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Detecting chronic kidney disease through leveraging screening initiatives for other non-communicable diseases - A cross-sectional analysis

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1 DETECTING CHRONIC KIDNEY DISEASE THROUGH 2 LEVERAGING SCREENING INITIATIVES FOR OTHER NON- 3 COMMUNICABLE DISEASES – A CROSS-SECTIONAL 4 ANALYSIS

5
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17 Word count: 3,459

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19 Keywords: chronic kidney disease; screening; Africa

31 Abstract

32

33 **Introduction:** Early diagnosis of chronic kidney disease (CKD) slows disease progression and
34 reduces mortality; yet screening programmes are not advocated due to the high cost-implications.

35 However, opportunities exist to implement CKD screening as an extension to existing screening
36 programmes for hypertension and type 2 diabetes mellitus (T2DM), which are major CKD risk
37 factors. Therefore, the aim of the study was to evaluate the viability of CKD screening, by
38 assessing the yield of CKD cases in the South African Diabetes Prevention Programme (SA-DPP).

39 **Methods:** The SA-DPP was conducted across 16 resource-poor communities in Cape Town, South
40 Africa, between 2017 and 2019. Participants at high-risk for T2DM, aged 25-65 years, were
41 identified using the African Diabetes Risk Score. Those identified underwent a confirmatory oral
42 glucose tolerance test and other assessments. CKD was based on an estimated glomerular filtration
43 rate of <60 ml/min/1.73m² and/or albumin-to-creatinine ratio >3 mg/mmol.

44 **Results:** Of the 2,039 individuals screened in the community, 690 participants underwent further
45 testing. Of these participants, 9.6% (n=66) and 18.1% (n=125) had screen-detected T2DM and
46 CKD, respectively. Of those with CKD, 73.6% (n=92), 17.6% (n=22) and 8.8% (n=11) presented
47 with stages 1, 2 and 3, respectively. Furthermore, 72.8%, 68.2% and 36.4% of those with CKD
48 stages 1, 2 and 3 had microalbuminuria, with 27.2%, 31.8% and 27.3% presenting with
49 macroalbuminuria, respectively. In those with T2DM and hypertension, 22.7% and 19.8% had
50 CKD, respectively, with nearly all participants with CKD being overweight (23.2%) or obese
51 (72.0%).

52 **Conclusion:** The fact that almost one in five participants identified as high-risk for T2DM had
53 CKD underscores the value of including markers of kidney function in an existing screening
54 programme. By utilizing an opportunistic approach to screen high-risk individuals, those with
55 CKD can be identified and appropriately treated to reduce disease progression.

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62 Summary box

63 What is already known on this topic:

- 64 • Early diagnosis of chronic kidney disease (CKD) slows disease progression and reduces
65 mortality. However, population-based screening programmes are not advocated due to the
66 high cost-implications of such undertakings.

68 What this study adds:

- 69 • This is the first study to show that utilizing an opportunistic approach to screen individuals
70 at high-risk of type 2 diabetes mellitus (T2DM), can identify people with CKD; allowing
71 for early referral for specialized testing to confirm diagnosis and subsequent care.

73 How this study might affect research, practice, or policy:

- 74 • Our findings lend support to the view that capitalizing on existing resources and
75 capabilities is a more sustainable approach to screen for CKD as it could reduce overall
76 screening cost and avoid many limitations associated with community-based CKD
77 screening, but still identify individuals with CKD.
- 78 • This study has highlighted the importance of screening for albuminuria as the majority of
79 those with CKD would have gone undetected if CKD were based on eGFR alone.

93 INTRODUCTION

94 Chronic kidney disease (CKD) is a leading cause of morbidity and mortality globally ¹, affecting
95 more than 840 million individuals worldwide ². The increasing burden of CKD is demonstrated by
96 its ascent in ranking among the global causes of disability-adjusted life years (DALYs), rising
97 from 29th in 1990 to 18th in 2019 overall, and from 14th to 8th in the older aged groups (aged ≥ 50
98 years) ³. However, despite being a global problem, the prevalence of CKD is increasing most
99 rapidly in low-and-middle income countries (LMICs) where the burden of disease is more
100 pronounced ⁴. This is worrisome as the health care systems in most LMICs are already under
101 pressure, and options for kidney replacement therapy are not frequently available or affordable ⁵.
102 ⁶. Given the inequity in access to healthcare services, which disproportionately affects
103 disadvantaged populations, and the costs of kidney replacement therapies, early detection of CKD
104 followed by low-cost treatments should be encouraged ⁷.

105
106 Early-stage CKD presents with no or non-specific symptoms and is commonly diagnosed
107 opportunistically from screening tests for other diseases, or when the disease has progressed, and
108 symptoms appear ⁸. Therefore, screening for CKD plays an important role in early detection, as
109 implementing treatment on diagnosis can slow the rate of kidney function loss and reduce
110 morbidity and mortality ^{9,10}. However, there is often a strong argument against community-based
111 CKD screening due to the potential harm arising from screening and the cost-implications of such
112 an undertaking. According to a recent study, community-based CKD screening is unlikely to be
113 effective or cost-effective anywhere in the world ¹¹. In contrast, community-based screening for
114 CKD risk factors like hypertension and type 2 diabetes mellitus (T2DM) are deemed effective.
115 Community-based screening programmes for hypertension and T2DM provide an opportunity to
116 incorporate screening for CKD. Certainly, using the screening of hypertension and T2DM, which
117 are common risk factors for CKD, as a gateway for CKD screening in clinical settings will involve
118 minimal additional costs. Furthermore, (1) the yield of screen-detected cases is likely to be high,
119 considering the high prevalence and incidence of CKD in the presence of these risk factors; (2)
120 awareness of the presence of CKD with hypertension or T2DM can prompt the intensification or
121 modification of treatments to enhance kidney protection and prevent CKD progression; and (3) a
122 large proportion of people with CKD likely have a combination of sub-optimal risk factors with
123 raised levels of blood pressure and/or glucose that fall below the threshold for disease

124 classification. These individuals with prediabetes and/or prehypertension are not generally
125 targeted for CKD screening in routine practice but may already have CKD. The opportunistic
126 incorporation of CKD testing in hypertension or T2DM screening programmes can therefore
127 identify CKD that may otherwise be missed if only those with established hypertension or T2DM
128 are screened for the condition.

129
130 The aim of this study was to evaluate the viability of CKD screening when incorporated into an
131 existing disease screening programme. The yield of CKD cases in the South African Diabetes
132 Prevention Programme (SA-DPP) was determined by assessing markers of kidney function (serum
133 and urinary creatinine levels and urinary albumin) among participants at high-risk for T2DM.

134 135 **MATERIAL AND METHODS**

136 **Study population and setting**

137 The SA-DPP is a “real-world” randomised implementation trial, of a structured lifestyle
138 intervention programme, adapted from programmes previously shown to be effective in Finland
139 ¹², Australia ¹³, and India ¹⁴. The SA-DPP uses an open-labelled cluster randomized control design,
140 conducted across 16 resource-poor communities in Cape Town, South Africa. In the current study,
141 baseline data were obtained from black and mixed ancestry participants, aged between 25 and 65
142 years, who were at high-risk for T2DM ¹⁵. The data were collected between 2017 and 2019 and
143 the details have been previously described ¹⁵. The study was conducted in accordance with the
144 Declaration of Helsinki and approved by the by the Research Ethics Committee of the South
145 African Medical Research Council (SAMRC) (approval no. EC018-7/2015).

146 147 **Community-based screening to identify high-risk individuals**

148 For the community-based risk screening, the African Diabetes Risk Score (ADRS) ¹⁶, which is a
149 validated African screening tool comprising non-laboratory-based variables including age, waist
150 circumference (WC) and the presence of hypertension, was used to identify adults at high-risk for
151 T2DM. Trained fieldworkers administered a brief questionnaire, which included age, gender,
152 population group, and measured anthropometry and blood pressure. Standard anthropometric
153 methods were used to measure weight, height, and WC ¹⁷. Body weight (nearest 0.1 kg) was
154 measured with a calibrated Omron digital scale, with the participant in light clothing and without

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3 155 shoes. A stadiometer was used to measure the participant height (nearest cm), with the participant
4 156 standing in an upright position, on a flat surface. Waist circumference was measured using a non-
5 157 elastic tape measure at the level of the umbilicus. Blood pressure measurements were taken in a
6 158 seated position after five minutes of rest. The systolic and diastolic blood pressures (SBP and DBP,
7 159 respectively) were recorded three times at 2-min intervals, using an appropriately sized cuff and
8 160 an automated blood pressure monitor (Omron 711, Omron Health Care, Hamburg, Germany). An
9 161 average of the last two readings was used in the analyses.
10 162

17 163 **Clinic-based assessments of high-risk participants**

18 164 Participants deemed at high-risk, based on the ADRS, were invited for further clinical and
19 165 biochemical assessments. At the clinic, trained fieldworkers administered questionnaires to obtain
20 166 information on participant sociodemographic and personal and family medical history.
21 167 Anthropometric and blood pressure measurements were repeated using standardized techniques as
22 168 described above.
23 169

