Relationship between estimated glomerular filtration rate and incident cardiovascular disease in an ethnically diverse primary care cohort

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ABSTRACT

AIM: To investigate eGFR as an independent risk factor for CVD in a New Zealand primary care cohort, stratified by disease status (prior CVD, diabetes or no CVD or diabetes).

METHOD: The PREDICT-CVD open cohort study is a large, ethnically diverse, New Zealand primary care cohort, generated by using a web-based CVD risk assessment tool. Using encrypted identifiers, participant profiles were linked anonymously to a regional laboratory database (to determine renal function) and to national hospitalisation and mortality datasets. Analyses using a single baseline eGFR measurement were undertaken in three clinical sub-cohorts of participants: those with prior CVD (n=29,742), with diabetes (n=44,416) and with neither CVD nor diabetes (n=192,696). The association between baseline eGFR (by category ≥90, 60–89.9, 30–59.9, and <30ml/min/1.73m^2) and incident CVD was analysed with Kaplan Meier plots and Cox regression models.

RESULTS: After adjustment for traditional CVD risk factors, there was an inverse relationship between CVD risk and eGFR, up to an eGFR of 60ml/min/1.73m^2 in all three clinical sub-cohorts, and up to an eGFR of 90ml/min/1.73m^2 in the sub-cohort with CVD or diabetes. Compared to eGFR ≥90ml/min/1.73m^2, the adjusted hazard ratios of a new CVD event for eGFR <30ml/min/1.73m^2 in the CVD, diabetes and no CVD/no diabetes sub-cohorts were 2.29 (95% CI 2.00–2.61), 4.71 (3.92–5.67) and 2.78 (2.05–3.77), respectively. Compared to European/Other ethnic groups, Māori participants remained at greater adjusted risk of a new CVD event in all clinical sub-cohorts and Pacific people only in the no CVD/no diabetes sub-cohort, whereas Indian participants had a similar adjusted risk to European/Other, and Other Asian patients were consistently at lower adjusted risk. Sensitivity analyses for individuals with consecutive eGFR results (>90 days apart) yielded similar results.

CONCLUSION: This study has confirmed that, in a large ethnically diverse primary care cohort, eGFR is a significant independent predictor of CVD risk, and the risk varies by ethnic group.

Estimated glomerular filtration rate (eGFR) is used in the detection and classification of chronic kidney disease (CKD) as a marker of chronic renal impairment. CKD classification is based on two consecutive eGFR results at least 90 days apart. It is usually categorised into five levels from eGFR ≥90ml/min/1.73m^2 (normal), 60–89ml/min/1.73m^2 (mildly decreased), 30–59ml/min/1.73m^2 (moderately decreased), 15–29 ml/min/1.73m^2 (severely decreased) and <15ml/min/1.73m^2 (end stage renal disease).[1] International population-based cohorts indicate that the lower the level of eGFR, the greater the risk of incident cardiovascular disease (CVD) events, hospitalisation and deaths.[2,3] A Chronic Kidney Disease-Prognosis Consortium (CKD-PC) meta-analysis of 1.4

million participants from 30 cohort studies in the US showed that, after adjustment for traditional cardiovascular risk factors and albuminuria, the risk gradient for cardiovascular mortality increased linearly with decreasing eGFR below the threshold of 75ml/min/1.73m^2.[4]

Existing studies differ in terms of populations studied, definitions of CVD and CKD, estimating equations for GFR, and thresholds below which eGFR increases CVD risk. Currently there are no epidemiological studies investigating the impact of renal impairment on CVD risk in New Zealanders and ethnic subgroups who have higher risk of both CKD and CVD.[5,6]The relationship between renal function and new CVD events may also differ by disease status (prior CVD or diabetes). Both patients with diabetes and/or prior CVD have higher risk of new CVD events and increased risk of renal impairment due to underlying vascular disease, shared risk factors or diabetic nephropathy.[7] Kerr et al found that people with a history of CVD had an additional 20% five-year CVD risk on top of the observed risk of participants without a history of CVD.[8] Given these differences, stratifying analyses into three distinct risk groups (prior CVD, diabetes and no CVD/no diabetes) when examining the relationship between renal function and CVD, increases the homogeneity of the subgroups assessed and provides more clinically meaningful results.

Using a large ethnically diverse primary care cohort generated in the course of routine CVD risk assessment in New Zealand primary care, we aimed to determine the impact of eGFR on fatal and non-fatal CVD events independent of other known CVD risk factors and whether the risk varied by disease status (prior CVD or diabetes) and ethnic group.

Methods

Study design

The PREDICT-CVD cohort study has been previously described.[9] Briefly, patients have their CVD risk assessed by general practitioners (GPs) using PREDICT online forms that are integrated with their enrolled patients' electronic health records. This web-based tool is used in primary care for the assessment and management of CVD risk. The risk score and evidence-based recommendations incorporating national guidelines are displayed after the online form has been completed. The anonymised patient profiles are stored on a secure off-site server (Enigma Solutions Ltd) and form the research cohort. The cohort can be linked to regional and national databases through a patient's encrypted National Health Index (a unique identifier in New Zealand health services [NHI]) providing data on laboratory tests, deaths, hospitalisations and medication dispensing history. Over 95% of New Zealanders have an NHI.[10] Good agreement has been found between the data stored in PREDICT and patient data within primary care electronic records.[11]

Study population

Between 2002 and 2015, over 450,000 people between the ages of 35 and 74 years had a CVD risk assessment undertaken using the PREDICT online forms. The PREDICT software is available in approximately 35–40% of primary care practices in New Zealand (mainly Auckland and Northland) serving around 35% of the resident population.[9] After excluding patients who had an International Classification of Disease-10 Australian modification (ICD-10-AM) coded history of dialysis or kidney transplantation, participants were divided into the three sub-cohorts: CVD, diabetes (without CVD) or no CVD/no diabetes. The CVD cohort was derived in three ways. Firstly, if a GP or nurse reported a patient's prior history of angina, myocardial infarction, coronary artery bypass grafting (CABG), percutaneous coronary intervention (PCI), transient ischaemic attack (TIA), ischaemic stroke, peripheral vascular disease (PVD) or atherosclerotic vascular procedure during the PREDICT risk assessment. Secondly, from ICD-10-AM coded CVD-related hospital admissions in the state-funded system (over 95% of acute CVD events are managed in publicly funded hospitals).[12] Thirdly, linkage to the national pharmaceutical database (PHARMS) identified patients with three or more prescriptions of anti-anginal medications in the previous five years from records of subsidised pharmaceutical dispensing.

