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Prediction of cardiovascular death and non-fatal cardiovascular events by the Kidney age–Chronological age Difference (KCD) score in men and women of different ages in a community-based cohort

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ABSTRACT
Objective We examined the utility of the Kidney age–Chronological age Difference (KCD) score, an age-adapted measure of kidney function, to identify increased cardiovascular (CV) death or non-fatal CV event risk in participants of the Australian Diabetes, Obesity, and Lifestyle Study (AusDiab), a community-based cohort aged 23–95 years.

Setting Community.

Participants 11205 randomly selected participants from urban and non-urban areas across Australia.

Outcome measures Mortality status and underlying and contributory causes of death obtained from the Australian National Death Index, and non-CV events from adjudicated hospital records. The association of CV death or non-CV event risk with KCD score was examined using penalised spline curve analysis.

Results Of 11180 participants with serum creatinine measurement at baseline and 5-year outcome data, there were 308 CV deaths or non-CV events after 5 years. Penalised spline curve analysis showed similar progressive increase in CV death or non-CV event risk with increasing KCD score in men and women, and participants aged <50 years to >80 years. Receiver operating characteristic curve analysis showed optimal discrimination at a KCD score ≥20 years (KCD20) for all participants. Among 148 participants aged<70 years with CV death or non-CV event, KCD20 identified 24 (16%) participants, whereas estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m² identified 8 (5%) participants (p=0.0001), with specificities of 95% and 99%, respectively (p<0.0001).

Conclusion KCD20 predicted CV death or non-fatal CV event risk similarly in men and women of different ages in this population-based cohort. The higher sensitivity for prediction of CV death or non-fatal CV event risk in participants aged <70 years by KCD20 than by eGFR <60 mL/min/1.73 m² offers opportunity for earlier renoprotective therapy in individuals with eGFR-associated increased CV death or non-fatal CV event risk.

STRENGTHS AND LIMITATIONS OF THIS STUDY
⇒ AusDiab participants were a large representative sample of the Australian population aged 23–95 years; 11180 participants had baseline serum creatinine measurement and 5-year outcome data, allowing comparison of men and women, and participants of different ages.
⇒ The number of events was limited by the high proportion of younger participants at low cardiovascular risk.
⇒ Creatinine-based measures of kidney function were confounded by lean body mass.
⇒ Our analysis was based on a single estimated glomerular filtration rate measurement for each participant.

INTRODUCTION
Chronic kidney disease (CKD) 'is defined as abnormalities of kidney structure or function, present for ≥3 months, with implications for health'.1 Relevant health outcomes include end-stage kidney disease (ESKD), but are predominantly premature mortality and cardiovascular (CV) events. Thus, CKD identifies impaired kidney function as a risk factor for impaired health, particularly CV disease, and the criteria for the definition of CKD are based on threshold levels of impairment of kidney function that predict increased risk. In adults, these criteria are: (1) signs of kidney damage, most often determined by an elevated urine albumin (or protein)-to-creatinine ratio; or (2) reduced kidney function, indicated by glomerular filtration rate (GFR) <60 mL/min/1.73 m².1,2 Previous reports that estimated GFR (eGFR) <60 mL/min/1.73 m² was associated with increased all-cause and CV mortality in the absence of increased albuminuria,23 emphasise the importance of...
eGFR-related criteria for CKD diagnosis. However, the eGFR cut point of 60 mL/min/1.73 m² does not take account of the normal age-related decline in eGFR, and may lead to underdiagnosis of CKD in younger individuals and overdiagnosis of CKD in older individuals. Individuals aged ≤64 years of age with eGFR 60–74 mL/min/1.73 m² are at increased risk for all-cause mortality in comparison with individuals with eGFR of 75–89 mL/min/1.73 m². Underdiagnosis of CKD in younger individuals may delay therapeutic intervention to slow the rate of decline in their kidney function.

