Khoo Teck Puat Hospital
NHG Health

Kidney Disease Index (KDI) as a Predictor of Mortality and Chronic Kidney Disease Progression in Asians with Type 2 Diabetes Mellitus (T2DM)

YIA-CR-01

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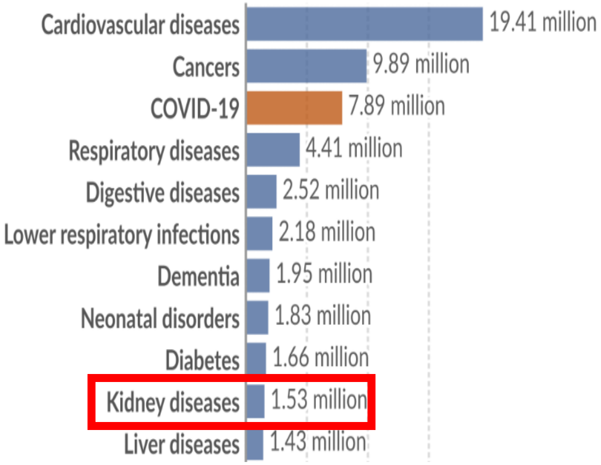
Chronic Kidney Disease

Global

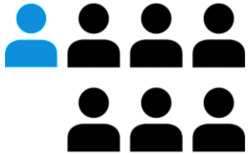
- affects approximately 10% of the adult population

- 10th leading cause of death according to WHO[1]



Asian Region

- CKD affects 1 in 7 adults in Singapore



- In 2021, 2,100 new dialysis cases were reported by National Kidney Foundation

- DM increases risk for CKD, with DN being a significant factor of end-stage renal disease (ESRD)

Early identification of CKD is essential for prompting intervention which can delay its progression to ESRD and reduce associated morbidity and mortality[2]

Evidence-based intervention

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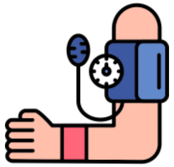

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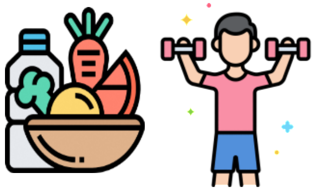


Glycaemic control: SGLT2 inhibitors and GLP-1 receptor agonists

blood pressure regulation: ACE inhibitors or ARB

Lifestyle modification

significantly reduce CKD progression and mortality risks in people with DM

1. Global, regional, and national burden of chronic kidney disease 2020; 709-33;
2. Francis A, Wainstein M et al. Kidney International Supplements. 2024;13(1):110-22.

Current CKD Assessment

Based on KDIGO (Kidney Disease: Improving Global Outcomes) classification system for CKD

Glomerular filtration rate (eGFR)

- stages (G1–G5)[1]
- lower eGFR predict higher risks of mortality, cardiovascular events, and CKD progression
- values are sensitive to race and age adjustments
- lose discriminative ability in advanced CKD stages[2-3]

Urinary albumin-to-creatinine ratio (uACR)

- albuminuria categories (A1–A3) [1]
- higher uACR levels predict higher risks
- values may fluctuate under certain conditions (acute illness, exercise, or hydration status, limiting their standalone reliability)
- suffers from low specificity in older populations [2-3]

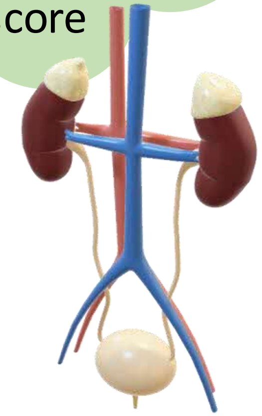
↓

- Both predictive performance particularly for mortality and cardiovascular outcomes are limited when used in isolation
- These metrics often underperform due to inter-individual variability, non-linear associations, and confounding factors[4]

These limitations have motivated the development of composite indices

Kidney Disease Index (KDI)

- integrates **1/eGFR x ln(100 × uACR)**
- to provide a composite score



1. Andrassy KM. Comments on 'KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease'. Kidney Int. 2013;84(3):622-3.
2. Matsushita K, Coresh J et al. Estimated glomerular filtration rate and albuminuria for prediction of cardiovascular outcomes: a collaborative meta-analysis of individual participant data. Lancet Diabetes Endocrinol. 2015;3(7):514-25.
3. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. The Lancet. 2010;375(9731):2073-81.
4. Wada T, Haneda M et al. Clinical impact of albuminuria and glomerular filtration rate on renal and cardiovascular events, and all-cause mortality in Japanese patients with type 2 diabetes. Clin Exp Nephrol. 2014;18(4):613-20.