The diabetes sub-cohort does not include any patients with a history of CVD. This sub-cohort was also derived in three ways: reported by their practitioner as having diabetes, prior hospitalisation with

ICD-10-AM diabetes codes, and linkage to the PHARMS database detecting at least one prescription for insulin or oral hypoglycaemic agents in the six months prior to the patient's CVD assessment (see Appendix for full definitions and ICD-10-AM codes).

Additional CVD history

History of heart failure was defined as any prior hospitalisation for heart failure, dispensing of metolazone in the last six months, or dispensing of loop-diuretics at least three times in the previous five years. History of atrial fibrillation was defined as any prior hospitalisation or if recorded in the PREDICT online form.

Ascertainment of renal function

Serum creatinine results were provided where available through linkage to 'TestSafe', the repository for results in Northland and Auckland. We identified the serum creatinine result nearest to the first PREDICT assessment and within either the two years prior or 14 days after that assessment. From the serum creatinine, a baseline eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[13] The analysis was stratified by eGFR categories ≥90 (reference group), 60–89.9, 30–59.9, and <30ml/min/1.73m^2.

The Jaffe method for serum creatinine measurement is used by all laboratories providing results for this cohort (S. Musaad, personal communication, 2017). Creatinine testing standardised to the isotope-dilution mass spectrometry (IDMS) methodology was gradually introduced into New Zealand laboratories after 2008.

The procedure for identifying patients with albuminuria in the diabetes sub-cohort was using the protein/creatinine ratio (mg/mmol or g/mol), urine protein/24 hours (mg/24 hours) or albumin/creatinine ratio (mg/mmol [ACR]), with thresholds as defined in the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines.[1] The albuminuria result closest to baseline was used within two years prior and 14 days post PREDICT assessment.

Ethnicity

Ethnic groups were based on national ethnicity data prioritisation protocols in the following order: NZ Māori, Pacific, Indian (including individuals who identified as both Indian and Fijian and who were therefore assumed to be Fijian Indian), Other Asian and finally European and Other ethnic groups (European/Other). [14]

Covariates

Variables from PREDICT include age (derived from date of birth), sex, ethnicity, self-reported family history of premature CVD, smoking status, systolic and diastolic blood pressure (BP), and total cholesterol-to-high density lipoprotein ratio (TC/HDL). Body mass index (BMI) was included in the PREDICT template but was not a mandatory field for CVD risk assessment.

Family history of premature CVD was defined as a self-reported familial history of ischaemic heart disease or ischaemic stroke occurring in a father or brother before 55 years of age, or a mother or sister before 65 years of age. Smoking status was defined as never smoked, previous smoker (giving up over 12 months ago or within the previous 12 months) or current smoker (of any amount). Linkage to the primary health organisation enrolment database provided information on the New Zealand Deprivation Index (NZDep). The NZDep score assigns a measure of socioeconomic status to a patient's geographical area of residence.[15] It is derived from variables in the Census that signify eight dimensions of relative deprivation and has been used as quintiles in this analysis from the least deprived (1) to the most deprived (5).

The PHARMS database also provided information on dispensed cardiovascular and diabetes-related medications.

Follow-up and outcomes

Entry to the study was prospective from 1 August 2002 and participants were electronically followed up until they either died, were lost to follow-up or reached the date of data extraction (31 December 2015). The index date for this study was taken as the date of the first completed PREDICT assessment (baseline assessment).

New CVD events were identified using ICD-10-AM codes from mortality records and hospital discharges. New CVD events include fatal and non-fatal acute coronary syndromes, unstable angina, myocardial infarction, coronary heart disease, heart failure, PVD, TIA, ischaemic stroke and haemorrhagic stroke (See Appendix for ICD-10-AM codes).

Statistical analysis

Statistical analyses centred on developing survival models for incidence of any CVD event, taking serum eGFR as a potential predictor. Kaplan-Meier plots were produced to show disease-free survival over time in each of the three sub-cohorts, stratified by eGFR category. Time from baseline assessment was used as the time scale in multivariable Cox regression models stratified by the three sub-cohorts.

All models controlled for age group, ethnicity, sex, smoking status, NZDep quintile, systolic BP, diastolic BP, TC/HDL, family history of premature CVD, any lipid-lowering, BP-lowering, diabetes-related, antiplatelet or anticoagulant medications at baseline. The CVD sub-cohort was also adjusted for any history of atrial fibrillation or heart failure, and the diabetes sub-cohort was adjusted for BMI (as it was the only sub-cohort with sufficient data). For all models, the proportional hazards assumption was assessed using Schoenfeld residual plots and the linearity of the association between continuous predictors and the hazard function via Martingale residual plots.

Due to missing data, a single eGFR result was used in the main analyses, with sensitivity analyses conducted using confirmed eGFR results for patients with eGFR <60ml/min/1.73m^2 meeting the KDIGO guideline requirements (two consecutive measures of renal function less than 60ml/min/1.73m^2, at least 90 days apart) for the diagnosis of CKD.[1] Sensitivity analyses were performed for the diabetes sub-cohort by also controlling for albuminuria as a binary variable (positive or negative result). Albuminuria was not included in the main analyses as only 68% of participants had a baseline result from any source.