24 170 As per the World Health Organization's (WHO) guidelines¹⁸, blood samples were collected after
25 171 a 10-hour overnight fast by a qualified nurse for the oral glucose tolerance test (OGTT). Following
26 172 the administration of 75 g anhydrous glucose dissolved in 250 ml, blood samples were taken two
27 173 hours later. Biochemical analyses were conducted at an ISO accredited laboratory (PathCare
28 174 Laboratories, Cape Town, SA). Plasma glucose was determined by the glucose oxidase method
29 175 (Glucose Analyzer 2, Beckman Instruments, Fullerton, CA, USA), serum insulin, determined by
30 176 a Microparticle Enzyme Immunoassay (AxSym Insulin Kit, Abbot, IL, USA) and glycated
31 177 haemoglobin (HbA1c) was analysed with high-performance liquid chromatography (Biorad
32 178 Variant Turbo, BioRad, Johannesburg, SA). Vitamin D (25(OH)D3) was measured using liquid
33 179 chromatography mass spectrometry and enzymatic colorimetric methods were used to measure
34 180 serum calcium, phosphate, aspartate aminotransferase (AST), alanine aminotransferase (ALT),
35 181 and gamma-glutamyl transferase (GGT). Full blood counts, including total red blood cells (RBC),
36 182 total white blood cells (WBC), haemoglobin, haematocrit, and platelets were measured on a
37 183 Coulter LH 750 haematology analyser (Beckman Coulter, South Africa).
38 184

185 For the current study, we utilized the blood and urine samples in the SA-DPP biobank to conduct
186 secondary laboratory analyses. To determine the levels of serum and urinary creatinine, the
187 modified Jaffe-Kinetic method (calibrated to isotope dilution mass spectrometry standards)
188 (Beckman AU, Beckman Coulter, SA) was used, and the colorimetric (using bromocresol purple)
189 method (Beckman AU, Beckman Coulter, SA) was used to determine the level of urine albumin.

191 **Classification of kidney function and co-morbidities**

192 Kidney function was estimated using the serum creatinine-based CKD Epidemiology
193 Collaboration equation¹⁹, and CKD was defined as an estimated glomerular filtration rate (eGFR)
194 of <60 ml/min/1.73 m² and/or urinary albumin-to-creatinine ratio (uACR) >3 mg/mmol. CKD
195 staging was based on the Kidney Disease Improving Global Outcomes (KDIGO) guidelines²⁰ as,
196 stage 1 (eGFR ≥ 90 ml/min/1.73m² and uACR >3 mg/mmol), stage 2 (eGFR 60–89 ml/min/1.73m²
197 and uACR >3 mg/mmol) and stage 3 (eGFR <60 ml/min/1.73m²). Microalbuminuria was defined
198 as uACR between 3 and 30 mg/mmol and macroalbuminuria as >30 mg/mmol²¹.

200 Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared
201 (kg/m²). This was categorised as normal weight (BMI ≤ 24.9 kg/m²), overweight (BMI 25.0–29.9
202 kg/m²) and obese (BMI ≥ 30 kg/m²). Hypertension was defined as SBP ≥ 140 mmHg and/or DBP
203 ≥ 90 mmHg,²² or taking anti-hypertensive medications. We further categorized our study
204 participants into four groups related to the level of blood pressure control, namely, 1) normotensive
205 (defined as no use of anti-hypertensive medication and SBP/DBP $<140/90$ mmHg), 2) treated and
206 controlled blood pressure (defined as use of anti-hypertensive medication and SBP/DBP
207 $<140/90$ mmHg), 3) treated but uncontrolled blood pressure (defined as use of anti-hypertensive
208 medication but SBP/DBP $\geq 140/90$ mmHg), 4) newly detected hypertension (defined as no use of
209 anti-hypertensive medication and SBP/DBP $\geq 140/90$ mmHg). Normal and dysglycaemia
210 categories, based on the OGTT, were defined according to WHO criteria¹⁸ as: (1) normal glucose
211 tolerance [fasting glucose (FG) <6.1 mmol/L and 2-h glucose <7.8 mmol/L]; or (2) prediabetes
212 including impaired FG (IFG) [$6.1 \leq \text{FG} < 7.0$ mmol/L and 2-h glucose <7.8 mmol/L], impaired
213 glucose tolerance (IGT) [FG <7.0 mmol/L and $7.8 \leq 2\text{-h glucose} < 11.1$ mmol/L]; and (3) T2DM
214 (FG ≥ 7.0 mmol/L and/or 2-h glucose ≥ 11.1 mmol/L). High GGT was defined as levels >38 IU/L,
215 and based on the laboratory (PathCare, South Africa) reference standards. Liver fibrosis was

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3 216 classified based on the fibrosis-4 (FIB-4) index, where FIB-4 index was calculated using the
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5 217 formula: $[\text{age (years)} \times \text{AST (IU/L)}] / [\text{platelet (10}^9\text{/L)} \times \sqrt{\text{ALT (IU/L)}}]$ ²³. Low risk for advanced
6
7 218 fibrosis was defined a FIB-4 score <1.30, intermediate risk as a value between 1.30 and 2.67, and
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9 219 high risk as FIB-4 >2.67²⁴. Anaemia was defined using the National Kidney Foundation Kidney
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11 220 Disease Outcome Quality Initiative (K/DOQI) guidelines as haemoglobin level <13.5 g/dL for
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13 221 men and <12 g/ dL for women²⁵.
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15 223 **Statistical analysis**

16
17 224 Due to the non-Gaussian distribution of most variables, the participant characteristics were
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19 225 summarised as median (25th-75th percentile) or counts and percentages. Group comparisons were
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21 226 analysed by chi-square tests, Wilcoxon rank-sum and Kruskal-Wallis tests. The Dunn's test was
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23 227 used as nonparametric pairwise multiple-comparison post-hoc test when the Kruskal-Wallis test
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25 228 was rejected. All statistical analyses were performed using STATA version 17 (Statcorp, College
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27 229 Station, TX) and statistical significance was based on a p-value <0.05.
28 230

29 231 **Patient and public involvement:** Participants and/or the public were not involved in the design,
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31 232 or conduct, or reporting or dissemination plans of this research.
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34 234 **RESULTS**

35
36 235 Of the 2,039 individuals screened in the community, 690 participants, deemed at high-risk of
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38 236 T2DM based on the ADRS, presented at our research clinic for an OGTT and other assessments.
39
40 237 The sociodemographic, clinical, and biochemical characteristics are summarised by CKD status in
41
42 238 Table 1. Among the 690 participants included in this study, 80.9% were female, with a group
43
44 239 median age of 52 years. Of these participants, 9.6% had screen-detected T2DM and 18.1% had
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46 240 CKD, with 2.2% presenting with both CKD and T2DM. Furthermore, there were high rates of
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48 241 obesity (77.1%), hypertension (55.0%), raised GGT levels (45.8%), intermediate risk of advanced
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50 242 liver fibrosis (21.4%) and anaemia (14.2%) among participants in this study. There were no
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52 243 significant differences in the sociodemographic and anthropometric variables between participants
53
54 244 with and without CKD. However, SBP (128.0 vs. 123.5 mmHg; p=0.004) and DBP (86.0 vs. 83.0
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56 245 mmHg; p=0.014) were higher in participants with CKD compared to those without. Although
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58 246 hypertension prevalence was not significantly different by CKD status (p=0.215), uncontrolled

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3 247 hypertension on treatment was significantly higher in those with than without CKD (42.7% vs.
4 248 23.4%). The median levels of GGT (47.0 vs. 35.0 IU/L; p=0.008), AST (26.0 vs. 23.0 IU/L;
5 249 p=0.004), and FIB-4 index (1.0 vs. 0.9; p=0.016), were higher in participants with CKD compared
6 250 to those without CKD, while RBC count (4.5 vs. 4.6 x10¹²/L; p=0.046) was lower in CKD compared
7 251 to those with normal kidney function. The prevalence of high GGT (p=0.008) and anaemia
8 252 (p=0.042) were significantly higher in participants with CKD compared to those without CKD.
9 253 All other biochemical variable were similar between groups.
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278 **Table 1:** Sociodemographic, clinical, and biochemical characteristics presented in the overall sample and by CKD status