We recently described the Kidney age–Chronological age Difference (KCD) score as a means to obtain an age-adapted measure of kidney function. In calculating the KCD score, an individual’s kidney age is calculated from their eGFR and the age-dependent GFR decline observed in a metaanalysis of 5482 healthy living potential kidney donors. Thus, an individual’s KCD score is the difference between their calculated kidney age and their chronological age. This concept of kidney age is analogous to the concept of heart age, described by D’Agostino et al.

We showed that the KCD score provided an age-adapted measure of eGFR-associated increased risk of death or CV event in a cohort of individuals aged ≥60 years at increased CV risk. A KCD score ≥20 years (KCD20) was associated with increased death or CV event risk in unadjusted analysis and after adjustment for age, sex and CV risk factors. Moreover, addition of KCD20 to a CV risk factor model improved net reclassification and integrated discrimination, and identified individuals aged <70 years who experienced death or CV event with greater sensitivity than did eGFR <60 mL/min/1.73 m², with similar sensitivities for men and women.

Our previous study raised the question of how the KCD score would perform in a population-based cohort, and whether the KCD score would perform similarly for men and women, and for individuals of different ages. We now address these questions using data from the prospective Australian Diabetes, Obesity, and Lifestyle Study (AusDiab), a national, population-based study designed to investigate the prevalence of diabetes and abnormal glucose metabolism, lifestyle, health behaviours and early indicators of kidney disease in Australian adults.

METHODS
Patient and public involvement
Patients and the public were not involved in the design, planning, conduct or reporting of this study.

Study population
The recruitment of AusDiab participants is described in detail elsewhere. In brief, between May 1999 and December 2000, a sample of the national population was drawn from 42 randomly selected urban and non-urban areas (census collector districts) across Australia, with six census-collector districts in each of the six states and the Northern Territory. The Alfred Hospital Ethics Committee (no. 39/11) approved the study and written informed consent was obtained from all participants.

At baseline, all participants attended a local examination site and completed a series of questionnaires, physical examinations and specific laboratory tests, including an oral glucose tolerance test (OGTT), examining diabetes status, CV risk factors and kidney function, as previously described. Categories of abnormal glucose metabolism were determined according to the 1999 WHO criteria. Participants were classified as having known diabetes mellitus (DM) if they reported having physician-diagnosed DM and were either taking hypoglycaemic medication or had fasting plasma glucose (FPG) ≥7.0 mmol/L or plasma glucose 2 hours post oral glucose load (PG) ≥11.1 mmol/L in the OGTT. Of those classified as having known DM at baseline, 92% had type 2 DM, and the results for participants with type 1 and type 2 DM were pooled for the present analysis. Participants not reporting having DM but who had FPG ≥7.0 mmol/L or 2-hour PG ≥11.1 mmol/L were classified as having newly diagnosed DM. Participants determined not to have DM were classified as having either impaired fasting glucose (FPG ≥6.1 and <7.0 mmol/L with 2-hour PG<7.8 mmol/L), impaired glucose tolerance (2-hour PG ≥7.8 and <11.1 mmol/L with FPG <7.0 mmol/L) or normal glucose tolerance (FPG <6.1 mmol/L and 2-hour PG <7.8 mmol/L). Prevalent hypertension was defined as systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg or self-reporting of blood pressure-lowering medication. Body mass index (BMI) was calculated as weight (kg)/height (m)². Lean body mass was calculated as a function of sex, height, weight and impedance using the Tanita body fat analyser TBF 105, and indexed to height² as previously described. Biochemistry and haematology were measured by a central laboratory (HITECH Pathology, Melbourne, Australia). Serum creatinine was initially measured with the Jaffe reaction by HITECH Pathology. However, in 2010, creatinine was remeasured in stored frozen (~80°C) serum samples by Melbourne Pathology using a Roche IDMS aligned enzymatic assay (Roche Modular, Roche Diagnostics) and the present analysis used results from the enzymatic assay. The eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. Albumin was measured in a morning spot urine sample by the immunoturbidimetric method (Olympus AU600 auto-analyser).