All analyses were done using R software version 3.2.3.

Ethical approval

The PREDICT study was approved by the Northern Region Ethics Committee Y in 2003 (AKY/03/12/314) with subsequent annual approval by the National Multi Region Ethics Committee since 2007 (MEC07/19/EXP).

Results

Between 1 August 2002 and 31 December 2015, 455,822 patients aged 35–74 years had a CVD risk assessment using the PREDICT online form. Those with an ICD-10-AM coded history of hospitalisation for renal dialysis or transplantation (n=14,256) or missing eGFR (n= 174,712) were excluded. Participants were then allocated to disease status sub-cohorts; 29,742 with prior CVD, 44,416 with diabetes but no prior CVD and 192,696 in the no CVD/no diabetes sub-cohort (Figure 1). The baseline characteristics are displayed in Table 1, stratified by sub-cohort.

Figure 1: Flowchart of PREDICT-CVD cohort with sub-cohorts.

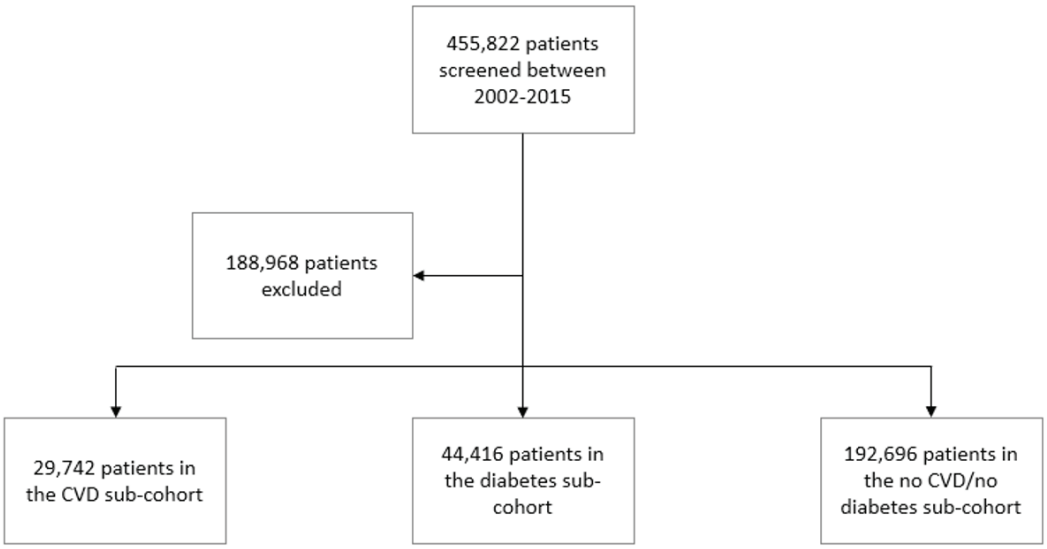


Table 1: Baseline characteristics of each sub-cohort.

Characteristic	CVD n=29,742	Diabetes n=44,416	No CVD/no diabetes n=192,696
Age group			
35–44	1,117 (4)	7,529 (17)	24,229 (13)
45–54	5,259 (18)	14,482 (33)	68,098 (35)
55–64	10,599 (36)	13,743 (31)	66,202 (34)
65–74	12,767 (43)	8,662 (20)	34,167 (18)
Female	10,954 (37)	21,344 (48)	88,515 (46)
Ethnicity			
NZ Māori	4,001 (14)	5,791 (13)	20,215 (10)
Pacific	3,492 (12)	12,225 (28)	21,646 (11)
Indian	2,527 (9)	7,063 (16)	14,957 (8)
Other Asian	1,779 (6)	5,135 (12)	19,294 (10)
European/Other	17,943 (60)	14,202 (32)	116,584 (61)
NZDep quintile 1 (least deprived)	5,681 (19)	5,892 (13)	49,303 (26)
quintile 2	5,349 (18)	6,454 (15)	40,334 (21)
quintile 3	5,238 (18)	6,953 (16)	34,193 (18)
quintile 4	5,879 (20)	9,502 (21)	33,142 (17)
quintile 5 (most deprived)	7,594 (26)	15,613 (35)	35,712 (19)
Diabetes	10,487 (35)	44,416 (100)	~
Heart failure	4,588 (15)	~	~
Atrial fibrillation	4,138 (14)	~	~
Current smoker	4,391 (15)	6,450 (15)	25,656 (13)
Previous smoker	7,944 (27)	7,460 (17)	30,930 (16)
Never smoked	17,406 (59)	30,505 (69)	136,110 (71)
Systolic BP (mmHg)	131 (17.5)	132 (17.2)	129 (16.7)
TC/HDL ratio	3.8 (1.20)	4.2 (1.31)	4.0 (1.18)
BP-lowering medication	22,971 (77)	26,430 (60)	45,474 (24)
Lipid-lowering medication	21,500 (72)	23,863 (54)	28,293 (15)
Antiplatelet/anticoagulant medication	21,649 (73)	16,947 (38)	16,890 (9)
Diabetes-related medication	6,920 (23)	27,840 (63)	~
BMI (kg/m^2)			
<25	~	5,815 (13)	~
25–29.9	~	25,097 (57)	~
≥30	~	12,013 (27)	~

Table 1: Baseline characteristics of each sub-cohort (continued).

eGFR (ml/min/1.73m^2)			
≥90	9,139 (31)	21,863 (49)	96,371 (50)
60–89.9	16,046 (54)	18,909 (43)	89,814 (47)
30–59.9	4,096 (14)	3,302 (7)	6,269 (3)
<30	461 (2)	342 (1)	242 (0.1)
Mean follow-up (years)	5.0	5.4	4.1
Median follow-up (years)	4.6	5.3	3.6
Person-years	149,793	238,794	782,542
Number of fatal and non-fatal first events	7,560	4,328	6,527
Crude event rate per 1,000 person-years with 95% confidence intervals	50 (49–52)	18 (18–19)	8 (8–9)

Categorical values given as n (%) and continuous variables as mean (standard deviation).
Three missing values for NZDep quintile; two missing values for smoking status; two missing values for diastolic BP; 43 missing values for TC/HDL.