Sociodemographic variables	Total (n=690)	Without CKD (n=565)	CKD (n=125)	p-value
Age (years)	52 (45-59)	52 (45-59)	53 (45-60)	0.241
Gender (n,% female)	558 (80.9)	460 (81.4)	98 (78.4)	0.438
African Diabetes Risk Score	2.3 (1.7-3.4)	2.3 (1.7-3.4)	2.4 (1.7-3.4)	0.882
Anthropometry				
Weight (kg)	91.0 (79.6-103.6)	92.2 (80.4-104.6)	88.0 (76.2-101.3)	0.050
Waist circumference (cm)	102.7 (95.3-111.1)	103.4 (95.7-111.1)	101.3 (93.4-111.1)	0.242
Hip circumference (cm)	112.6 (103.2-121.7)	113.0 (104.3-122.4)	111.3 (102.1-118.3)	0.067
Body mass index (kg/m ²)	35.6 (30.5-40.5)	35.7 (30.6-40.6)	33.9 (29.4-39.9)	0.185
Body mass index categories (n, %)				0.316
Normal	29 (4.2)	23 (4.1)	6 (4.8)	
Overweight	129 (18.7)	100 (17.7)	29 (23.2)	
Obese	532 (77.1)	442 (78.2)	90 (72.0)	
Blood pressure				
Systolic blood pressure (mmHg)	124.5 (113.5-137.0)	123.5 (113.5-135.0)	128.0 (116.0-145.5)	0.004
Diastolic blood pressure (mmHg)	83.0 (77.0-91.5)	83.0 (77.0-90.3)	86.0 (78.5-94.5)	0.014
Hypertension	379 (55.0)	304 (53.9)	75 (60.0)	0.215
Among participants with hypertension (n=379):				<0.0001
Treated and controlled BP	143 (37.7)	127 (41.8)	16 (21.3)	
Treated and uncontrolled BP	103 (27.2)	71 (23.4)	32 (42.7)	
Screen-detected HPT	133 (35.1)	106 (34.9)	27 (36.0)	
Biochemical				
Fasting blood glucose (mmol/L)	5.0 (4.6-5.5)	5.0 (4.6-5.5)	5.0 (4.6-5.6)	0.691
2-hour glucose (mmol/L)	6.0 (4.9-7.4)	6.0 (4.9-7.3)	6.3 (5.1-7.6)	0.205
Glucose categories (n, %)				0.600
Normoglycaemia	520 (75.6)	428 (76.0)	92 (73.6)	
Prediabetes (IFG/IGT)	102 (14.8)	84 (14.9)	18 (14.4)	
Type 2 diabetes	66 (9.6)	51 (9.1)	15 (12.0)	
HbA1c (%)	5.8 (5.6-6.1)	5.8 (5.6-6.1)	5.9 (5.6-6.2)	0.740
Fasting insulin (IU/L)	8.8 (6.2-12.6)	8.5 (5.9-12.1)	11.1 (7.7-14.8)	0.144

Vitamin D (ng/mL)	6.1 (5.0-7.8)	6.0 (5.0-7.7)	6.2 (5.0-8.1)	0.222
Calcium (mmol/L)	2.3 (2.3-2.4)	2.3 (2.3-2.4)	2.4 (2.3-2.4)	0.644
Phosphate (mmol/L)	1.1 (1.0-1.2)	1.1 (1.0-1.2)	1.1 (1.0-1.2)	0.981
Gamma-glutamyl transferase (IU/L)	36.0 (24.0-61.0)	35.0 (24.0-55.0)	47.0 (26.0-78.0)	0.008
High gamma-glutamyl transferase	315 (45.8)	245 (43.4)	70 (6.5)	0.008
Aspartate aminotransferase (IU/L)	24.0 (20.0-29.0)	23.0 (20.0-29.0)	26.0 (21.0-34.0)	0.004
Alanine aminotransferase (IU/L)	22.0 (16.0-32.0)	22.0 (16.0-32.0)	22.0 (17.0-33.0)	0.372
AST/ALT ratio	1.1 (0.9-1.4)	1.1 (0.9-1.4)	1.2 (0.9-1.5)	0.110
Fibrosis-4 index	0.9 (0.7-1.3)	0.9 (0.7-1.3)	1.0 (0.8-1.4)	0.016
Liver fibrosis (n, %)				0.065
No risk	497 (77.2)	413 (78.4)	84 (7.8)	
Intermediate risk	138 (21.4)	109 (20.7)	29 (2.8)	
High risk	9 (1.4)	5 (0.9)	4 (0.4)	
Red blood cells (x10 ¹² /L)	4.6 (4.2-4.9)	4.6 (4.3-4.9)	4.5 (4.2-4.8)	0.046
White blood cells (x10 ⁹ /L)	23.0 (18.0-28.0)	23.0 (18.3-28.0)	23.0 (17.0-28.0)	0.270
Platelet count (x10 ⁹ /L)	276 (235-325)	276.0 (234.5-322.5)	276.0 (233.0-333.0)	0.705
Haematocrit (volume %)	0.4 (0.4-0.4)	0.4 (0.4-0.4)	0.4 (0.4-0.4)	0.442
Haemoglobin (g/dL)	13.5 (12.6-14.3)	13.5 (12.7-14.3)	13.4 (12.4-14.4)	0.491
Anaemia, n (%)	103 (14.9)	77 (13.6)	26 (2.8)	0.042

Data is presented as median (25th-75th percentiles) or count and percentages. Abbreviations: CKD, chronic kidney disease; BP, blood pressure; HPT, hypertension; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; HbA1c, glycated haemoglobin; AST/ALT ratio, aspartate aminotransferase to alanine aminotransferase ratio.

286 The prevalence of CKD in the overall sample and grouped by glucose and blood pressure
287 categories are shown in Figure 1. In those with prediabetes, T2DM, and hypertension, 17.6%,
288 22.7% and 19.8% had CKD, respectively. Of the participants with hypertension, the prevalence of
289 CKD was highest in those on anti-hypertensive treatment but with uncontrolled blood pressure
290 (31.1%), while 20.3% of those newly identified with hypertension and 11.2% of those on treatment
291 with controlled blood pressure had CKD.

292

293 **Figure 1**

294

295 Table 2 describes the participant characteristics by CKD stage. The majority of individuals with
296 CKD presented with stage 1 CKD (73.6%), with 17.6% and 7.2% presenting with stage 2 and 3,
297 respectively. Of those with CKD stages 1, 2 and 3, 72.8%, 68.2% and 36.4% had
298 microalbuminuria, with 27.2%, 31.8% and 27.3% presenting with macroalbuminuria, respectively.
299 Four participants (36.4%) with an eGFR $<60\text{ml/min/1.73m}^2$ (CKD stage 3) had no albuminuria.
300 Two participants (1.6% of CKD cases) had an eGFR value $<30\text{ ml/min/1.73m}^2$.

301

302 Participants with stage 3 CKD were older than those with normal kidney function and stage 1 CKD
303 ($p=0.030$ for both). Levels of AST were significantly higher with stage 2 CKD compared with
304 stage 3 CKD ($p=0.042$). SBP and DBP did not differ by stages of CKD but differed between those
305 with normal kidney function and those with CKD as follows: normal kidney function vs. CKD
306 stage 1 (SBP: $p=0.007$ and DBP: $p=0.010$), stage 2 (SBP: $p=0.039$) and stage 3 (DBP: $p=0.013$).

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317 **Table 2:** Sociodemographic, clinical, and biochemical characteristics in participants by CKD stages

Sociodemographic variables	No CKD (n=565)	Stage 1 (n=92)	Stage 2 (n=22)	Stage 3 (n=11)	p-value
Age (years)	52 (45-59)*	52 (45-59)*	56 (51-61)	57 (52-63)	0.029
Gender (n,% female)	460 (81.4)	75 (81.5)	15 (68.2)	8 (72.7)	0.408
African Diabetes Risk Score	2.3 (1.7-3.4)	2.4 (1.8-3.1)	2.2 (1.7-4.8)	2.8 (1.9-3.9)	0.865
Kidney function					
Serum creatinine (µmol/L)	57.0 (48.0-67.0)	54.0 (46.5-62.0)	78.5 (72.0-88.0)	122.0 (96.0-160.0)	0.0001
eGFR (ml/min/1.73m ²)	103.0 (95.0-114.0)	106.0 (98.0-117.5)	79.5 (75.0-83.0)	49.0 (32.0-57.0)	0.0001
uACR (mg/mmol)	0.6 (0.4-1.0)	6.0 (4.1-14.1)	6.5 (3.6-17.3)	3.9 (0.8-43.2)	0.0001
uACR categories (n, %)					<0.0001
None	565 (100)	-	-	4 (36.4)	
Microalbuminuria	-	67 (72.8)	15 (68.2)	4 (36.4)	
Macroalbuminuria	-	25 (27.2)	7 (31.8)	3 (27.3)	
Anthropometry					
Weight (kg)	92.2 (80.4-104.6)	89.1 (77.8-101.7)	84.4 (70.6-95.3)	78.7 (63.2-102.4)	0.117
Waist circumference (cm)	103.4 (95.7-111.1)	101.6 (93.9-111.4)	97.2 (93.1-109.7)	100.6 (93.4-107.0)	0.497
Hip circumference (cm)	113.0 (104.3-122.4)	112.7 (102.3-120.9)	110.4 (99.4-117.9)	108.6 (96.4-108.9)	0.085
BMI (kg/m ²)	35.7 (30.6-40.6)	34.7 (30.5-40.7)	31.6 (26.9-39.5)	31.9 (27.2-36.9)	0.121
BMI categories (n, %)					0.039
Normal	23 (4.1)	2 (2.2)	2 (9.1)	2 (18.2)	
Overweight	100 (17.7)	19 (20.7)	8 (36.4)	2 (18.2)	
Obese	442 (78.2)	71 (77.2)	12 (54.5)	7 (63.6)	
Blood pressure					
SBP (mmHg)	123.5 (113.5-135.0)	129.5 (115.0-145.5)**	126.5 (123.5-153.0)***	127.5 (106.5-156.0)	0.031
DBP (mmHg)	83.0 (77.0-90.3)	86.5 (78.3-94.0)#	80.8 (75.0-94.5)	90.5 (82.5-105.5)##	0.017
Hypertension	304 (53.9)	54 (58.7)	12 (54.5)	9 (81.8)	0.263
Among participants with hypertension (n=379):					0.010
Treated and controlled BP	127 (41.8)	10 (18.5)	3 (25.0)	3 (33.3)	
Treated and uncontrolled BP	71 (23.4)	23 (42.6)	5 (41.7)	4 (44.4)	
Screen-detected HPT	106 (34.9)	21 (38.9)	4 (33.3)	2 (22.2)	
Biochemical					

