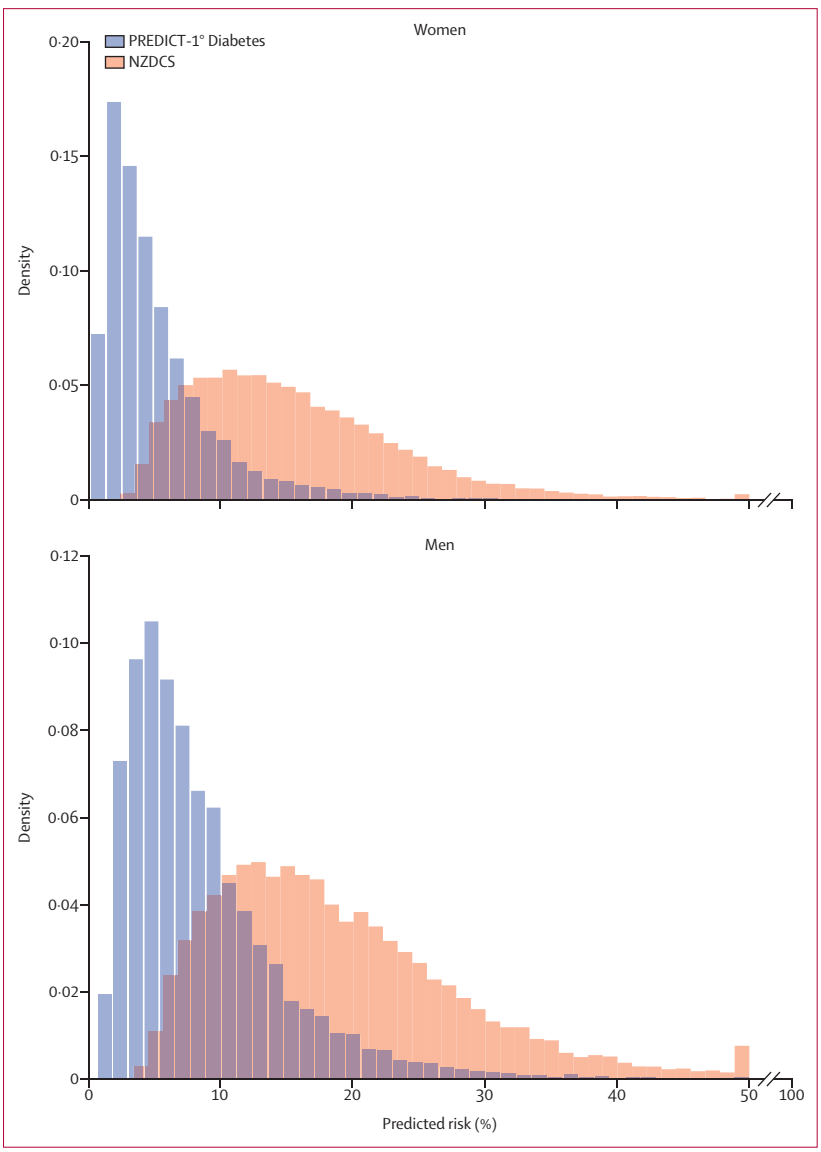

Figure 3: **Distribution of predicted risk in the PREDICT-1° Diabetes subcohort, estimated using the PREDICT-1° Diabetes equations and the NZDCS equation**
NZDCS=New Zealand Diabetes Cohort Study.

fibrillation, use of insulin, and increased SBP, TC:HDL, ACR, HbA_{1c}, and BMI were all significant predictors of cardiovascular disease in both sexes. Family history of premature cardiovascular disease was a significant predictor in men only and eGFR in women only. Baseline use of oral hypoglycaemic drugs was a significant predictor of increased risk in women only, blood pressure-lowering medication in men only, and antithrombotic medications in neither sex. Use of lipid-lowering medications was associated with a decreased risk in women but not in men. No significant interactions were observed. Alternative models developed using complete-case data were very similar (data not shown).

Regression coefficients, means of centred variables, and baseline survival functions for the new sex-specific 5-year cardiovascular disease risk equations are presented in the appendix (p 7), and an example risk calculation is shown in table 3.

Predicted versus observed 5-year risk plots for total cardiovascular disease using the new PREDICT-1° Diabetes equations showed excellent calibration across all risk deciles in both sexes (figure 2A). By contrast, the original NZDCS equation significantly overpredicted observed 5-year risk of cardiovascular disease in all deciles of predicted risk in both men and women (figure 2B). After recalibration, the NZDCS equation was well calibrated in men, but slightly underestimated risk in the top three deciles of predicted risk in women (figure 2C).