In comparison to the other sub-cohorts, the group with prior CVD were older and included fewer women. People with CVD or diabetes were more likely to live in the most deprived areas of residence (NZDep quintile 5). The proportions of Māori patients were similar across all three sub-cohorts. However, there were higher proportions of Pacific, Indian and Other Asian patients in the diabetes sub-cohort compared to those with prior CVD. In the CVD sub-cohort, over one-third had diabetes, over 15% had heart failure and nearly 14% had atrial fibrillation. In the diabetes sub-cohort, nearly 63% were prescribed diabetes-related medications, and 84% were either overweight or obese. The median times between the eGFR result and the baseline PREDICT visit were 56, 29 and 88 days for the CVD, diabetes and no CVD/no diabetes sub-cohorts, respectively. Using a definition of CKD as eGFR under 60ml/min/1.73m^2, the CVD sub-cohort had the highest proportion of individuals with CKD (16%) and the no CVD/no diabetes sub-cohort the lowest (3%). Of the 30,350 patients who were tested in the diabetes sub-cohort, 40% were found to have albuminuria.

The crude event rates for ischaemic CVD were highest in the CVD sub-cohort at 50 per 1,000-person years (95% confidence interval [CI] 49–52). The diabetes and no CVD/no diabetes sub-cohorts had event rates of 18 per 1,000-person years (95% CI 18–19), and eight per 1,000-person years (95% CI 8–9), respectively (Table 1).

The Kaplan-Meier plots in Figure 2 show incident hospitalisations or deaths occurring during follow-up in each of the three sub-groups by eGFR category. With each category of decreasing eGFR, the plots show reduced disease-free survival probability over time, and a sharp decrease within the first 500 days under 60ml/min/1.73m^2 in the CVD sub-cohort and under 30ml/min/1.73m^2 in the diabetes sub-cohort, compared to a more gradual event rate in the sub-cohort with no CVD or diabetes.

Adjusted hazard ratios (adjHR) for new CVD events by sub-cohort are shown in Table 2. Compared to an eGFR ≥90ml/min/1.73m^2, there was an increase in the adjHR by each category of worsening renal impairment, with a nearly five-fold higher risk of a fatal or non-fatal CVD event among people with diabetes and an eGFR under 30ml/min/1.73m^2 (adjHR 4.71[95% CI 3.92–5.67]). There were significant increases in the risk of new CVD events for eGFR results under 90ml/min/1.73m^2 in the CVD and diabetes sub-cohorts, and under 60ml/min/1.73m^2 in the no CVD/no diabetes sub-cohort. The 60–89.9ml/min/1.73m^2 category of eGFR remained significant in the diabetes sub-cohort when albuminuria was included in the model.

Table 2: Adjusted hazard ratios (with 95% confidence intervals) for fatal and non-fatal cardiovascular events by sub-cohort.

	CVD	Diabetes	No CVD/no diabetes
eGFR(ml/min/1.73m^2)			
≥90	1	1	1
60–89	**1.10 (1.03–1.17)**	**1.12 (1.04–1.20)**	1.00 (0.94–1.05)
30–59	**1.50 (1.39–1.61)**	**1.95 (1.76–2.17)**	**1.54 (1.40–1.70)**
<30	**2.29 (2.00–2.61)**	**4.71 (3.92–5.67)**	**2.78 (2.05–3.77)**
Ethnicity			
Euro/Other	1	1	1
NZ Māori	**1.09 (1.02–1.17)**	**1.38 (1.25–1.52)**	**1.57 (1.45–1.69)**
Pacific	**0.90 (0.84–0.98)**	1.02 (0.93–1.12)	**1.17 (1.08–1.27)**
Indian	1.05 (0.96–1.14)	1.09 (0.98–1.21)	0.98 (0.88–1.10)
Other Asian	**0.68 (0.60–0.78)**	**0.62 (0.53–0.72)**	**0.65 (0.58–0.73)**
Age group (years)			
35–44	1	1	1
45–54	1.13 (0.98–1.30)	**1.46 (1.29–1.64)**	**1.87 (1.67–2.10)**
55–64	**1.21 (1.05–1.39)**	**1.95 (1.72–2.20)**	**3.24 (2.88–3.64)**
65–74	**1.54 (1.33–1.77)**	**2.61 (2.28–2.99)**	**6.23 (5.51–7.04)**
Sex			
Male	1	1	1
Female	**0.81 (0.77–0.85)**	**0.67 (0.63–0.71)**	**0.65 (0.61–0.68)**
NZDep quintile 1	1	1	1
quintile 2	1.01 (0.93–1.11)	1.06 (0.92–1.21)	1.06 (0.98–1.15)
quintile 3	**1.24 (1.14–1.35)**	1.14 (1.00–1.29)	**1.25 (1.15–1.35)**
quintile 4	**1.30 (1.20–1.41)**	**1.36 (1.21–1.54)**	**1.31 (1.21–1.42)**
quintile 5	**1.48 (1.37–1.60)**	**1.45 (1.29–1.63)**	**1.59 (1.46–1.72)**
Diabetes	**1.29 (1.21–1.38)**	~	~
Heart failure	**1.39 (1.31–1.47)**	~	~
Atrial fibrillation	**1.29 (1.21–1.38)**	~	~
Never smoked	1	1	1
Previous smoker	**1.13 (1.07–1.19)**	**1.12 (1.03–1.22)**	**1.15 (1.07–1.22)**
Current smoker	**1.49 (1.40–1.59)**	**1.50 (1.38–1.63)**	**1.76 (1.64–1.87)**
Systolic BP (mmHg)	**1.00 (1.00–1.01)**	**1.01 (1.01–1.01)**	**1.01 (1.01–1.01)**
Diastolic BP (mmHg)	**0.99 (0.99–1.00)**	**1.00 (0.99–1.00)**	1.00 (1.00–1.00)
TC/HDL ratio	**1.07 (1.05–1.09)**	**1.10 (1.08–1.12)**	**1.15 (1.13–1.17)**

Table 2: Adjusted hazard ratios (with 95% confidence intervals) for fatal and non-fatal cardiovascular events by sub-cohort (continued).