Geometric mean[1]

- combines eGFR and uACR
- originate from different units

Enhances prediction of all-cause mortality[1]

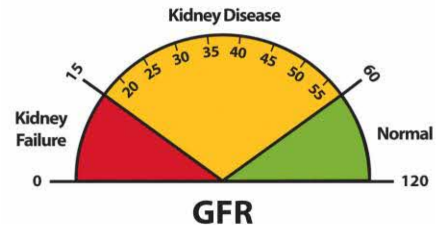
- includes multidimensional prognostic factors alongside eGFR

Linear relationship[2]

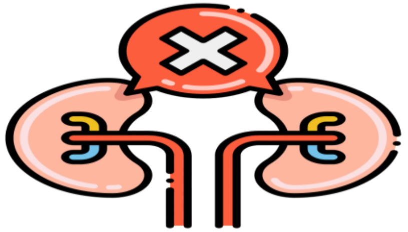
- with major cardiovascular and renal outcomes

Kidney Disease Index (KDI)

Better reflects two aspects of CKD[3]



Abnormality of kidney function **low eGFR**



kidney damage indicated by **increased albuminuria**

Research Gap: Existing studies on the use of KDI to predict mortality and CKD progression have not been well validated in Asian populations with T2DM and remain under-explored

1. Gerstein HC, Ramasundarahettige C, Bangdiwala SI. Creating Composite Indices From Continuous Variables for Research: The Geometric Mean. Diabetes Care. 2021;44(5):e85-e6.
2. Gerstein HC, Ramasundarahettige C, Avezum A et al. A novel kidney disease index reflecting both the albumin-to-creatinine ratio and estimated glomerular filtration rate, predicted cardiovascular and kidney outcomes in type 2 diabetes. Cardiovasc Diabetol. 2022;21(1):158.
3. Stevens PE, Levin A. Evaluation and management of chronic kidney disease: synopsis of the kidney disease: improving global outcomes 2012 clinical practice guideline. Ann Intern Med. 2013;158(11):825-30.

Aim

This study aimed to evaluate KDI as a predictor for mortality and CKD progression in Asian T2DM cohort

Hypothesis

KDI is a better assessment marker to predict mortality and CKD progression in Asians with T2DM

Materials and Methods

Study Population

Prospective design: To study KDI as a Predictor of Mortality and Chronic Kidney Disease Progression in Asians with T2DM (SMART2D)

Inclusion

- 21-90 y/o
- diagnosed with T2DM

Exclusion

- Pregnancy
- Active inflammation
- Cancer
- Inability to consent
- Cardiovascular disease*
- eGFR less than 2 eGFR measurements*

Phase 1

2011-2014

Started recruitment from diabetes centre in tertiary hospital and polyclinics

- N= 2258

Phase 2

2014-2018

1st recall of phase 1 participants

- N= 1660

Phase 3

2018-2024

2nd recall

- N= 1417

Phase 4

2025-2027 (ongoing)

3rd recall

- N= Ongoing

*Excluded for purpose of this analysis. Cardiovascular disease includes acute myocardial infarction, coronary artery disease, heart block and stroke

Patient Flow Chart

N=2232

2232 patient included for all cause mortality and cvs mortality

1993 patient included for CKD progression with >2 eGFR measurements

Median follow-up period
11.1 years (IQR 9.8-11.6; max 12.9)

Data Collection and Measurement

Questionnaire
Demographics,
History of CVS,
Medication

Clinical and Lab Measurements
BP, FPG, uACR, Cr,
Lipid

Generation of KDI value
Estimated eGFR utilising the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation computed[1]

$$\text{Equation} = \sqrt{1/\text{eGFR} \times \ln(100 \times \text{uACR})}$$

Cardiovascular mortality was ascertained using the International Classification of Diseases 10th Revision codes for cardiovascular disease (I00-I99), heart disease (I00-I09, I11, I13, I20-I51)