Model and discrimination metrics indicated that the new equations performed significantly better than the NZDCS equation on every metric (table 4).

The adjusted hazard ratios for the additional variables available in the PREDICT-1° Diabetes equations, when added to the NZDCS equation, are shown in the appendix (p 9). With the exception of oral hypoglycaemic drugs and antiplatelet or anticoagulant drugs, all were significant predictors of cardiovascular disease risk in at least one sex.

Figure 3 illustrates the extent of overestimation of 5-year cardiovascular risk in the PREDICT-1° Diabetes subcohort when predicted using the NZDCS equation, compared with the observed distribution as predicted by the PREDICT-1° Diabetes equations. Medians and IQRs of the NZDCS equation scores were more than three times as high as PREDICT-1° Diabetes equation scores in women (median 14·2% [IQR 9·7–20·0] *vs* 4·0% [2·3–6·8]) and more than twice as high in men (17·1% [4·5–20·0] *vs* 7·1% [4·5–11·2]).

Discussion

This unique study has documented how recent widespread diabetes screening has radically changed the cardiovascular risk profile of people diagnosed with type 2 diabetes in New Zealand. The cardiovascular risk distribution of a contemporary representative population

of New Zealanders with diabetes bears little resemblance to the much higher risk distribution predicted by an equation developed in New Zealand just a few years before introduction of widespread screening. The main implication of these findings is that cardiovascular risk prediction equations derived from populations without widespread screening should not be applied to populations where screening is increasingly common, as they will significantly overestimate risk in many screen-detected patients.

The strengths and weaknesses of the PREDICT study have been described previously.[5,6] The key strengths of this study are that it is large and representative of the contemporary New Zealand primary care population eligible for cardiovascular risk assessments; it has minimal missing data on risk predictors; it has comprehensive follow-up using the country's national health index number, which is attached to more than 95% of all individual records in national health databases; and the establishment of a funded national health target in the middle of the study period led to approximately 90% of all New Zealanders, meeting national guideline criteria, completing cardiovascular risk assessments (which included assessing diabetes status) by 2016, up from about 15% in 2001[23] and 50% in 2012.[3] Therefore, we can be confident that the study population is representative of almost all New Zealanders with type 2 diabetes who are eligible for cardiovascular risk assessments.

A potential weakness of the study is that outcome events were all determined from reported ICD codes without individual adjudication, given the use of anonymised linkage. All deaths in New Zealand are coded at one central location, while hospital discharge coding is done at each hospital by trained coders following standardised national guidelines. Given the small size of the New Zealand population (approximately 5 million people), and with one centrally funded public health-care service that is responsible for the care of more than 98% of all acute cardiovascular hospitalisations, admission policies and coding practices are likely to be relatively consistent. Unfortunately, there have been no formal assessments of changes in either admission policies or coding practices over the past two decades in New Zealand and it is possible that some cardiovascular disease events, which have been declining for decades,[24] are now less likely to be coded as cardiovascular disease. However, as all-cause death rates in New Zealand have been declining in parallel to cardiovascular disease death rates,[25] any secular changes in coding are likely to be small. It is also possible that the approximately 10% of eligible people who have not been screened in New Zealand are at higher average cardiovascular risk than those who were included in the PREDICT cohort, but this proportion is too small to have a substantial effect on the reported findings.

There were many similarities and some differences between the PREDICT-1° Diabetes subcohort and the NZDCS that could account in part for the study findings. With regard to similarities, both studies included large representative samples of patients with diabetes, but without previously diagnosed cardiovascular disease. Patients with diabetes and previous cardiovascular disease were excluded from both studies due to their very high cardiovascular risk. Both sets of equations were developed using Cox regression models predicting 5-year cardiovascular risk, with similar outcome definitions and including many participants recruited from the same regions. By contrast, most international comparisons of cardiovascular risk equations involve assessing studies with substantial differences in study populations and settings, inclusion criteria, predictor and outcome definitions, and modelling approaches.[9,26] Therefore, the differences in the performance of the PREDICT-1° Diabetes and NZDCS equations are unlikely to be explained by methodological differences between the studies. It is acknowledged that in regard to the discrimination metrics, the PREDICT-1° Diabetes equations have a home advantage over the NZDCS equation as both sets of equations were assessed in the PREDICT cohort. However, the more important evidence of improved discrimination relates to the additional statistically significant predictors in the PREDICT equations that were not included in the NZDCS equation.