Outcome assessment
Mortality status and underlying and contributory causes of death were determined as previously described, by linking the AusDiab cohort to the Australian National Death Index (NDI) in 2019, with ICD codes available up to 2017. The accuracy of the NDI for ascertainment of CV deaths and vital status has been established previously. Only high-level matches were accepted as confirmed deaths and, wherever possible, deaths were confirmed by direct communication with the decedent’s family.
People who were not matched to the NDI were assumed to be alive. Deaths were attributed to CV disease if the underlying cause of death was coded I10–I25, I46.1, I48, I50–I99 or R96 according to the 2006 International Classification of Diseases 10th revision (ICD-10). In addition, participants with uncomplicated DM (ICD-10 codes E109, E119 or E149) or unspecified hyperlipidaemia (ICD-10 code E785) as an underlying cause of death on the death certificate were attributed a CV death if any of the CV disease codes (I10–I25, I46.1, I48, I50–I99 or R96) were recorded in the first position on the death certificate.

Additional to collection of NDI data, non-fatal CV events were collected by participant interviews in 2004–2005 and in 2010–2011, and self-reported CV events: myocardial infarction (MI), stroke, coronary artery bypass graft (CABG) surgery or percutaneous transluminal coronary angioplasty (PTCA), that occurred between baseline and follow-up were adjudicated by physician review of medical records, as described by Barr et al.²³

Calculation of KCD score

Based on a metaanalysis of 5482 healthy living potential kidney donors,³ assuming a mean eGFR of 105 mL/min/1.73 m² at age 40 years and decline of 0.9 mL/min/1.73 m² per year after age 40 years for a healthy individual, an individual’s kidney age in years was calculated from: \[
\left( \frac{1}{0.9} \times (105 - \text{eGFR}) \right) + 40.12
\]
The KCD score was calculated from the difference between an individual’s kidney age and chronological age. Given that eGFR is approximately stable at 105 mL/min/1.73 m² for healthy living potential kidney donors aged <40 years,⁴ for AusDiab participants aged <40 years their chronological age was set at 40 years for the calculation of the KCD score to prevent overestimation of the KCD score in these participants.

Statistical analysis

Continuous variables were summarised as medians (IQR) and categorical variables summarised as numbers (percentages). The study outcome was CV death or non-fatal CV event (incident MI, stroke, CABG or PTCA). Data were censored at 1826 days of follow-up. Sensitivities, specificities and positive predictive value (PPV) and negative predictive value (NPV) for identification of individuals who experienced a study outcome were compared using the \( \chi^2 \) statistic with Yates correction. Hazard ratios for prediction of CV death or non-fatal CV event by continuous KCD score were calculated from Cox proportional hazards models. Inspection of Schoenfeld residuals confirmed that proportional hazards assumptions were satisfied. Penalised spline curve analysis was performed using the Survival package in R to examine the association of KCD score with relative risk of CV death or CV event, referenced to a KCD score=0 years. KCD scores <−20 were set at −20 years, and KCD scores ≥50 were set at 50 years for spline analyses. Threshold KCD scores for increased relative risk of CV death or non-fatal CV event were obtained from pointwise 95% CIs of the spline

RESULTS

Characteristics of study population

Baseline characteristics of the AusDiab cohort are shown in table 1.

Compared with the 1998 Australian Census, younger men and women were less frequently represented in AusDiab than in the general population, with individuals in middle-age slightly over-represented.²⁷ Of the 11205 AusDiab participants with baseline creatinine measurement, 11 180 had 5-year outcome data. Five-year outcomes according to age category are shown in online supplemental table 1.