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3	FBG (mmol/L)	5.0 (4.6-5.5)	5.0 (4.6-5.6)	4.9 (4.4-5.6)	4.8 (4.7-5.3)	0.886
4	2-hour glucose (mmol/L)	6.0 (4.9-7.3)	6.3 (5.1-7.6)	6.3 (4.7-8.5)	6.4 (5.6-7.2)	0.624
5	Glucose categories (n, %)					0.543
6	Normoglycaemia	428 (76.0)	70 (76.0)	13 (59.1)	9 (81.8)	
7	Prediabetes (IFG/IGT)	84 (14.9)	11 (12.0)	6 (27.3)	1 (9.1)	
8	Type 2 diabetes	51 (9.1)	11 (12.0)	3 (13.6)	1 (9.1)	
9	HbA1c (%)	5.8 (5.6-6.1)	5.9 (5.6-6.2)	5.7 (5.3-6.2)	5.7 (5.6-6.2)	0.591
10	Fasting insulin (IU/L)	8.5 (5.9-12.1)	11.1 (6.4-15.5)	11.0 (8.7-13.2)	-	0.334
11	Vitamin D (ng/mL)	6.0 (5.0-7.7)	6.2 (5.0-7.8)	6.7 (5.9-8.1)	6.8 (5.2-10.6)	0.361
12	Calcium (mmol/L)	2.3 (2.3-2.4)	2.3 (2.3-2.4)	2.4 (2.3-2.4)	2.3 (2.3-2.4)	0.794
13	Phosphate (mmol/L)	1.1 (1.0-1.2)	1.1 (1.0-1.2)	1.1 (1.0-1.2)	1.2 (0.9-1.3)	0.777
14	GGT (IU/L)	35.0 (24.0-55.0)	45.0 (26.0-81.0)	46.5 (25.0-64.0)	49.0 (24.0-122.0)	0.071
15	High GGT	245 (43.4)	51 (56.0)	13 (59.1)	6 (54.5)	0.071
16	AST (IU/L)	23.0 (20.0-29.0)	26.0 (21.1-34.0)	26.5 (22.0-34.0)###	21.0 (20.0-28.0)	0.009
17	ALT (IU/L)	22.0 (16.0-32.0)	23.0 (17.0-33.0)	21.0 (18.0-31.0)	18.5 (15.5-37.5)	0.799
18	AST/ALT ratio	1.1 (0.9-1.4)	1.2 (0.9-1.5)	1.3 (1.1-1.4)	1.3 (0.9-1.5)	0.413
19	Fibrosis-4 index	0.9 (0.7-1.3)	1.0 (0.8-1.3)	1.1 (0.9-1.5)	1.3 (0.7-1.6)	0.063
20	Liver fibrosis (n, %)					0.124
21	No risk	413 (78.4)	66 (75.0)	14 (66.7)	4 (50.0)	
22	Intermediate risk	109 (20.7)	19 (21.6)	6 (28.6)	4 (50.0)	
23	High risk	5 (0.9)	3 (3.4)	1 (4.8)	0 (0)	
24	Red blood cells (x10 ¹² /L)	4.6 (4.3-4.9)	4.5 (4.2-4.9)	4.5 (4.2-4.6)	4.7 (4.5-5.1)	0.071
25	White blood cells (x10 ⁹ /L)	23.0 (18.3-28.0)	22.0 (17.0-28.0)	26.0 (16.0-31.9)	25.0 (19.0-26.0)	0.550
26	Platelet count (x10 ⁹ /L)	276.0 (234.5-322.5)	276.5 (235.0-333.5)	271.0 (244.0-335.0)	261.0 (217.0-325.0)	0.956
27	Haematocrit (volume %)	0.4 (0.4-0.4)	0.4 (0.4-0.4)	0.4 (0.4-0.4)	0.4 (0.4-0.5)	0.433
28	Haemoglobin (g/dL)	13.5 (12.7-14.3)	13.3 (12.3-14.5)	13.5 (13.3-14.4)	13.7 (12.9-15.8)	0.390
29	Anaemia, n (%)	77 (13.6)	22 (23.9)	2 (9.1)	2 (18.2)	0.063

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319 Data is presented as median (25th-75th percentiles) or count and percentages. Abbreviations: CKD, chronic kidney disease; eGFR,
 320 estimated glomerular filtration rate; uACR, urinary albumin-to-creatinine ratio; BMI, body mass index; SBP, systolic blood pressure;
 321 DBP, diastolic blood pressure; FBG, fasting blood glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; HbA1c,

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3 322 glycated haemoglobin; GGT, gamma-glutamyl transferase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; eGFR,
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5 323 estimated glomerular filtration rate; uACR, urinary albumin-to-creatinine ratio. Keys: *p=0.030 (CKD stage 2 vs. no CKD; CKD stage
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7 324 3 vs. CKD stage 1); **p=0.007 (no CKD vs. CKD stage 1); ***p=0.039 (no CKD vs. CKD stage 2); #p=0.016 (no CKD vs. CKD stage
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9 325 1); ##p=0.013 (no CKD vs. CKD stage 3); ###p=0.042 (CKD stage 3 vs. CKD stage 2).

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342 **DISCUSSION**

343 To our knowledge, this is the first study to show that by utilizing an opportunistic approach, CKD
344 can be detected early, allowing for timely referral for specialized testing to confirm diagnosis and
345 subsequent care. This was achieved through leveraging the information already collected in an
346 existing screening programme that targeted individuals at high-risk for T2DM and included a few
347 additional kidney-related biochemical markers to the variables for testing. The yield of screen-
348 detected cases was high for a low investment which cost ZAR 237.80 (USD 14.59) per person and
349 highlights the potential cost-effectiveness of such a strategy.

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351 By including a minimal number of markers of kidney function (namely serum and urinary
352 creatinine, and urinary albumin) to the scope of markers already collected, we found that 18.1%
353 of those at high-risk for developing T2DM had CKD with the majority (73.6%) having mild CKD
354 (CKD stage 1). The CKD burden, at 22.7%, was even higher in participants with newly diagnosed
355 T2DM, which underscores the need for frequent screening of individuals at high-risk for T2DM
356 to avoid T2DM presenting with complications at diagnosis. Therefore, using T2DM as a gateway
357 for CKD screening through existing screening programmes is justified as such an approach,
358 together with diagnosing new T2DM, simultaneously identified those with complications i.e.,
359 CKD. The newly diagnosed T2DM may receive comprehensive care with tight control of both
360 their T2DM and CKD. This intensification of treatment could contribute to a delay in CKD
361 progression and consequently help reduce the risk of developing end-stage kidney disease (ESKD)
362 or CVD-related complications²⁶. Further support for CKD screening in individuals at high-risk
363 for T2DM was the substantial CKD burden in prediabetes (17.6%). Notably, if screening for CKD
364 was initiated only after the development of T2DM, the identification of CKD in individuals with
365 prediabetes, which generally fall below the threshold for disease management in clinical practice,
366 would have been missed. This would then have been a lost opportunity to identify and manage
367 CKD early and delay progression of the disease in this high-risk group.

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369 Our study also highlights the importance of screening for albuminuria as 91.2% of those with CKD
370 would have gone undetected if CKD were based on eGFR alone. Guidelines recommend
371 albuminuria testing using ACR, like we did in our study, however this is not always possible in
372 many low-resource settings. In these instances, low-cost semiquantitative methods, like urinary