BP-lowering medication	**1.29 (1.19–1.39)**	**1.41 (1.30–1.53)**	**1.51 (1.42–1.60)**
Lipid-lowering medication	**0.93 (0.87–0.99)**	**0.91 (0.84–0.97)**	**0.90 (0.84–0.96)**
Antiplatelet/anticoagulant medication	**1.15 (1.07–1.22)**	**1.14 (1.06–1.22)**	**1.38 (1.29–1.48)**
Diabetes-related medication	**1.16 (1.09–1.25)**	1.06 (0.98–1.14)	~
BMI (kg/m²)			
<25	~	1	~
25–29.9	~	0.93 (0.83–1.03)	~
≥30	~	0.93 (0.83–1.04)	~

Statistically significant results in bold.

Figure 2: Kaplan-Meier curves showing disease-free survival by eGFR category in each sub-cohort.

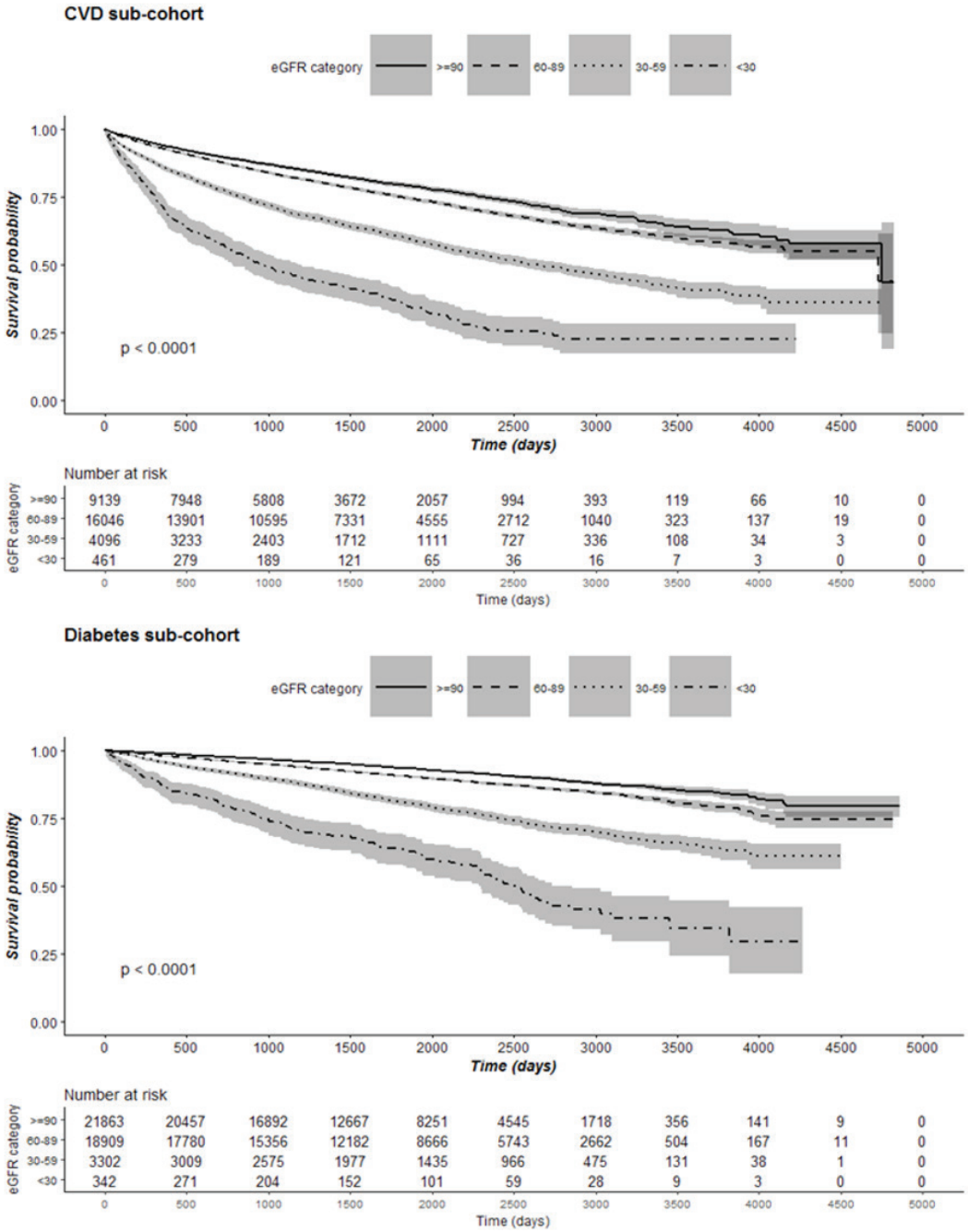
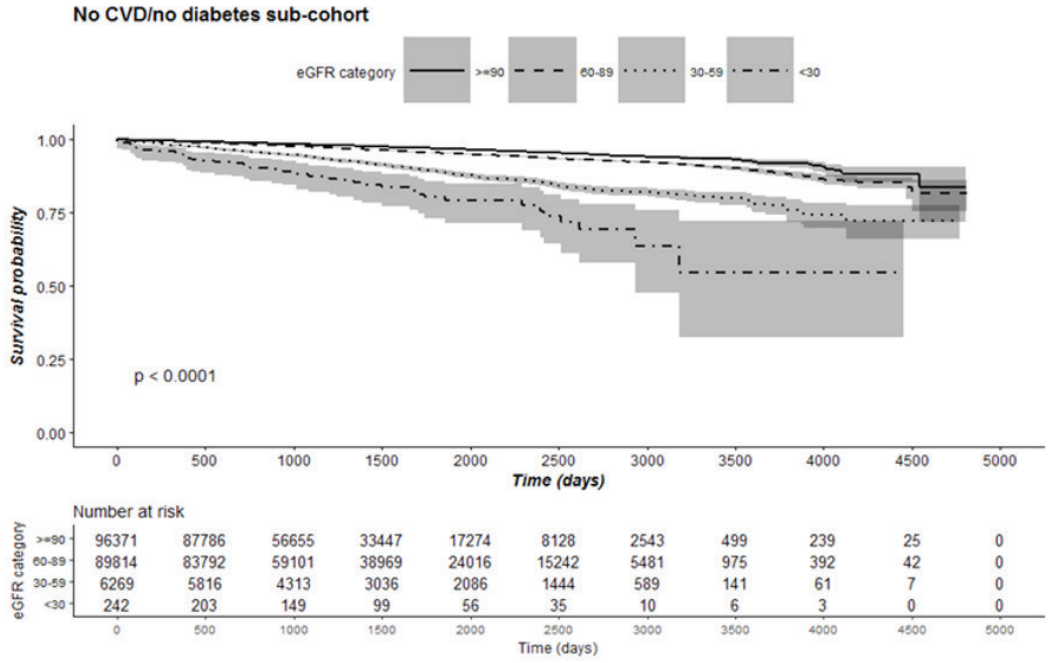