The numbers of participants with eGFR <60 mL/min/1.73 m², KCD20 and albuminuria, according to age, are shown in online supplemental table 2. Of 171 men and 208 women with eGFR<60 mL/min/1.73 m² and urine albumin/creatinine ratio measured, 73 men (43%) and 55 women (26%) had micro or greater albuminuria, whereas of 315 men and 389 women with KCD20 and urine albumin/creatinine ratio measured, 63 men (20%) and 45 women (12%) had micro or greater albuminuria.

Relationship of eGFR to age

The relationship between participant age and eGFR is shown in figure 1, where the black bar representing the decrease in eGFR of 0.9 mL/min/1.73 m² per year from 105 mL/min/1.73 m² at age 40 in healthy living potential kidney donors,⁴ was an approximation of the age-related decline in eGFR in the AusDiab cohort. An eGFR value below this bar represented an eGFR less than the mean eGFR of healthy living potential kidney donors of the same age, and corresponded to a kidney age that exceeded the chronological age. Also shown in figure 1 is the red bar indicating KCD score=20 years. Thus, a 70-year old individual with an eGFR of 60 mL/min/1.73 m² had an eGFR corresponding to that predicted for a healthy 90-year-old individual (kidney age of 90 years), and their kidney age was 20 years greater than their chronological age (KCD score=20 years). Similarly, a 40-year old individual with an eGFR of 80 mL/min/1.73 m² had an eGFR corresponding to that predicted for a healthy 62.5-year-old
### Table 1  Baseline characteristics of 11 205 AusDiab study participants with serum creatinine measurement on enrolment