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3 373 dipsticks, can be used to measure albuminuria with subsequent confirmation of positive dipstick
4 374 result with a quantitative laboratory test to confirm CKD diagnosis ²⁰. Or repeated dipstick
5 375 assessments can be employed to reduce the possibility of false-negative results as this could delay
6 376 the timely diagnosis and management of CKD.
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11 378 Given that this is the first study to report the prevalence of CKD in people at high-risk for
12 379 developing T2DM, based on the ADRS, the prevalence estimates cannot be directly compared to
13 380 other studies as no similar data have been published. Nevertheless, at a similar median age (52 vs.
14 381 53 years), the prevalence of CKD in those with prediabetes in our study was comparable to that
15 382 reported in a large representative sample in the United States of America (17.6% vs. 17.7%,
16 383 respectively) ²⁷. Also, albeit an older population (median age of 68 years) with a higher prevalence
17 384 of advanced CKD (stage 3-5), a South African study found that the prevalence of CKD in those
18 385 with prediabetes was 19.8% ²⁸. The similarly high CKD prevalence in prediabetes across several
19 386 studies suggests that perhaps there should be regular CKD screening for all individuals with
20 387 prediabetes.
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30 389 A likely contributor to the substantial CKD burden in this study is the high prevalence of
31 390 hypertension, which at 55% is higher than the 44%-46% reported for South Africa ²⁹. While the
32 391 high reported prevalence of hypertension is consequent to the score used to identify high-risk
33 392 individuals, a larger proportion of the participants with hypertension had CKD compared to those
34 393 with normal blood pressure (19.8% vs. 16.1%, respectively). The prevalence of CKD may be
35 394 related to the delayed detection of hypertension or the suboptimal control of blood pressure in
36 395 treated hypertension, as reported in the current study and in several South African studies ^{29, 30}.
37 396 Indeed, a high proportion of participants with treated but uncontrolled hypertension had CKD
38 397 (31.1%) in this study as did participants with newly detected hypertension (20.3%). This further
39 398 highlights the benefit of screening high-risk individuals for CKD. Notably, adequate blood
40 399 pressure control is fundamental to slowing the progression of CKD ^{31, 32} and timeous treatment
41 400 with anti-hypertensive medication can improve both kidney and cardiovascular outcomes ^{33, 34}
42 401 thereby preventing the progression to ESKD and reducing the risk of all-cause and cardiovascular
43 402 mortality ^{33, 35, 36}.
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3 404 Elevated GGT and the FIB-4 index, which are commonly used markers of liver injury and non-
4 405 alcoholic fatty liver disease (NAFLD)³⁷, have been linked to increased CKD risk in various
5 406 populations³⁸⁻⁴¹. In our study, 56.5% of the participants with CKD presented with higher-than-
6 407 normal GGT levels, compared to 43.4% of participants without CKD. Also, a significant
7 408 proportion of people with CKD presented with intermediate and high risk for advanced liver
8 409 fibrosis, based on the FIB-4 index, compared to those without CKD (28.2% vs. 21.6%). Early
9 410 recognition and interventions directed at reducing the risk of liver injury among individuals with
10 411 CKD could reduce CKD progression.
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19 413 Anaemia was prevalent in our study population (14.9% of total sample), with nearly twice as many
20 414 participants with CKD having anaemia compared to those without CKD, as shown in other studies
21 415 as well^{42, 43}. Although the overall prevalence of anaemia in this study was not uncommon for
22 416 South Africa⁴⁴, the prevalence in participants with CKD is concerning. While erythropoiesis
23 417 stimulating agents and iron supplementation to treat anaemia are unlikely to be prescribed to
24 418 people in the early stages of CKD, anaemia can accelerate the decline in kidney function by
25 419 causing kidney haemodynamic alterations and tissue hypoxia⁸. It is strongly predictive of all-
26 420 cause and cardiovascular mortality^{45, 46}, and should thus be closely monitored.
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34 422 Although lifestyle interventions addressing unhealthy diets, physical inactivity, tobacco smoking
35 423 and alcohol misuse are advocated to reduce the growing global burden of non-communicable
36 424 diseases^{47, 48}, little is known about the impact of reducing unhealthy lifestyle behaviours on kidney
37 425 health. The SA-DPP intervention, implemented in individuals with prediabetes, will provide a
38 426 unique opportunity to examine the effects of improving lifestyle behaviours on changes in CKD
39 427 status.
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46 429 This is the first study to show that utilizing an opportunistic approach, through leveraging the
47 430 information already collected in an existing screening programme is advantageous to screen for
48 431 CKD. However, our study does have limitations. The SA-DPP study included participants at high-
49 432 risk of T2DM and our findings might not be reproducible across other non-communicable diseases
50 433 screening programmes. The small number of participants identified with CKD in this study
51 434 reduced the statistical power of our analyses when stratifying by CKD stage. Our study findings
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3 435 cannot be generalised to other South African populations because factors like socioeconomic
4 436 status, lifestyle behaviours and disease prevalence (hypertension and T2DM) differ significantly
5 437 across provinces and by urban-rural residence in South Africa²⁹. Another limitation is that CKD
6 438 was defined based on a single time-point serum and urinary creatinine and albumin assessment
7 439 and not on repeated measurements, at least three months apart, as per KDIGO guidelines²⁰.
8 440 However, a strength of our study is that both eGFR and albuminuria were used to define CKD,
9 441 unlike most other population-based CKD prevalence studies in South Africa and Africa in general
10 442 which rely on eGFR only for CKD classification.
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19 444 **CONCLUSION**

20 445 The fact that almost one in five participants identified as high-risk for T2DM had CKD underscores
21 446 the value of including markers of kidney function in existing disease screening programmes. Our
22 447 findings provide support for key stakeholders and policy makers to adapt current strategies for
23 448 hypertension and T2DM screening to include screening for CKD. Indeed, by utilizing an
24 449 opportunistic approach to screen high-risk individuals, those with early-stage CKD can be
25 450 identified and appropriately managed to reduce disease progression. Existing cardiovascular or
26 451 non-communicable disease screening programmes should perhaps explore including markers for
27 452 CKD evaluations to maximise limited resources without compromising on effectiveness.
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3 **495 Figure legends**

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5 **496 Figure 1:** Prevalence (%) of chronic kidney disease overall and by glucose and blood pressure
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7 categories. Data presented as percentages. Abbreviations: T2DM, type 2 diabetes mellitus; HPT,
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9 hypertension; BP, blood pressure

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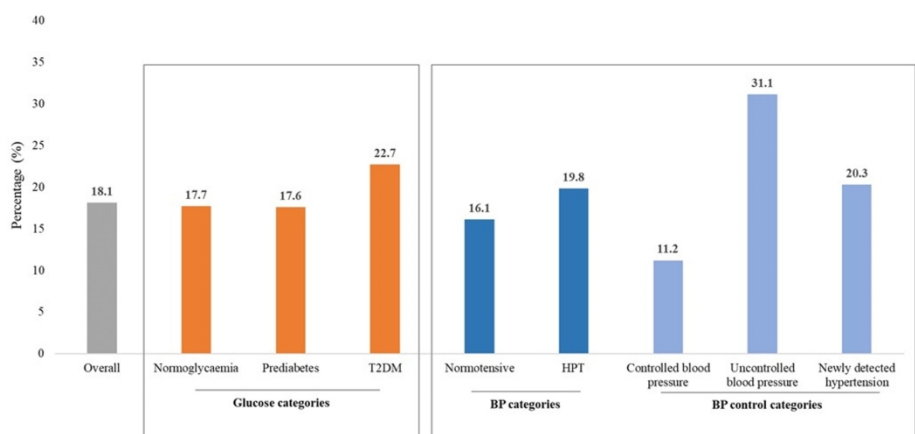


Figure 1: Prevalence (%) of chronic kidney disease overall and by glucose and blood pressure categories. Data presented as percentages. Abbreviations: T2DM, type 2 diabetes mellitus; HPT, hypertension; BP, blood pressure

190x96mm (330 x 330 DPI)

STROBE Statement—Checklist of items that should be included in reports of *cross-sectional studies*

	Item No	Recommendation	Page No
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-7
Bias	9	Describe any efforts to address potential sources of bias	5
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	8
		(b) Describe any methods used to examine subgroups and interactions	8
		(c) Explain how missing data were addressed	8
		(d) If applicable, describe analytical methods taking account of sampling strategy	NA
		(e) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	5-8
		(b) Indicate number of participants with missing data for each variable of interest	
Outcome data	15*	Report numbers of outcome events or summary measures	10-11 and 13-14

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Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	NA
		(b) Report category boundaries when continuous variables were categorized	8-15
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	16
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	18-19
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	19
Generalisability	21	Discuss the generalisability (external validity) of the study results	19
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	19

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

LEVERAGING THE SOUTH AFRICAN DIABETES PREVENTION PROGRAMME TO SCREEN FOR CHRONIC KIDNEY DISEASE – AN OBSERVATIONAL STUDY

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1 LEVERAGING THE SOUTH AFRICAN DIABETES 2 PREVENTION PROGRAMME TO SCREEN FOR CHRONIC 3 KIDNEY DISEASE – AN OBSERVATIONAL STUDY

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16 Word count: 3,735

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18 Keywords: chronic kidney disease; screening; Africa

31 Abstract

32 **Objective:** To evaluate the viability of leveraging an existing screening programme (the South
33 African Diabetes Prevention Programme [SA-DPP]) to screen for chronic kidney disease (CKD),
34 by assessing the yield of CKD cases among those participating in the programme.

35 **Design:** Observational study conducted between 2017 and 2019.

36 **Setting:** 16 resource-poor communities in Cape Town, South Africa.

37 **Participants:** 690 participants, aged between 25 and 65 years, identified as at high-risk for type 2
38 diabetes mellitus (T2DM) by the African Diabetes Risk Score.

39 **Primary outcome measure:** The prevalence of CKD among those participating in the SA-DPP.

40 **Results:** Of the 2,173 individuals screened in the community, 690 participants underwent further
41 testing. Of these participants, 9.6% (n=66) and 18.1% (n=125) had screen-detected T2DM and
42 CKD (defined as an estimated glomerular filtration rate of <60 ml/min/1.73m² (eGFR) and/or
43 albumin-to-creatinine ratio >3 mg/mmol), respectively. Of those with CKD, 73.6% (n=92), 17.6%
44 (n=22) and 8.8% (n=11) presented with stages 1, 2 and 3, respectively. Of the participants with an
45 eGFR <60 ml/min/1.73m², 36.4% had no albuminuria, and of those with normal kidney function
46 (eGFR ≥ 90 ml/min/1.73m²), 10.2% and 3.8% had albuminuria stage 2 and 3, respectively. Of those
47 with T2DM and hypertension, 22.7% and 19.8% had CKD, respectively.

48 **Conclusion:** The fact that almost one in five participants identified as high-risk for T2DM had
49 CKD underscores the value of including markers of kidney function in an existing screening
50 programme. By utilizing an opportunistic approach to screen high-risk individuals, those with
51 CKD can be identified and appropriately treated to reduce disease progression.