Mortality data were retrieved from the National Registry of Diseases Office (NRDO), which maintains birth records from the Registry of Births and Deaths

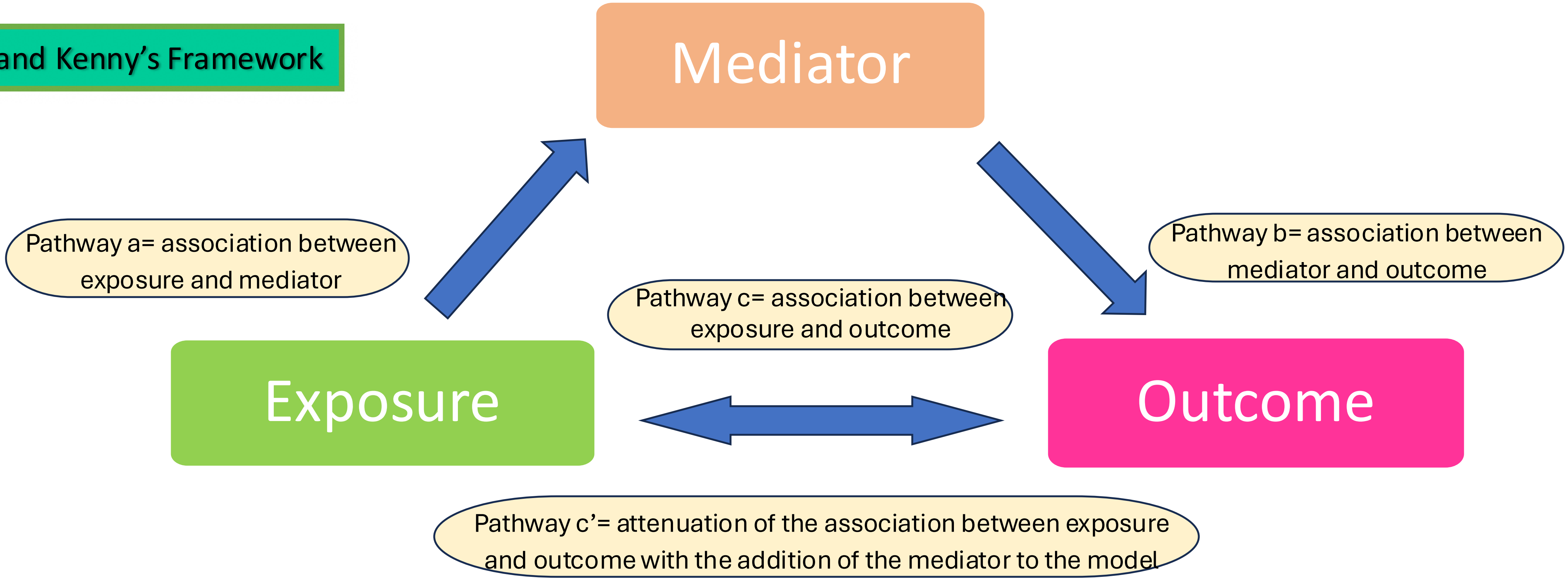
CKD progression was defined as a ≥30% decline in eGFR from baseline and captured through longitudinal follow-up within the SMART2D cohort

1. Levey AS, Stevens LA et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604-12.

Statistical analysis

- Cox regression models to assess the association of KDI (ln-transformed) with all-cause mortality, CVS mortality, and CKD progression
- Models were adjusted for demographics, CVS disease, diabetes duration, HbA1c, BP, triglycerides (log-transformed), RAS blockade usage
- Binary mediation analysis to estimate the proportion of KDI's effect on mortality mediated by eGFR progression based on the Baron and Kenny's Framework[1]