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Men n=5030</th>
<th>Women n=6175</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>51 (41, 63)</td>
<td>50 (41, 62)</td>
</tr>
<tr>
<td>Duration follow-up (years)</td>
<td>19.0 (18.6, 19.6)</td>
<td>19.1 (18.6, 19.6)</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>130 (121, 142)</td>
<td>122 (113, 137)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>75 (67, 82)</td>
<td>66 (59, 74)</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>67 (61, 75)</td>
<td>72 (65, 79)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>27 (24, 29)</td>
<td>26 (23, 30)</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>97 (90, 104)</td>
<td>84 (76, 94)</td>
</tr>
<tr>
<td><strong>Cardiovascular risk factors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>1309 (26.0%)</td>
<td>1719 (27.8%)</td>
</tr>
<tr>
<td>Diabetes (known or newly diagnosed)</td>
<td>530 (10.6%)</td>
<td>483 (8.0%)</td>
</tr>
<tr>
<td>Impaired fasting blood glucose</td>
<td>438 (8.8%)</td>
<td>184 (3.0%)</td>
</tr>
<tr>
<td>Impaired glucose tolerance</td>
<td>547 (11.0%)</td>
<td>786 (13.0%)</td>
</tr>
<tr>
<td>Overweight (25&lt;BMI&lt;30kg/m²)</td>
<td>2454 (49.3%)</td>
<td>1968 (32.5%)</td>
</tr>
<tr>
<td>Obesity (BMI &gt;30kg/m²)</td>
<td>1034 (20.8%)</td>
<td>1418 (23.4%)</td>
</tr>
<tr>
<td>eGFR &lt;60mL/min/1.73m²</td>
<td>173 (3.4%)</td>
<td>210 (3.4%)</td>
</tr>
<tr>
<td>KCD score ≥20 years (KCD20)</td>
<td>317 (6.3%)</td>
<td>391 (6.3%)</td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>377 (7.6%)</td>
<td>344 (5.6%)</td>
</tr>
<tr>
<td>Macroalbuminuria</td>
<td>66 (1.3%)</td>
<td>35 (0.6%)</td>
</tr>
<tr>
<td>Angina</td>
<td>314 (6.2%)</td>
<td>258 (4.2%)</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>287 (5.7%)</td>
<td>150 (2.4%)</td>
</tr>
<tr>
<td>Total ischaemic heart disease</td>
<td>443 (8.8%)</td>
<td>317 (5.1%)</td>
</tr>
<tr>
<td>Pre-existing stroke</td>
<td>132 (2.6%)</td>
<td>151 (2.4%)</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>523 (10.4%)</td>
<td>410 (6.6%)</td>
</tr>
<tr>
<td>Physical inactivity</td>
<td>3287 (65.3%)</td>
<td>3841 (62.2%)</td>
</tr>
<tr>
<td>Tobacco use:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>928 (18.4%)</td>
<td>926 (15.0%)</td>
</tr>
<tr>
<td>Former smoker</td>
<td>2089 (41.5%)</td>
<td>1726 (28.0%)</td>
</tr>
<tr>
<td>Non-smoker</td>
<td>2013 (40.0%)</td>
<td>3523 (57.1%)</td>
</tr>
<tr>
<td>Alcohol &gt;2 drinks/day</td>
<td>2585 (51.4%)</td>
<td>1441 (23.3%)</td>
</tr>
<tr>
<td><strong>Medication use</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antihypertensive therapy</td>
<td>754 (15.0%)</td>
<td>996 (16.1%)</td>
</tr>
<tr>
<td>Therapy for cholesterol and/or triglycerides</td>
<td>468 (9.3%)</td>
<td>481 (7.8%)</td>
</tr>
<tr>
<td><strong>Biochemistry</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>5.2 (5.0, 5.3)</td>
<td>5.1 (4.9, 5.3)</td>
</tr>
<tr>
<td>Fasting plasma glucose (mmol/L)</td>
<td>5.5 (5.2, 5.9)</td>
<td>5.2 (4.9, 5.6)</td>
</tr>
<tr>
<td>Plasma glucose 2-hour post-glucose load (mmol/L)</td>
<td>5.8 (4.8, 7.0)</td>
<td>5.9 (5.0, 7.2)</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>5.6 (4.9, 6.3)</td>
<td>5.6 (4.9, 6.3)</td>
</tr>
<tr>
<td>High density lipoprotein cholesterol (mmol/L)</td>
<td>1.2 (1.1, 1.4)</td>
<td>1.5 (1.3, 1.8)</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>1.4 (1.0, 2.1)</td>
<td>1.2 (0.8, 1.7)</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73 m²)</td>
<td>96 (85, 106)</td>
<td>99 (86, 109)</td>
</tr>
<tr>
<td>KCD score (years)</td>
<td>−5 (−11, 6)</td>
<td>−7 (−13, 4)</td>
</tr>
<tr>
<td>Urine albumin/creatinine ratio (mg/mmol)</td>
<td>0.47 (0.34, 0.83)</td>
<td>0.62 (0.43, 1.09)</td>
</tr>
</tbody>
</table>

Data shown as median (IQR) or n (%). Complete data for all variables except for blood pressure and pulse rate (n=11121), BMI and waist circumference (n=11026), HbA1c, and fasting and post-load blood glucose (n=10686), lipids (n=11202), urine albumin/creatinine ratio (n=11140) and duration of follow-up (n=11196). Angina, myocardial infarction and hypertension were based on participant report of information received from doctor or nurse. Total ischaemic heart disease refers to angina and/or myocardial infarction. Cardiovascular disease refers to total ischaemic heart disease and/or stroke. Physical inactivity refers to participants who walked and/or engaged in more vigorous exercise for <150 min/week. Alcohol >2 drinks/day refers to consumption of more than two standard drinks on any day. Microalbuminuria—urine albumin/creatinine ratio: 2.5–25.0 mg/mmol (male), 3.5–35.0 mg/mmol (female); macroalbuminuria—urine albumin/creatinine ratio: >25.0 mg/mmol (male), >35.0 mg/mmol (female).
individual (kidney age of 62.5 years), and their kidney age was 22.5 years greater than their chronological age (KCD score=22.5 years).