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61 **Strengths and limitations of this study**

- 62 • The strength of our study is that both estimated glomerular filtration rate (eGFR) and
63 albuminuria were used to define CKD, unlike most other population-based CKD
64 prevalence studies in South Africa and Africa in general which rely on eGFR only.
- 65 • Due to the self-selection approach of recruitment and the disproportionate female
66 participation, our study findings may not be generalisable.
- 67 • The small proportion of participants with chronic kidney disease (CKD) in this study
68 resulted in reduced statistical power when analysis was stratifying by CKD stage.
- 69 • CKD was defined based on a single time-point serum and urinary creatinine and albumin
70 assessment and not on repeated measurements, at least three months apart, as per
71 guidelines.

91 INTRODUCTION

92 Chronic kidney disease (CKD) is a leading cause of morbidity and mortality globally ¹, affecting
93 more than 840 million individuals worldwide ². The increasing burden of CKD is demonstrated by
94 its ascent in ranking among the global causes of disability-adjusted life years (DALYs), rising
95 from 29th in 1990 to 18th in 2019 overall, and from 14th to 8th in the older aged groups (aged ≥ 50
96 years) ³. However, despite being a global problem, the prevalence of CKD is increasing most
97 rapidly in low-and-middle income countries (LMICs) where the burden of disease is more
98 pronounced ⁴. This is worrisome as the health care systems in most LMICs are already under
99 pressure, and options for kidney replacement therapy are not frequently available or affordable ⁵.
100 ⁶. Given the inequity in access to healthcare services, which disproportionately affects
101 disadvantaged populations, and the costs of kidney replacement therapies, early detection of CKD
102 followed by low-cost treatments should be encouraged ⁷.

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104 Early-stage CKD presents with no or non-specific symptoms and is commonly diagnosed
105 opportunistically from screening tests for other diseases, or when the disease has progressed, and
106 symptoms appear ⁸. Therefore, screening for CKD plays an important role in early detection, as
107 implementing treatment on diagnosis can slow the rate of kidney function loss and reduce
108 morbidity and mortality ^{9,10}. However, there is often a strong argument against community-based
109 CKD screening due to the potential harm arising from screening and the cost-implications of such
110 an undertaking. According to a recent study, community-based CKD screening is unlikely to be
111 effective or cost-effective anywhere in the world ¹¹. In contrast, community-based screening for
112 CKD risk factors like hypertension and type 2 diabetes mellitus (T2DM) are deemed effective.
113 Community-based screening programmes for hypertension and T2DM provide an opportunity to
114 incorporate screening for CKD. Certainly, using the screening of hypertension and T2DM, which
115 are common risk factors for CKD, as a gateway for CKD screening in clinical settings will involve
116 minimal additional costs. Furthermore, (1) the yield of screen-detected cases is likely to be high,
117 considering the high prevalence and incidence of CKD in the presence of these risk factors; (2)
118 awareness of the presence of CKD with hypertension or T2DM can prompt the intensification or
119 modification of treatments to enhance kidney protection and prevent CKD progression; and (3) a
120 large proportion of people with CKD likely have a combination of sub-optimal risk factors with
121 raised levels of blood pressure and/or glucose that fall below the threshold for disease

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3 122 classification. These individuals with prediabetes and/or prehypertension are not generally
4 123 targeted for CKD screening in routine practice but may already have CKD. The opportunistic
5 124 incorporation of CKD testing in hypertension or T2DM screening programmes can therefore
6 125 identify CKD that may otherwise be missed if only those with established hypertension or T2DM
7 126 are screened for the condition.
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13 128 The aim of this study was to evaluate the viability of CKD screening when incorporated into an
14 129 existing disease screening programme. The yield of CKD cases in the South African Diabetes
15 130 Prevention Programme (SA-DPP) was determined by assessing markers of kidney function (serum
16 131 and urinary creatinine levels and urinary albumin) among participants at high-risk for T2DM.
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22 133 **MATERIAL AND METHODS**

23 134 **Study population and setting**

24 135 The SA-DPP is a “real-world” randomised implementation trial, of a structured lifestyle
25 136 intervention programme, adapted from programmes previously shown to be effective in Finland
26 137 ¹², Australia ¹³, and India ¹⁴. The SA-DPP uses an open-labelled cluster randomized control design,
27 138 conducted across 16 resource-poor communities in Cape Town, South Africa. Participants were
28 139 recruited by self-selection approaches, by raising awareness of the study with flyers distributed in
29 140 the community or through local councillors’ offices, churches, and schools. Interested participants
30 141 were invited to pre-determined venues in their community for community-based risk screening.
31 142 In the current study, baseline data were obtained from black and mixed ancestry participants, aged
32 143 between 25 and 65 years, who were at high-risk for T2DM ¹⁵. The data included in this study was
33 144 collected between 2017 and 2019 and the details have been previously described ¹⁵. The study was
34 145 conducted in accordance with the Declaration of Helsinki and approved by the by the Research
35 146 Ethics Committee of the South African Medical Research Council (SAMRC) (approval no.
36 147 EC018-7/2015).
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50 149 **Community-based screening to identify high-risk individuals**

51 150 For the community-based risk screening, the African Diabetes Risk Score (ADRS) ¹⁶, which is a
52 151 validated African screening tool comprising non-laboratory-based variables including age, waist
53 152 circumference (WC) and the presence of hypertension, was used to identify adults at high-risk for

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3 153 T2DM. Trained fieldworkers administered a brief questionnaire, which included age, gender,
4 154 population group, and measured anthropometry and blood pressure. Standard anthropometric
5 155 methods were used to measure weight, height, and WC¹⁷. Body weight (nearest 0.1 kg) was
6 156 measured with a calibrated Omron digital scale, with the participant in light clothing and without
7 157 shoes. A stadiometer was used to measure the participant height (nearest cm), with the participant
8 158 standing in an upright position, on a flat surface. Waist circumference was measured using a non-
9 159 elastic tape measure at the level of the umbilicus. Blood pressure measurements were taken in a
10 160 seated position after five minutes of rest. The systolic and diastolic blood pressures (SBP and DBP,
11 161 respectively) were recorded three times at 2-min intervals, using an appropriately sized cuff and
12 162 an automated blood pressure monitor (Omron 711, Omron Health Care, Hamburg, Germany). An
13 163 average of the last two readings was used in the analyses.
14 164

15 165 **Clinic-based assessments of high-risk participants**

16 166 Participants deemed at high-risk, based on the ADRS, were invited for further clinical and
17 167 biochemical assessments. At the clinic, trained fieldworkers administered questionnaires to obtain
18 168 information on participant sociodemographic and personal and family medical history.
19 169 Anthropometric and blood pressure measurements were repeated using standardized techniques as
20 170 described above.
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22 172 As per the World Health Organization's (WHO) guidelines¹⁸, blood samples were collected after
23 173 a 10-hour overnight fast by a qualified nurse for the oral glucose tolerance test (OGTT). Following
24 174 the administration of 75 g anhydrous glucose dissolved in 250 ml, blood samples were taken two
25 175 hours later. Biochemical analyses were conducted at an ISO accredited laboratory (PathCare
26 176 Laboratories, Cape Town, SA). Plasma glucose was determined by the glucose oxidase method
27 177 (Glucose Analyzer 2, Beckman Instruments, Fullerton, CA, USA), serum insulin, determined by
28 178 a Microparticle Enzyme Immunoassay (AxSym Insulin Kit, Abbot, IL, USA) and glycated
29 179 haemoglobin (HbA1c) was analysed with high-performance liquid chromatography (Biorad
30 180 Variant Turbo, BioRad, Johannesburg, SA). Vitamin D (25(OH)D3) was measured using liquid
31 181 chromatography mass spectrometry and enzymatic colorimetric methods were used to measure
32 182 serum calcium, phosphate, aspartate aminotransferase (AST), alanine aminotransferase (ALT),
33 183 and gamma-glutamyl transferase (GGT). Full blood counts, including total red blood cells (RBC),
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184 total white blood cells (WBC), haemoglobin, haematocrit, and platelets were measured on a
185 Coulter LH 750 haematology analyser (Beckman Coulter, South Africa).

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187 For the current study, we utilized the blood and urine samples in the SA-DPP biobank to conduct
188 secondary laboratory analyses. To determine the levels of serum and urinary creatinine, the
189 modified Jaffe-Kinetic method (calibrated to isotope dilution mass spectrometry standards)
190 (Beckman AU, Beckman Coulter, SA) was used, and the colorimetric (using bromocresol purple)
191 method (Beckman AU, Beckman Coulter, SA) was used to determine the level of urine albumin.

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193 **Classification of kidney function and co-morbidities**

194 Kidney function was estimated using the serum creatinine-based CKD Epidemiology
195 Collaboration 2009 (CKD-EPI) equation¹⁹, with the race correction factor omitted. CKD was
196 defined as an estimated glomerular filtration rate (eGFR) of <60 ml/min/1.73 m² and/or urinary
197 albumin-to-creatinine ratio (uACR) >3 mg/mmol. CKD staging was based on the Kidney Disease
198 Improving Global Outcomes (KDIGO) guidelines²⁰ as, stage 1 (eGFR ≥ 90 ml/min/1.73m² and
199 uACR >3 mg/mmol), stage 2 (eGFR 60–89 ml/min/1.73m² and uACR >3 mg/mmol) and stage 3
200 (eGFR <60 ml/min/1.73m²). Albuminuria (stage 2) was defined as uACR between 3 and 30
201 mg/mmol and albuminuria (stage 3) as >30 mg/mmol²¹.