There were some differences between the studies that could partly account for the findings. While the PREDICT study recruitment and follow-up period (October, 2004, to December, 2016) overlapped with the NZDCS (January, 2000, to December, 2007), cardiovascular disease event rates in New Zealand declined by approximately 3–4% per year between 2008 and 2016.[24] These secular trends in cardiovascular disease events rates, which are likely to be due to a range of population-based and clinical interventions, will be partly responsible for the lower event rates estimated by the PREDICT-1° Diabetes equations compared with the NZDCS equation. However, they could not account for the observed two-to-three-times differences in predicted risk. Similar secular trends have been observed in most high-income and many middle-income countries[25] and provide additional support for our recommendation that cardiovascular risk prediction equations derived in patients with diabetes need to be updated. The PREDICT study included people aged 30–74 years, whereas there were no age restrictions in the NZDCS. Approximately 15% of the NZDCS cohort were older than 75 years and the median age was 60 years (IQR 51–70) compared with 54 years (46–62) in PREDICT. However, as age was one of the major predictors of risk in both the PREDICT-1° Diabetes and NZDCS equations, it is adjusted for in the respective models. Patients with substantial renal impairment were excluded from the PREDICT-1° Diabetes subcohort whereas the NZDCS included them, but fewer than 4% of the PREDICT cohort were excluded for this reason and it had little effect on proportions with microalbuminuria and

macroalbuminuria in the two studies. Median BMI and HbA_{1c} in the NZDCS and PREDICT cohorts were also similar. While the median reported duration of diabetes was almost identical in the two studies, reported duration is a misnomer and refers to time since diabetes diagnosis, which will be much earlier in the course of diabetes in a regularly screened population. Unfortunately, the PREDICT data entry forms do not document general practitioners' reasons for assessing patients' diabetes status, so it was not possible to differentiate between screen-detected diabetes and those identified through case finding.

Another difference between the PREDICT study and the NZDCS was the inclusion of some patients with prediabetes. One of the PREDICT-1° Diabetes inclusion criteria was a recent dispensing of metformin and, although not widely recommended, some patients with prediabetes are likely to have been prescribed metformin. In comparison, all patients in the NZDCS were on a diabetes register. Nevertheless, 94% of the PREDICT-1° Diabetes subcohort were classified as having diabetes by their primary care practitioner. Some participants will also have initiated glucose-lowering and cardioprotective medications during follow-up, which would have reduced their observed cardiovascular risk. However, similar proportions of both cohorts were taking glucose-lowering, blood pressure-lowering, and lipid-lowering drugs at baseline, and uptake of these medications during follow-up is likely to have been similar.

We made an a-priori decision to include common oral diabetes medications (ie, acarbose, chlorpropramide, glibenclamide, gliclazide, glipizide, metformin, pioglitazone, rosiglitazone, tolazamide, and tolbutamide) and insulin (all forms) as predictors in the PREDICT-1° Diabetes equations, which were not included in the NZDCS equation. Modern cardiovascular risk prediction equations already include blood pressure-lowering treatment[26] and it is recommended that risk prediction equations should include treatment variables.[27] Oral hypoglycaemic drugs in women and insulin in both sexes were significant predictors. Newer classes of glucose-lowering medications, including SGLT2 inhibitors, GLP-1 receptor agonists and DPP4-inhibitors,[28] were not subsidised in New Zealand during the study period and were seldom used. While the new PREDICT-1° Diabetes equations included several additional variables not included in the NZDCS equation (ie, socioeconomic status, family history of cardiovascular disease, atrial fibrillation, eGFR, and BMI), these are all routinely available for patients with diabetes in New Zealand. Socioeconomic status will not be available to clinicians in many countries; however, we have previously described how an individual socioeconomic deprivation score can be derived.[5] This information is also provided in the appendix (p 10).

People with diabetes in New Zealand are socioeconomically and ethnically diverse, with substantial populations of Pacific Island, Indian, and Chinese people as well as the indigenous Māori population and Europeans. Pacific and Indian people in New Zealand have the highest prevalence of diabetes, followed by Māori and Chinese.[29] The adjusted hazard ratios for non-European ethnic groups were all lower in the PREDICT-1° Diabetes equations than in the NZDCS equation, particularly for Māori and Pacific people. These two ethnic groups had higher BMI, worse renal function, and were more socioeconomically deprived than other ethnic groups in the study population (data not shown), and these variables were adjusted for in the PREDICT-1° Diabetes equations but not the NZDCS equation.