Figure 2: Kaplan-Meier curves showing disease-free survival by eGFR category in each sub-cohort (continued).



Compared to people of European/Other descent, Māori were at increased risk in all three sub-cohorts, particularly in the sub-cohort with no CVD or diabetes (adjHR 1.57 [95% CI 1.45–1.69]). In the diabetes sub-cohort, Indian participants were at higher risk than their European/Other counterparts, but this difference was not significant. However, those of Other Asian ethnicity were at significantly lower risk than European/Other in all three sub-cohorts. Pacific participants had reduced CVD risk in comparison to European/Other in the CVD sub-cohort after controlling for renal function and CVD risk factors but higher risk in the no CVD/ no diabetes sub-cohort.

Men, increasing age group, increasing quintile of deprivation, current smokers, higher systolic BP and TC/HDL ratio and receiving BP-lowering medications were associated with higher risk.

The definition of CKD is limited as it was based on a single measure of creatinine and may include participants with acute kidney injury (AKI). For the participants with an eGFR <60ml/min/1.73m^2, confirmatory eGFR results were available for 3,163 participants in the CVD sub-cohort (69.4%), 2,473 participants in the diabetes sub-cohort (67.9%) and 3,223 participants in the sub-cohort with no CVD or diabetes (49.5%). Sensitivity analyses using confirmatory eGFR <60ml/min/1.73m^2 in all three sub-cohorts, showed similar results to the main analyses (see Appendix 2).

Discussion

This study is the first to examine the relationship between reduced eGFR and incident CVD in New Zealanders, including ethnic subpopulations. CVD risk increased with each category of worsening eGFR in all three sub-cohorts. The main insight from our study is that, controlling for known risk factors, there were significant increases in incident CVD risk for people with eGFR under 90ml/min/1.73m^2 in the CVD and diabetes sub-cohorts, and under 60ml/min/1.73m^2 in the no CVD/no diabetes sub-cohort. The significance of findings in the 60–89.9ml/min/1.73m^2 eGFR category in the CVD and the diabetes sub-cohorts is important because this is considered to be in the non-CKD range. Of note, full CKD staging according to KDIGO guidelines[1] could not be used in our study because of limited data regarding albuminuria. It is therefore possible that some of those with eGFR in the non-CKD range did in fact have albuminuria and therefore CKD at baseline. However, the insight from our study remains: people with mildly reduced eGFR but CVD or diabetes have an increased risk of incident CVD compared with those with a normal eGFR.

Our study also provided insights into effect modification of eGFR on incident CVD risk by ethnicity. Māori had an elevated risk of a new CVD event compared to European/Other in all three sub-cohorts, over and above their eGFR category. Importantly, these findings persisted after controlling for multiple covariates including socioeconomic deprivation, smoking and medication use. Of note, once eGFR is considered, the risk of CVD among Indian people is not significantly elevated in any sub-cohort. However, as 75% of the current Indian population in New Zealand are immigrants, it is unclear whether this will change over time as the healthy migrant effect abates. This situation is similar for Pacific people, and in fact the adjusted hazard ratio is lower for them in the CVD sub-cohort.