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203 Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared
204 (kg/m²). This was categorised as normal weight (BMI ≤ 24.9 kg/m²), overweight (BMI 25.0–29.9
205 kg/m²) and obese (BMI ≥ 30 kg/m²). Hypertension was defined as SBP ≥ 140 mmHg and/or DBP
206 ≥ 90 mmHg,²² or taking anti-hypertensive medications. We further categorized our study
207 participants into four groups related to the level of blood pressure control, namely, 1) normotensive
208 (defined as no use of anti-hypertensive medication and SBP/DBP $<140/90$ mmHg), 2) treated and
209 controlled blood pressure (defined as use of anti-hypertensive medication and SBP/DBP
210 $<140/90$ mmHg), 3) treated but uncontrolled blood pressure (defined as use of anti-hypertensive
211 medication but SBP/DBP $\geq 140/90$ mmHg), 4) newly detected hypertension (defined as no use of
212 anti-hypertensive medication and SBP/DBP $\geq 140/90$ mmHg). Normal and dysglycaemia
213 categories, based on the OGTT, were defined according to WHO criteria¹⁸ as: (1) normal glucose
214 tolerance [fasting glucose (FG) <6.1 mmol/L and 2-h glucose <7.8 mmol/L]; or (2) prediabetes

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3 215 including impaired FG (IFG) [$6.1 \leq \text{FG} < 7.0$ mmol/L and 2-h glucose < 7.8 mmol/L], impaired
4 216 glucose tolerance (IGT) [$\text{FG} < 7.0$ mmol/L and $7.8 \leq 2\text{-h glucose} < 11.1$ mmol/L]; and (3) T2DM
5 217 ($\text{FG} \geq 7.0$ mmol/L and/or 2-h glucose ≥ 11.1 mmol/L). High GGT was defined as levels > 38 IU/L,
6 218 and based on the laboratory (PathCare, South Africa) reference standards. Liver fibrosis was
7 219 classified based on the fibrosis-4 (FIB-4) index, where FIB-4 index was calculated using the
8 220 formula: $[\text{age (years)} \times \text{AST (IU/L)}] / [\text{platelet (} 10^9/\text{L)} \times \sqrt{\text{ALT (IU/L)}}]^{23}$. Low risk for advanced
9 221 fibrosis was defined a FIB-4 score < 1.30 , intermediate risk as a value between 1.30 and 2.67, and
10 222 high risk as FIB-4 > 2.67 ²⁴. Anaemia was defined using the National Kidney Foundation Kidney
11 223 Disease Outcome Quality Initiative (K/DOQI) guidelines as haemoglobin level < 13.5 g/dL for
12 224 men and < 12 g/dL for women²⁵.

205

226 **Statistical analysis**

227 The SA-DPP sample size was calculated based on the following assumptions, 1) a cumulative
228 incident diabetes rate of 13.6% at 2–3 years, as observed in our Bellville South cohort²⁶, 2) an
229 expected relative risk of 0.51, which is the pooled effect estimate of efficacy trials comparing
230 lifestyle intervention to usual care in diabetes prevention studies²⁷, 3) an intra-cluster correlation
231 coefficient for fasting glucose of 0.02²⁸, 4) a significance level of 5% with a type II error risk of
232 20%, and 5) an estimated 36-months loss to follow-up of 20–25%.

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234 Due to the non-Gaussian distribution of most variables, the participant characteristics were
235 summarised as median (25th-75th percentile) or counts and percentages. Group comparisons were
236 analysed by chi-square tests, Wilcoxon rank-sum and Kruskal-Wallis tests. The Dunn's test was
237 used as nonparametric pairwise multiple-comparison post-hoc test when the Kruskal-Wallis test
238 was rejected. The age-standardized prevalence of CKD was calculated using the standard world
239 population distribution as projected by the WHO for 2000–2025²⁹. All statistical analyses were
240 performed using STATA version 17 (Statcorp, College Station, TX) and statistical significance
241 was based on a p-value < 0.05 .

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243 **Patient and public involvement:** Participants and/or the public were not involved in the design,
244 or conduct, or reporting or dissemination plans of this research.

245

246 RESULTS

247 Of the 2,173 individuals screened in the community, 690 participants, deemed at high-risk of
248 T2DM based on the ADRS, presented at our research clinic for an OGTT and other assessments
249 (Supplementary File). The sociodemographic, clinical, and biochemical characteristics are
250 summarised by CKD status in Table 1. Among the 690 participants included in this study, 80.9%
251 were female, with a group median age of 52 years. Of these participants, 9.6% had screen-detected
252 T2DM and 18.1% had CKD (crude estimate), with 2.2% presenting with both CKD and T2DM.
253 The age-adjusted prevalence of CKD was lower, at 14.6%. Furthermore, there were high rates of
254 obesity (77.1%), hypertension (55.0%), raised GGT levels (45.8%), intermediate risk of advanced
255 liver fibrosis (21.4%) and anaemia (14.2%) among participants in this study. There were no
256 significant differences in the sociodemographic and anthropometric variables between participants
257 with and without CKD. However, SBP (128.0 vs. 123.5 mmHg; $p=0.004$) and DBP (86.0 vs. 83.0
258 mmHg; $p=0.014$) were higher in participants with CKD compared to those without. Although
259 hypertension prevalence was not significantly different by CKD status ($p=0.215$), uncontrolled
260 hypertension on treatment was significantly higher in those with than without CKD (42.7% vs.
261 23.4%). The median levels of GGT (47.0 vs. 35.0 IU/L; $p=0.008$), AST (26.0 vs. 23.0 IU/L;
262 $p=0.004$), and FIB-4 index (1.0 vs. 0.9; $p=0.016$), were higher in participants with CKD compared
263 to those without CKD, while RBC count (4.5 vs. $4.6 \times 10^{12}/L$; $p=0.046$) was lower in CKD compared
264 to those with normal kidney function. The prevalence of high GGT ($p=0.008$) and anaemia
265 ($p=0.042$) were significantly higher in participants with CKD compared to those without CKD.
266 All other biochemical variable were similar between groups.

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277 **Table 1:** Sociodemographic, clinical, and biochemical characteristics presented in the overall sample and by CKD status

Sociodemographic variables	Total (n=690)	Without CKD (n=565)	CKD (n=125)	p-value
Age (years)	52 (45-59)	52 (45-59)	53 (45-60)	0.241
Gender (n,% female)	558 (80.9)	460 (81.4)	98 (78.4)	0.438
African Diabetes Risk Score	2.3 (1.7-3.4)	2.3 (1.7-3.4)	2.4 (1.7-3.4)	0.882
Anthropometry				
Weight (kg)	91.0 (79.6-103.6)	92.2 (80.4-104.6)	88.0 (76.2-101.3)	0.050
Waist circumference (cm)	102.7 (95.3-111.1)	103.4 (95.7-111.1)	101.3 (93.4-111.1)	0.242
Hip circumference (cm) (n=632)	112.6 (103.2-121.7)	113.0 (104.3-122.4)	111.3 (101.1-118.3)	0.067
Body mass index (kg/m ²)	35.6 (30.5-40.5)	35.7 (30.6-40.6)	33.9 (29.4-39.9)	0.185
Body mass index categories (n, %)				0.316
Normal	29 (4.2)	23 (4.1)	6 (4.8)	
Overweight	129 (18.7)	100 (17.7)	29 (23.2)	
Obese	532 (77.1)	442 (78.2)	90 (72.0)	
Blood pressure				
Systolic blood pressure (mmHg)	124.5 (113.5-137.0)	123.5 (113.5-135.0)	128.0 (116.0-145.5)	0.004
Diastolic blood pressure (mmHg)	83.0 (77.0-91.5)	83.0 (77.0-90.3)	86.0 (78.5-94.5)	0.014
Hypertension	379 (55.0)	304 (53.9)	75 (60.0)	0.215
Among participants with hypertension (n=379):				<0.0001
Treated and controlled BP	143 (37.7)	127 (41.8)	16 (21.3)	
Treated and uncontrolled BP	103 (27.2)	71 (23.4)	32 (42.7)	
Screen-detected HPT	133 (35.1)	106 (34.9)	27 (36.0)	
Biochemical				
Fasting blood glucose (mmol/L)	5.0 (4.6-5.5)	5.0 (4.6-5.5)	5.0 (4.6-5.6)	0.691
2-hour glucose (mmol/L) (n=688)	6.0 (4.9-7.4)	6.0 (4.9-7.3)	6.3 (5.1-7.6)	0.205
Glucose categories (n, %) (n=688)				0.600
Normoglycaemia	520 (75.6)	428 (76.0)	92 (73.6)	
Prediabetes (IFG/IGT)	102 (14.8)	84 (14.9)	18 (14.4)	
Type 2 diabetes	66 (9.6)	51 (9.1)	15 (12.0)	
HbA1c (%) (n=685)	5.8 (5.6-6.1)	5.8 (5.6-6.1)	5.9 (5.6-6.2)	0.740
Fasting insulin (IU/L)	8.8 (6.2-12.6)	8.5 (5.9-12.1)	11.1 (7.1-14.8)	0.144