**Distribution of eGFR and KCD scores**

The distributions of eGFR values and KCD scores for AusDiab participants of different ages are shown in online supplemental figures 1 and 2. The distribution of eGFR values shifted to the left with increasing age, with few individuals aged <40 years with eGFR <60 mL/min/1.73 m², and a significant minority of individuals aged ≥80 years with eGFR <60 mL/min/1.73 m² (online supplemental figure 1). By contrast, the distribution of KCD scores was similar across the age spectrum for men and women (online supplemental figure 2).

**Association of KCD score with relative risk of CV death or non-fatal CV event**

During 5 years of follow-up, 308 participants experienced CV death or a CV event. Penalised spline curve analyses of relative risk (95% CI) for CV death or non-fatal CV event during follow-up are shown in figures 2 and 3, where relative risk is 1.0 for KCD scores of 0 years. The threshold KCD score for increased relative risk (derived from pointwise 95% CI) was similar for men (10.6 years) and women (9.3 years, figure 2). A similar increase in relative risk was seen for increasing KCD score in participants of different ages (figure 3).

It was of note that the spline curves were U-shaped, with increasing relative risk for negative KCD scores <−9.3 years for men, but not for women. We examined whether this U-shaped relationship may be explained by lower lean BMI (associated with lower serum creatinine and higher eGFR) in participants with negative KCD scores (online supplemental figure 3). BMI was not different between negative KCD scores, whereas lean BMI was lower for KCD scores <0 years for men and women. Thus, a proportion of the negative KCD scores may have reflected in part an artefactually increased eGFR due to lower lean BMI and lower serum creatinine level, and the lower lean BMI may have explained in part the increase in relative risk of CV death or non-fatal CV event for men with negative KCD scores.

Time-dependent ROC curves for different KCD thresholds for the whole AusDiab cohort showed a KCD score of approximately 20 years was optimal for discrimination of CV death or non-fatal CV event risk (online supplemental figure 4).

**Sensitivity, specificity and PPV and NPV for prediction of CV death or non-fatal CV event by KCD20 and eGFR <60 mL/min/1.73 m²**

For all participants across all age-groups in the cohort (figure 4, online supplemental table 3), KCD20 and eGFR <60 mL/min/1.73 m² predicted CV death or non-fatal CV event risk within 5 years with similar sensitivities of 18%, although the specificity for KCD20 was lower than for eGFR <60 mL/min/1.73 m² (94% vs 97%, p<0.0001). However, in contrast to KCD20, prediction of CV death or non-fatal CV event risk by eGFR <60 mL/min/1.73 m² varied with age, with lower sensitivities than KCD20 for participants <70 years of age and higher sensitivities than KCD20 for ages ≥70 years (figure 4). Of the 308 participants who experienced CV death or a non-fatal CV event, 148 (48%) were<70 years of age; among these 148 participants, KCD20 identified 24 (16%) whereas eGFR <60 mL/min/1.73 m² identified only 8 (5%) participants who experienced CV death or non-fatal CV event (p=0.0001), although the specificity for KCD20 was lower than for eGFR <60 mL/min/1.73 m² (online supplemental table 3). KCD20 had a lower PPV than eGFR <60 mL/min/1.73 m² for all participants, but for participants <70 years of age the PPVs for KCD20 and eGFR <60 mL/min/1.73 m² were not statistically significantly different, whereas the NPV (~98%) for KCD20 and eGFR <60 mL/min/1.73 m² was...
DISCUSSION

The KCD score performed similarly for men and women, and for individuals of different ages, in the population-based AusDiab cohort. More participants were identified with KCD20 than with eGFR <60 mL/min/1.73 m², and KCD20 identified increased CV death or non-fatal CV event risk with greater sensitivity than eGFR <60 mL/min/1.73 m² among participants <70 years of age, in agreement with our previous study of a high CV risk

were similar for all participants and for participants <70 years of age (online supplemental table 3).

Figure 2 Penalised spline curve analysis of relative risk (95% CI) for CV death or non-fatal CV event during 5 years follow-up, according to KCD score relative to KCD score of 0 years, for men and women combined (A) and for men (B) and women (C) separately, from proportional hazards analysis. The triangles represent upper and lower thresholds derived from pointwise 95% CI. KCD, Kidney age–Chronological age Difference.