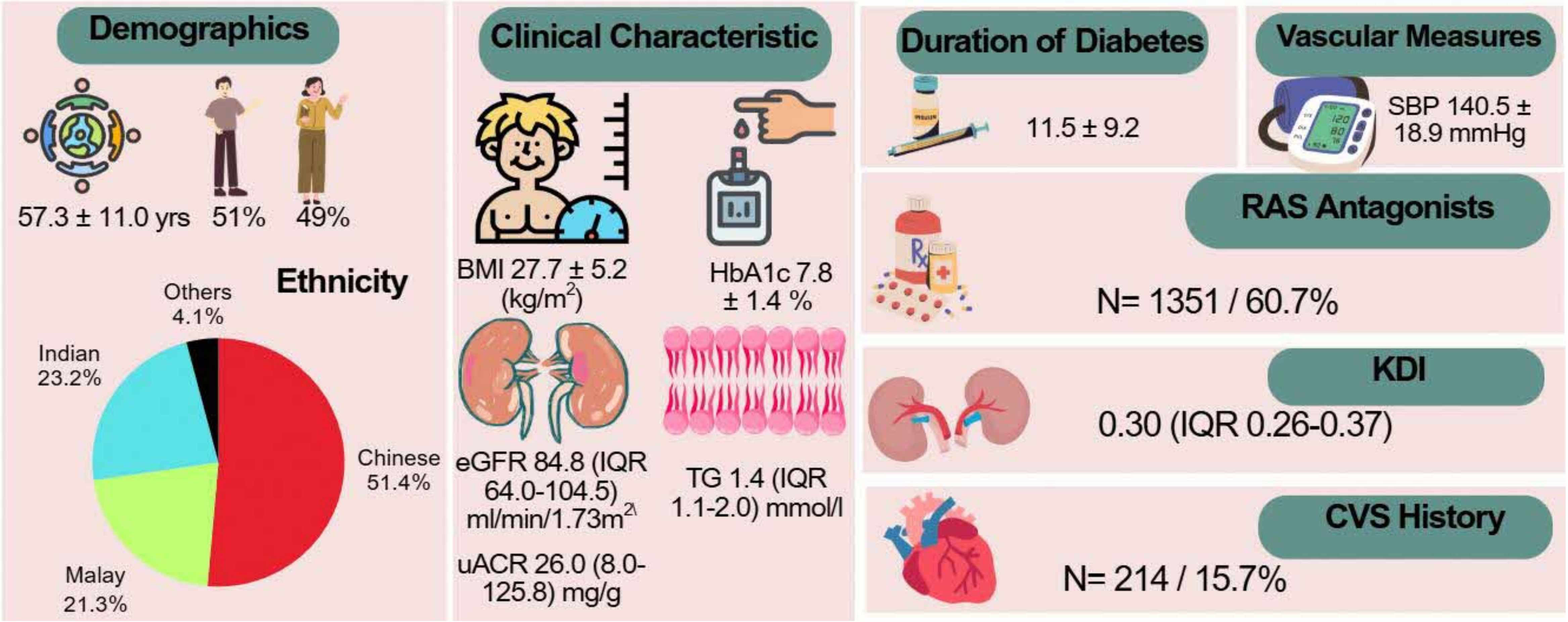
Baron and Kenny's Framework



1. Baron RM, Kenny DA. The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. J Pers Soc Psychol. 1986;51(6):1173-82

Results

Baseline Characteristics (N=2232)



440 participants (19.7%) succumbed to various causes of death, with 168 (7.5%) of those fatalities attributed to cardiovascular origins as per ICD coding during follow-up period

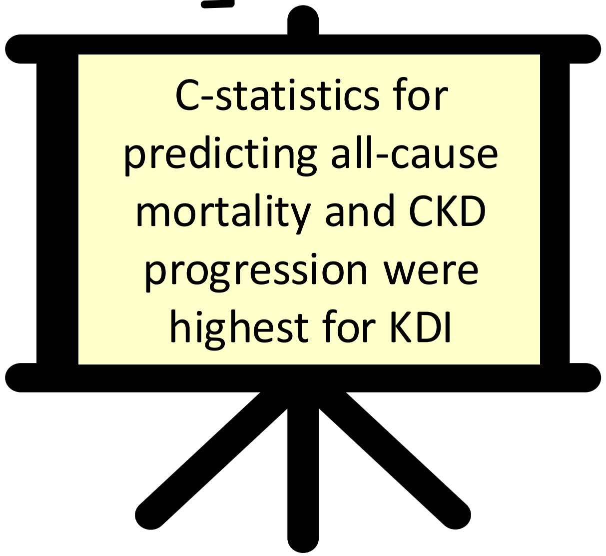
Among the 1,993 participants with follow-up eGFR data, 869 (43.6%) exhibited CKD progression