Limitations of this study arise from the measurement and modelling of renal function. Some of the creatinine results pre-2008 will not have been standardised to the IDMS methodology and more precise filtration markers (cystatin C) were not available in this study.[16] In New Zealand, the CKD-EPI equation has not been validated, and it is unclear whether the term for the African-American race should be applied to non-Asian non-white people.[17] Moreover, renal function testing was at the discretion of physicians, and 39.6% of people had missing values for eGFR. The largest limitation of this study was the use of a single baseline creatinine-based eGFR value. Acute and chronic kidney disease have different aetiologies and are differentiated in the KDIGO guidelines by duration (>90 days for CKD).[1] This has implications for using creatinine-based eGFR at an individual level to predict the risk of a new CVD event using a single creatinine measurement, since there can be significant variability in serum creatinine levels in the same individual on repeat testing and abnormal results may be due to acute fluctuation in renal function as opposed to CKD, or the presence of both CKD and AKI in the same individual (pre-existing CKD is a significant risk factor for AKI).[18] However, the new CVD consensus statement published in February 2018 recommends routine collection of eGFR for risk stratification and therefore it is likely that missingness of confirmatory eGFR values for CKD classification will be mitigated in the future.[19]

The results of this study were similar to the CKD-PC meta-analyses. However, those studies did not examine the patient group with prior CVD as a separate cohort. CKD-PC meta-analyses that have combined high- and low-risk cohorts show significance for CVD risk at eGFRs either below 75ml/min/1.73m^2 independent of albuminuria,[20,21] or between 75–89ml/min/1.73m^2 with albuminuria only.[22,23] Many studies have shown a link between renal insufficiency and cardiovascular outcomes in cohorts with diabetes and some studies have additionally linked mild renal insufficiency (60–90ml/min/1.73m^2) with these outcomes in diabetic cohorts.[24,25] In the sub-cohort with no CVD and no diabetes, increased CVD risk below eGFR 60ml/min/1.73m^2 is consistent with similar studies.[2,26] Most studies use single baseline eGFR results in their analyses, however, this study was also able to provide confirmed consecutive eGFR results (>90 days apart) for sensitivity analyses which yielded similar results to the main analyses.

Another critical unknown is the association of rate of decline in eGFR with subsequent incident CVD risk (adjusted for confounders and first eGFR), with implications for greater declines in eGFR as potential markers of even greater increases in incident CVD risk.[27]

As is usual with real-world evidence, there is potential for residual confounding from unmeasured but prognostically important variables, and information bias from misclassification. BMI was not included in the CVD and no CVD/no diabetes sub-cohort, and important variables such as physical activity and diet were also not included in our data source and may all have affected outcomes differentially between comparison groups. Linking and merging electronic health data is known to carry several limitations since the data has not been obtained to answer a specific research question, but for other clinical, administrative or financial purposes. The utility of the information is dependent on the quality of data from different sources, data completeness, data curation and the classification algorithms used for the disease states, risks factors and outcomes. For instance, medication data were derived from dispensed prescriptions from the national pharmaceutical claims warehouse but there is no way of actually knowing if patients took them. Finally, the NZDep score is a proxy

measure of deprivation based on meshblock area, which cannot indicate individual socio-economic position.

The ethnicity data used in this study, collected by the Ministry of Health, combined South Asian ethnicities other than the Indian group (eg, Sri Lankan, Pakistani, Bangladeshi), with Other Asian ethnicities (eg, Chinese, Japanese and other South East Asian ethnicities). Therefore, as South Asian people will have a similar risk factor profile to Indian people, it is likely that Chinese and people of South East Asian ethnicity will have even lower risk of CKD than represented here. Recent changes to the ethnicity protocols for the Health and Disability Sector in New Zealand in 2017, include the requirement to record up to six ethnicities at the most detailed level of classification (Level 4).[28] This will allow the different risk profiles between South Asian groups and Other Asian ethnicities to be distinguished, as currently intended in both the CVD risk assessment and CKD detection guidelines in New Zealand.[19,29]

This large primary care cohort of participants with representation of the main ethnic groups in New Zealand has provided evidence of the relationship between renal function and new CVD events at the population level. On the basis of this study, it would appear that eGFR is an independent predictor of new CVD events, and this relationship varies by ethnic group and by disease status. This may have several clinical implications for CVD risk assessment in New Zealand. Firstly, as an independent predictor of new CVD events, further New Zealand-based research is required to understand whether a single-creatinine-based eGFR result could improve risk prediction in multivariable CVD risk equations, particularly for subgroups at increased risk of CKD and CVD. Secondly, it is clear that ethnicity modifies the risk of a new CVD event, even after accounting for renal function, and there may be scope for improved clinical management of ethnic subgroups according to renal impairment and disease status. It is certainly plausible that ethnic-specific equations would result in improved prediction and therefore earlier intervention in high-risk ethnic groups. Finally, the results of our study may suggest that incident CVD risk is significant for people with ostensibly normal eGFRs between 60 and 90ml/min/1.73m^2 in the CVD and diabetes sub-cohorts, and there may be opportunity for heightened attention to modification of risk factors and preventive care in these patients.

Appendix 1

The definitions used for this study are outlined below. The dispensing history is taken from the time of patient's CVD assessment from the Pharmaceutical claims collection database (PHARMS) between 1 January 2005 to 31 December 2015. ICD-10-AM codes used to identify sub-cohorts and CVD events are from hospital records (and mortality records for CVD outcomes) from 1 January 2005 to 21 December 2015.

Sub-cohorts

CVD sub-cohort

Patients with prior CVD were identified based on meeting one of the following criteria:

PREDICT online form	Patients with a history of angina, myocardial infarction, coronary artery bypass grafting (CABG), percutaneous coronary intervention (PCI), transient ischaemic attack (TIA), ischaemic stroke, peripheral vascular disease (PVD) or atherosclerotic vascular procedure were identified by their practitioner.
Any hospital admissions with CVD-related codes	ICD-10-AM codes listed under "New CVD events."
Three or more prescriptions of anti-anginal medications in the previous five years	Subsidised pharmaceutical dispensing of glyceryl trinitrate, isosorbide dinitrate, isosorbide mononitrate, nicorandil, pentaerythritol tetranitrate or perhexiline maleate.