New Zealand and the PREDICT study provide a unique window to the future on a key implication of widespread diabetes screening. As far as we are aware, no other country currently has diabetes screening levels as high as New Zealand, with approximately 90% of people aged 30 years or older now estimated to have had blood tests for HbA_{1c} or blood glucose.[3,30] While universal diabetes screening is not explicitly recommended, HbA_{1c} tests are required for all New Zealanders meeting nationally recommended criteria for cardiovascular risk assessments,[2,7] which includes most middle-aged people. In Singapore, a funded national Screen for life programme recommends diabetes screening every 3 years from age 40 years, but only 50–60% of Singaporeans are estimated to have been screened.[31] To the best of our knowledge, no other country has a comprehensive funded national diabetes screening programme, although regular screening is recommended by many national health organisations. In 2015, the US Preventive Services Taskforce recommended screening for abnormal blood glucose as part of cardiovascular risk assessment in adults aged 40–70 years who are overweight or obese[32] and Diabetes Canada recommends screening every 3 years for people aged 40 years or older and earlier for those with additional diabetes risk factors.[33] With obesity rapidly increasing globally, the increasing use of cardiovascular risk prediction equations requiring diabetes assessments,[26] the increasing use of a simple non-fasting HbA_{1c} blood test for diagnosing diabetes,[4] and the increasing number of new-generation glucose-lowering medications,[28] it is inevitable that diabetes screening will expand worldwide.

A recent systematic review assessed the performance of 26 cardiovascular risk prediction equations used for patients with diabetes, including 15 diabetes-specific equations.[9] The PREDICT-1° Diabetes equations incorporated similar predictors and outcomes and used similar modelling approaches to many of these diabetes-specific equations. While the PREDICT-1° Diabetes equations included more predictors than most of the other equations, as well as ethnicity or socioeconomic predictors that are included in few other equations, differences in the predictors are unlikely to account for

our findings. The key difference is that none of these studies were likely to have recruited participants from populations with widespread screening.

Internationally, guidelines on cardiovascular risk factor management in people with type 2 diabetes vary substantially. Some appear to assume that most patients with diabetes are at high cardiovascular risk by recommending lipid-lowering medication to all patients older than 40 years with diabetes[34] and blood pressure-lowering medications without consideration of cardiovascular risk,[34,35] while others recommend that treatment should be largely informed by predicted cardiovascular risk.[2,36] The recent development of a number of expensive new-generation glucose-lowering medications that reduce cardiovascular risk adds to the implications of our study finding. The absolute cardiovascular benefits of these new medications are largely proportional to patients' pretreatment cardiovascular risk, and most participants in trials of these new drugs were at high cardiovascular risk.[28] Their cost-effective use will require accurate cardiovascular risk prediction to avoid overtreatment and substantial health system costs.

In conclusion, with the inevitable increase in diabetes screening worldwide, the cardiovascular risk distribution of the diabetes patient population is becoming more heterogeneous, and many patients with new-onset diabetes are likely to be at relatively low risk. The view articulated in a number of international guidelines that the majority of patients with diabetes are at high cardiovascular risk and should receive cardioprotective treatments[34,35] will no longer be valid in the presence of widespread screening. Our findings strongly suggest that most cardiovascular risk assessment equations derived in people with diabetes internationally will need to be validated and updated in contemporary diabetes populations to better inform both non-pharmacological and pharmacological management decisions. We have provided all the necessary information on our equations for others to incorporate into electronic calculators or to validate in their own populations.

Contributors

RJ, SW, and AK conceptualised and designed the study. RJ, SW, AK, KP, and BPW were involved in the data collection process. RP analysed the data with input from RJ, KP, SM, SW, BPW, and AK. All authors were involved in data interpretation. RJ and RP drafted the manuscript and all authors revised the manuscript. All authors approved the final submitted version and agreed to be accountable for the report. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. RP and BPW have directly accessed and verified the data.

Declaration of interests

We declare no competing interests.

Data sharing

All individual participant (deidentified) data, including a data dictionary defining each field, will be made available to university-based academic researchers if their proposed analyses are approved by the investigators' Data Access Proposal Committee. A proposal must be considered relevant to the original aims of the research, must meet the study's ethics approval criteria, and will require one or more of the study investigators as formal collaborators. A signed data access agreement will be required and the costs of preparing the datasets will need to be covered. There are no set dates for when these data will be made available. Please contact the corresponding author regarding data sharing requests.

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