BMI, body mass index; HbA1c, hemoglobin A1c; eGFR, estimated glomerular filtration rate; uACR, urine albumin-creatinine ratio; TG, triglycerides; SBP, systolic blood pressure; RAS; renin angiotensin system

Association between per unit increase in KDI of CVS disease, mortality and CKD Progression

	Hazards Ratio (95% CI) p-value		C-statistics
	Unadjusted	Model 1[a]	Model 1[a]
All-cause			
LnKDI	8.38 (7.02-10.00) p<0.001	4.89 (3.54-6.75) p<0.001	0.792
Ln(1/eGFR)	3.37 (3.02-3.76) p<0.001	2.34 (1.94-2.87) p<0.001	0.785
Ln(uACR*100)	1.49 (1.43-1.56) p<0.001	1.32 (1.23-1.42) p<0.001	0.780
Cardio-vascular			
LnKDI	7.04 (5.31-9.32) p<0.001	4.85 (2.92-8.06) p<0.001	0.793
Ln(1/eGFR)	3.02 (2.54-3.59) p<0.001	2.52 (1.87-3.39) p<0.001	0.795
Ln(uACR*100)	1.50 (1.40-1.61) p<0.001	1.21 (1.08-1.35) p=0.001	0.766
CKD Progression (N=1993)			
LnKDI	7.63 (6.55-8.88) p<0.001	4.75 (3.72-6.07) p<0.001	0.794
Ln(1/eGFR)	2.85 (2.59-3.14) p<0.001	2.10 (1.82-2.44) p<0.001	0.776
Ln(uACR*100)	1.57 (1.52-1.63) p<0.001	1.44(1.36-1.53) p<0.001	0.791

Per unit increase in natural log-transformed **(ln)KDI** was associated with a **markedly higher hazard** of **all-cause mortality, CVS mortality, and CKD progression** for all models



[a]Adjusted for age, gender, ethnicity, diabetes duration, history of cardiovascular disease, haemoglobin A1c, systolic blood pressure, log-transformed triglycerides, use of renin-angiotensin system antagonist

KDI versus uACR and eGFR on mortality outcomes

lnKDI= HR 4.89, (95% CI: 3.54–6.75)

ln(1/eGFR)= HR 2.34 (95% CI: 1.94-2.87)

ln(100 × uACR)= 1.32 (95% CI: 1.23-1.42)

KDI versus uACR and eGFR on CKD progression

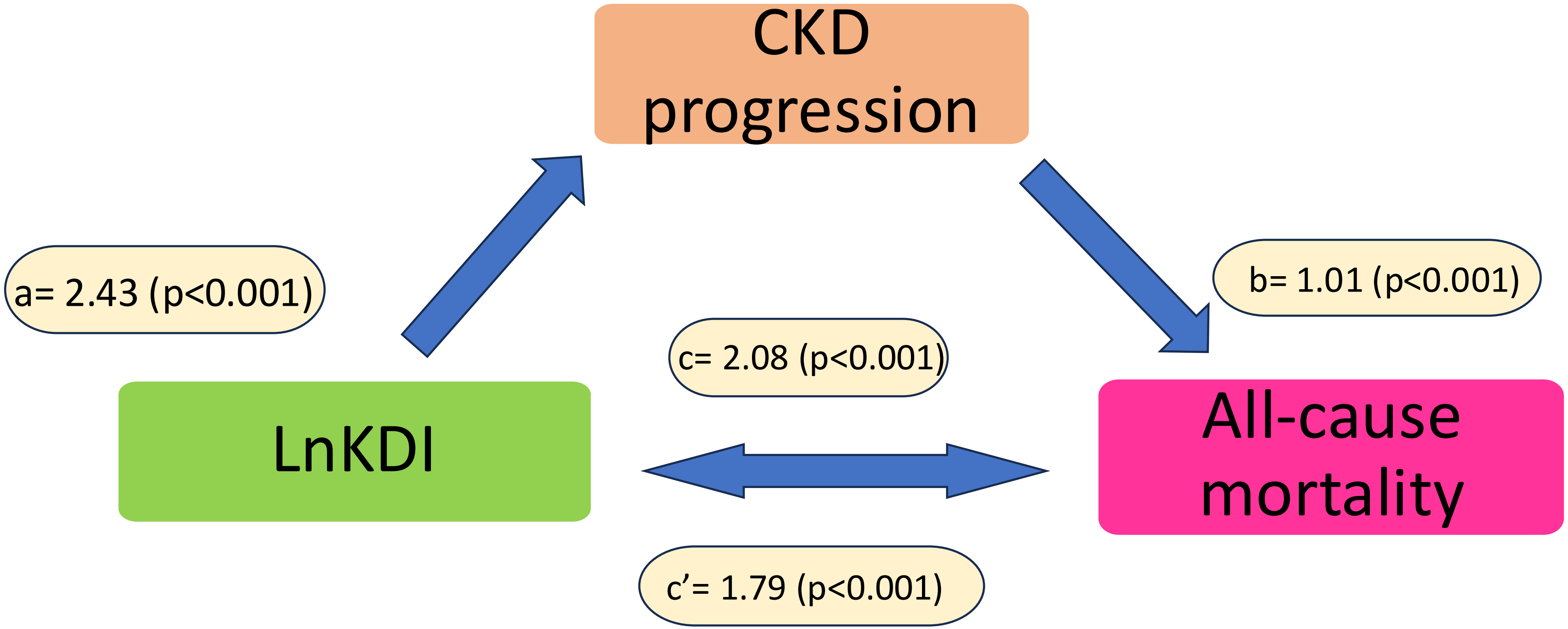
lnKDI= HR 4.75 (95%CI: 3.72-6.07)