Within the CVD sub-cohort, history of heart failure and atrial fibrillation were also identified through:

Heart failure	Any prior hospitalisation with heart failure-related code (ICD-10-AM codes listed under "New CVD events") OR Any dispensing of metolazone in the previous six months or dispensing of loop diuretics (bumetanide and frusemide) on at least three occasions in the previous five years.
Atrial fibrillation	History of atrial fibrillation identified from PREDICT OR Any hospital admission with atrial fibrillation-related code (ICD-10-AM I48).

Diabetes sub-cohort

The diabetes sub-cohort does not include any patients with a history of CVD. Patients with diabetes were identified based on meeting one of the following criteria:

PREDICT online form	Patients with type 1 or type 2 diabetes were identified by their practitioner.
Any hospital admission with diabetes-related codes	ICD-9 or 10-AM codes: ICD-9 250 and ICD-10-AM E10-E14.
At least one prescription for insulin or oral hypoglycaemic agents in the previous six months	Subsidised pharmaceutical dispensing of insulin, acarbose, chlorpropramide, glibenclamide, gliclazide, glipizide, metformin, pioglitazone, rosiglitazone, tolazamide, tolbutamide.

Medications at baseline

Multivariable analyses used any lipid-lowering, BP-lowering, diabetes-related, antiplatelet of anticoagulant medications in the six months prior to PREDICT risk assessment. This was identified either on the PREDICT online form or from medication dispensing history (PHARMS). Drug classes include:

Antiplatelet or anticoagulant	**Antiplatelet** Aspirin Clopidogrel Dipyridamole Prasugrel Ticagrelor Ticlopidine	**Anticoagulant** Dabigatran Phenindione Rivaroxiban Warfarin

BP-lowering	**ACE Inhibitor** Benazepril Captopril Cilazapril Enalapril Lisinopril Perindopril Quinepril Trandolapril **ARB** Candesartan Losartan **Other** Amiloride Clonidine Clopamide Hydralazine Methyldopa Triamterene **Thiazide** Bendrofluazide Chlorthiazide Cycylopenthiazide Hydrochlorothiazide Indapamide Methyclothiazide	**Beta-blocker** Acebutolol Alprenolol Atenolol Bisoprolol Carvedilol Celiprolol Labetolol Metoprolol Nadolol Oxprenolol Pindolol Propanolol Sotalol Timolol **CCB** Amlodipine Dilitiazem Felodipine Isradipine Nifedipine Verapamil
Lipid-lowering	**Statin** Atorvastatin Ezetimibe with Simvastatin Fluvastatin Pravastatin Simvastatin	**Other** Acipimox Bezafibrate Cholestyramine Clofibrate Colestipol hydrochloride Ezetimibe Gemfibrozil Nicotinic acid
Diabetes-related	Insulin Acarbose Chlorpropramide Glibenclamide Gliclazide Glipizide	Metformin Pioglitazone Rosiglitazone Tolazamide Tolbutamide

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CVD events

CVD events were identified using ICD-10-AM codes from mortality records and hospital discharges from 1 January 1988 to 31 December 2015. Prior and new CVD events include:

- fatal and non-fatal acute coronary syndromes (I200, I210-I214, I219-I221, I228, I229),
- unstable angina (I200),
- myocardial infarction (I210-I214, I219-I221, I228, I229),
- coronary heart disease (I200, I201, I218-I214, I219-I221, I228-I236 I238, I240, I248, I249, I253-I256, I460-1469),
- heart failure (I50, I110, I130, I132, I500, I501, I 509),
- peripheral vascular disease (I711, I713, I715, I718, I7100-I7103, I7021-I7024, I739-I745, I748, I749, E1050-E1052, E1150-E1151, E1451, E1452),
- transient ischaemic attack (G450-G453, G458-G468),
- ischaemic stroke (I630-I636, I638, I639, I64) and
- haemorrhagic stroke (I600-I616, I618, I619).

Appendix 2

Confirmed CKD results, with two measurements greater than 90 days apart recommended by the KDIGO guidelines, have been used in separate sensitivity analyses, different to the fully adjusted models which used a single baseline eGFR in the main analyses. For the comparison group, results were counted as normal if they had a confirmed result ≥60ml/min/1.73m^2 or a patient had an index result alone in this same range, as normal results do not need to be repeated. The diabetes sub-cohort in this analysis was also adjusted for confirmed albuminuria result. Compared to a reference group of greater than or equal to 60ml/min/1.73m^2, the adjusted hazard ratios for the three sub-cohorts are all similar to the main analyses.

Sensitivity analyses using confirmed CKD (sequential measurements >90 days apart), displaying adjusted hazard ratios and 95% confidence intervals by eGFR category in each sub-cohort.

eGFR (ml/min/1.73m^2)	CVD sub-cohort	Diabetes sub-cohort	No CVD/No diabetes sub-cohort
≥60	1	1	1
30–60	1.47 (1.37–1.57)	1.74 (1.53–1.97)	1.70 (1.53–1.89)
<30	2.34 (2.03–2.68)	3.38 (2.69–4.26)	3.25 (2.33–4.55)

Adjusted for age group, ethnicity, sex, smoking status, NZDep quintile, systolic BP, diastolic BP, TC/HDL, family history of premature CVD, and any lipid-lowering, BP-lowering, diabetes-related, antiplatelet or anticoagulant drugs in the six months prior to PREDICT risk assessment. CVD sub-cohort also adjusted for diabetes status, any history of heart failure and any history of atrial fibrillation. Diabetes sub-cohort also adjusted for confirmed albuminuria and BMI.

Competing interests:
SW had a Stevenson Fellowship in Health Innovation and Quality Improvement during the conduct of the study. KP holds the Heart Foundation Hynds Senior Fellowship. MM is a full-time employee of Baxter Healthcare (Asia) Pte Ltd. CG holds a fellowship from the National Heart Foundation. SM, VS, CG and KP report grants from Health Research Council of New Zealand during the conduct of the study. EC reports grants from NZ College of Public Medicine during the conduct of the study.

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