Figure 3 Penalised spline curve analysis of relative risk (95% CI) for CV death or non-fatal CV event during 5 years follow-up, according to KCD score relative to KCD score of 0 years, for men and women of different age categories, from proportional hazards analysis. The triangles represent upper thresholds derived from pointwise 95% CI. KCD, Kidney age–Chronological age Difference.
The KCD score avoids the ‘birthday paradox’ specific age category. A key advantage of the KCD score is that it assists the identification of individuals with deterioration in kidney function beyond that which can be explained by ageing, and for whom renoprotective therapy may improve outcomes. Younger individuals (<70 years of age) with accelerated decline in kidney function have potential to benefit from early intervention to slow the rate of decline in their kidney function and thereby preserve kidney function while their eGFR is still >60 mL/min/1.73 m², rather than when their eGFR is <60 mL/min/1.73 m². The KCD score was similarly predictive in older individuals (figure 3) who may also benefit from renoprotective therapy.

The 95% CIs from spline curve analysis were dependent on the numbers of participants and events included in each analysis. Thus, analysis of the whole cohort produced narrower CIs and a lower threshold for prediction of CV death or non-fatal CV event risk than analysis of men and women separately, or individual age categories. KCD20 was a conservative threshold in relation to the thresholds for the whole cohort (6.4 years) and for men (10.6 years) and women (9.3 years), separately. Although a lower threshold KCD score would have resulted in a higher sensitivity for prediction of CV death or non-fatal CV event risk, this would have been at the expense of lower specificity. Based on ROC curve analysis, KCD20 offered optimal discrimination for the whole cohort. However, in providing a continuous measure of GFR-associated CV death or non-fatal CV event risk, the KCD score allows the clinician to identify patients at increased risk with KCD scores less than 20 years. For example, a KCD score >10 years may prompt a clinician to check for proteinuria and/or refer a patient for specialist review. Furthermore, a clinician may choose a KCD score ≤10 years as a criterion for selection of living kidney donors.

The CKD-EPI equation, which includes age, was optimised to produce an estimate of GFR as close as possible to measured GFR. Thus, the CKD-EPI equation does not account for the age-related decline in GFR any more than measured GFR, and the cross-sectional change in GFR with age in healthy potential kidney donors provided both the rationale and the basis for the calculation of the KCD score in this study. The KCD score serves to alert the clinician to an eGFR that is inconsistent with the patient’s age, thereby prompting the clinician to further investigate kidney function and consider renoprotective therapy.

Strengths and limitations
A strength of our study was that AusDiab participants were a large representative sample of the Australian population aged 23–95 years; 11 180 participants had baseline
CONCLUSION

We demonstrated that the KCD score is an age-adapted measure of kidney function, with similar ability to predict risk of CV death or non-fatal CV event in men and women of different ages in this large national population-based cohort. The higher sensitivity for prediction of CV death or non-fatal CV event risk in participants aged <70 years by KCD20 than eGFR <60 mL/min/1.73 m² offers opportunity for earlier renoprotective therapy in individuals with eGFR-associated increased CV death or non-fatal CV event risk.

Contributors All authors made substantial contributions to the conception and design of the work and the acquisition, analysis and interpretation the data for the work; and participated in revising the manuscript critically for important intellectual content; and provided final approval of the version to be published; and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. DC designed the study, had full access to all the data in the study, takes responsibility for the integrity of the data and the accuracy of the data analysis and wrote the manuscript. DM and JES made contributions to the conception and design of the study and the acquisition of data. DC is responsible for the overall content as the guarantor, accepting full responsibility for the work and the conduct of the study, had access to the data, and controlled the decision to publish. All authors performed revisions for important intellectual content, and approved the final manuscript.

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REFERENCES


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