ln(1/eGFR)= HR 2.10 (95% CI: 1.82-2.44)

ln(100 × uACR)= HR 1.44 (95% CI: 1.36-1.53)

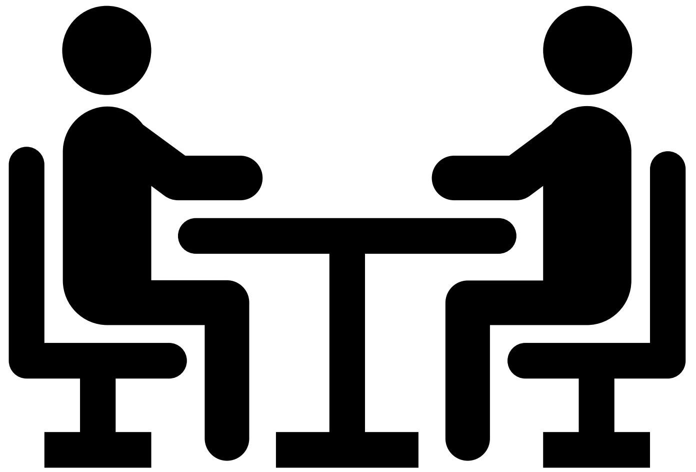
- Demonstrated KDI has superior predictive performance compared to a separate component

Mediation analysis



This analysis revealed that 25.2% of the effect of KDI on all-cause mortality was mediated through CKD progression ($p<0.001$) and fulfilled all criteria of Baron and Kenny's framework.

Discussion



Key Findings

Elevated KDI values are associated with higher risks of

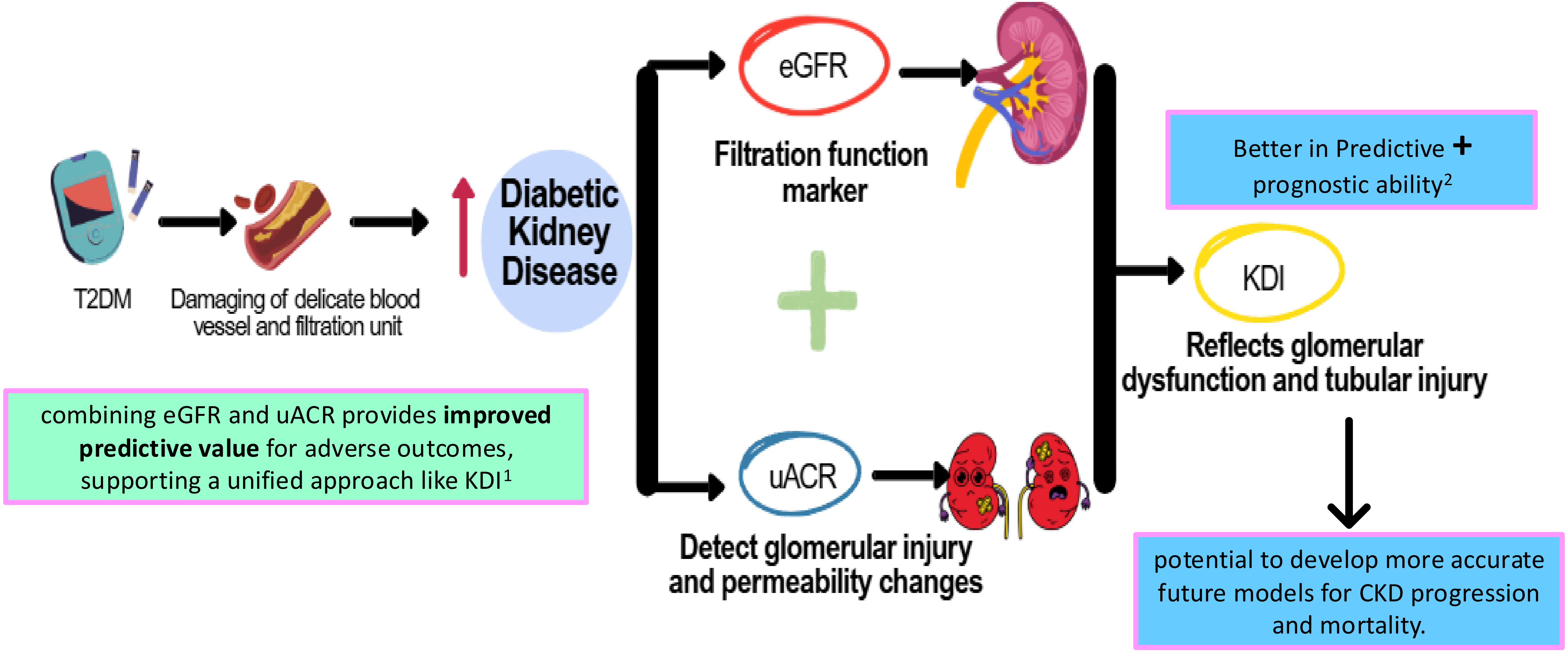
- All-cause mortality
- CVS mortality
- CKD Progression

Combined effect of eGFR and uACR appeared stronger than either component alone

CKD progression mediated the association between LnKDI and all-cause mortality

Mechanistic pathway suggests that renal dysfunction may precede mortality

Conventional Markers Versus Proposed Marker



1. Matsushita K, Coresh J, Sang Y et al Estimated glomerular filtration rate and albuminuria for prediction of cardiovascular outcomes: a collaborative meta-analysis of individual participant data. The Lancet Diabetes & Endocrinology. 2015;3(7):514-25.
2. Astor BC, Matsushita K et al. Lower estimated glomerular filtration rate and higher albuminuria are associated with mortality and end-stage renal disease. A collaborative meta-analysis of kidney disease population cohorts. Kidney Int. 2011;79(12):1331-40.

Clinical Implications and future directions

- Importance of monitoring both eGFR and uACR
  - Kidney dysfunction may precede mortality
  - Inexpensive routine tests in T2DM management
  - Potential prognostic marker to assess kidney decline and mortality

- Future clinical trials may benefit from exploring KDI to better understand and study interplay of kidney + heart + mortality

Strengths

- **Novel utilization of the KDI in an Asian population**, where the prevalence of CKD and T2DM is rising rapidly
- **1st study** to look at KDI relationship with the progression of CKD.
- **Extensive data, strong event capture** via the national registry with complete mortality under mandatory law and **good follow-up** rates by utilizing the prospective SMART2D cohort.
- **Well-validated, clinically meaningful outcomes** are produced by using globally recognized definitions of CKD progression and standardized ICD-coded mortality data

Limitations

- The **observational design** limits causal inference even with statistical adjustment and mediation analysis.
- Although KDI showed enhanced predictive capability, the benefits need to be considered a longside the ease and familiarity of conventional metrics.
- Limited generalizability to other study populations

Nonetheless, KDI is an effective and more reliable indicator for predicting mortality and CKD progression in T2DM than uACR or eGFR used individually

Future studies should validate its use in other populations and explore integration into clinical decision tools.

Conclusion

This study demonstrates KDI’s superior prognostic capability for mortality and renal outcomes, highlighting its potential for integration into clinical risk stratification frameworks in Asian populations with T2DM.

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