Vitamin D (ng/mL)	6.1 (5.0-7.8)	6.0 (5.0-7.7)	6.2 (5.0-8.1)	0.222
Calcium (mmol/L) (n=688)	2.3 (2.3-2.4)	2.3 (2.3-2.4)	2.4 (2.3-2.4)	0.644
Phosphate (mmol/L) (n=688)	1.1 (1.0-1.2)	1.1 (1.0-1.2)	1.1 (1.0-1.2)	0.981
Gamma-glutamyl transferase (IU/L) (n=688)	36.0 (24.0-61.0)	35.0 (24.0-55.0)	47.0 (26.0-78.0)	0.008
High gamma-glutamyl transferase (n=688)	315 (45.8)	245 (43.4)	70 (6.5)	0.008
Aspartate aminotransferase (IU/L) (n=688)	24.0 (20.0-29.0)	23.0 (20.0-29.0)	26.0 (21.0-34.0)	0.004
Alanine aminotransferase (IU/L) (n=646)	22.0 (16.0-32.0)	22.0 (16.0-32.0)	22.0 (17.0-33.0)	0.372
AST/ALT ratio	1.1 (0.9-1.4)	1.1 (0.9-1.4)	1.2 (0.9-1.5)	0.110
Fibrosis-4 index (n=644)	0.9 (0.7-1.3)	0.9 (0.7-1.3)	1.0 (0.8-1.4)	0.016
Liver fibrosis (n, %)				0.065
No risk	497 (77.2)	413 (78.4)	84 (7.8)	
Intermediate risk	138 (21.4)	109 (20.7)	29 (2.8)	
High risk	9 (1.4)	5 (0.9)	4 (0.4)	
Red blood cells (x10 ¹² /L)	4.6 (4.2-4.9)	4.6 (4.3-4.9)	4.5 (4.2-4.8)	0.046
White blood cells (x10 ⁹ /L)	23.0 (18.0-28.0)	23.0 (18.3-28.0)	23.0 (17.0-28.0)	0.270
Platelet count (x10 ⁹ /L)	276 (235-325)	276.0 (234.5-322.5)	276.0 (233.0-333.0)	0.705
Haematocrit (volume %)	0.4 (0.4-0.4)	0.4 (0.4-0.4)	0.4 (0.4-0.4)	0.442
Haemoglobin (g/dL)	13.5 (12.6-14.3)	13.5 (12.7-14.3)	13.4 (12.4-14.4)	0.491
Anaemia, n (%)	103 (14.9)	77 (13.6)	26 (2.8)	0.042

Data is presented as median (25th-75th percentiles) or count and percentages. Abbreviations: CKD, chronic kidney disease; BP, blood pressure; HPT, hypertension; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; HbA1c, glycated haemoglobin; AST/ALT ratio, aspartate aminotransferase to alanine aminotransferase ratio.

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3 285 The prevalence of CKD in the overall sample and grouped by glucose and blood pressure
4 286 categories are shown in Figure 1. In those with prediabetes, T2DM, and hypertension, 17.6%,
5 287 22.7% and 19.8% had CKD, respectively. Of the participants with hypertension, the prevalence of
6 288 CKD was highest in those on anti-hypertensive treatment but with uncontrolled blood pressure
7 289 (31.1%), while 20.3% of those newly identified with hypertension and 11.2% of those on treatment
8 290 with controlled blood pressure had CKD.
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11 292 **Figure 1 to be included here**

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13 294 The stages of CKD according to eGFR and albuminuria following KDIGO classification are
14 295 presented in Figure 2. Of the 11 participants with an eGFR <60 ml/min/1.73m², four (36.4%) had
15 296 no albuminuria, with 36.4% (n=4) and 27.3% (n=3) presenting with moderate (uACR: 3-
16 297 30mg/mmol) and severe albuminuria (uACR: >30mg/mmol), respectively. Furthermore, of the
17 298 those with normal kidney function (eGFR ≥90 ml/min/1.73m²), 67 (10.2%) and 25 (3.8%) had
18 299 moderate and severe albuminuria, respectively.
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21 301 **Figure 2 to be included here**

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23 303 Table 2 describes the participant characteristics by CKD stage. The majority of individuals with
24 304 CKD presented with stage 1 CKD (73.6%), with 17.6% and 8.8% presenting with stage 2 and 3,
25 305 respectively. Participants with stage 3 CKD were older than those with normal kidney function
26 306 and stage 1 CKD (p=0.030 for both). Levels of AST were significantly higher with stage 2 CKD
27 307 compared with stage 3 CKD (p=0.042). SBP and DBP did not differ by stages of CKD but differed
28 308 between those with normal kidney function and those with CKD as follows: normal kidney
29 309 function vs. CKD stage 1 (SBP: p=0.007 and DBP: p=0.010), stage 2 (SBP: p=0.039) and stage 3
30 310 (DBP: p=0.013).
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316 **Table 2:** Sociodemographic, clinical, and biochemical characteristics in participants by CKD stages

Sociodemographic variables	No CKD (n=565)	Stage 1 (n=92)	Stage 2 (n=22)	Stage 3 (n=11)	p-value
Age (years)	52 (45-59)*	52 (45-59)*	56 (51-61)	57 (52-63)	0.029
Gender (n,% female)	460 (81.4)	75 (81.5)	15 (68.2)	8 (72.7)	0.408
African Diabetes Risk Score	2.3 (1.7-3.4)	2.4 (1.8-3.1)	2.2 (1.7-4.8)	2.8 (1.9-3.9)	0.865
Kidney function					
Serum creatinine (µmol/L)	57.0 (48.0-67.0)	54.0 (46.5-62.0)	78.5 (72.0-88.0)	122.0 (96.0-160.0)	0.0001
eGFR (ml/min/1.73m ²)	103.0 (95.0-114.0)	106.0 (98.0-117.5)	79.5 (75.0-83.0)	49.0 (32.0-57.0)	0.0001
uACR (mg/mmol)	0.6 (0.4-1.0)	6.0 (4.1-14.1)	6.5 (3.6-17.3)	3.9 (0.8-43.2)	0.0001
Anthropometry					
Weight (kg)	92.2 (80.4-104.6)	89.1 (77.8-101.7)	84.4 (70.6-95.3)	78.7 (63.2-102.4)	0.117
Waist circumference (cm)	103.4 (95.7-111.1)	101.6 (93.9-111.4)	97.2 (93.1-109.7)	100.6 (93.4-107.0)	0.497
Hip circumference (cm) (n=632)	113.0 (104.3-122.4)	112.7 (102.3-120.9)	110.4 (99.4-117.9)	108.6 (96.4-108.9)	0.085
BMI (kg/m ²)	35.7 (30.6-40.6)	34.7 (30.5-40.7)	31.6 (26.9-39.5)	31.9 (27.2-36.9)	0.121
BMI categories (n, %)					0.039
Normal	23 (4.1)	2 (2.2)	2 (9.1)	2 (18.2)	
Overweight	100 (17.7)	19 (20.7)	8 (36.4)	2 (18.2)	
Obese	442 (78.2)	71 (77.2)	12 (54.5)	7 (63.6)	
Blood pressure					
SBP (mmHg)	123.5 (113.5-135.0)	129.5 (115.0-145.5)**	126.5 (123.5-153.0)***	127.5 (106.5-156.0)	0.031
DBP (mmHg)	83.0 (77.0-90.3)	86.5 (78.3-94.0)#	80.8 (75.0-94.5)	90.5 (82.5-105.5)##	0.017
Hypertension	304 (53.9)	54 (58.7)	12 (54.5)	9 (81.8)	0.263
Among participants with hypertension (n=379):					0.010
Treated and controlled BP	127 (41.8)	10 (18.5)	3 (25.0)	3 (33.3)	
Treated and uncontrolled BP	71 (23.4)	23 (42.6)	5 (41.7)	4 (44.4)	
Screen-detected HPT	106 (34.9)	21 (38.9)	4 (33.3)	2 (22.2)	
Biochemical					
FBG (mmol/L)	5.0 (4.6-5.5)	5.0 (4.6-5.6)	4.9 (4.4-5.6)	4.8 (4.7-5.3)	0.886
2-hour glucose (mmol/L) (n=688)	6.0 (4.9-7.3)	6.3 (5.1-7.6)	6.3 (4.7-8.5)	6.4 (5.6-7.2)	0.624
Glucose categories (n, %) (n=688)					0.543
Normoglycaemia	428 (76.0)	70 (76.0)	13 (59.1)	9 (81.8)	

Prediabetes (IFG/IGT)	84 (14.9)	11 (12.0)	6 (27.3)	1 (9.1)	
Type 2 diabetes	51 (9.1)	11 (12.0)	3 (13.6)	1 (9.1)	
HbA1c (%) (n=685)	5.8 (5.6-6.1)	5.9 (5.6-6.2)	5.7 (5.3-6.2)	5.7 (5.6-6.2)	0.591
Fasting insulin (IU/L)	8.5 (5.9-12.1)	11.1 (6.4-15.5)	11.0 (8.7-13.2)	-	0.334
Vitamin D (ng/mL)	6.0 (5.0-7.7)	6.2 (5.0-7.8)	6.7 (5.9-8.1)	6.8 (5.2-10.6)	0.361
Calcium (mmol/L) (n=688)	2.3 (2.3-2.4)	2.3 (2.3-2.4)	2.4 (2.3-2.4)	2.3 (2.3-2.4)	0.794
Phosphate (mmol/L) (n=688)	1.1 (1.0-1.2)	1.1 (1.0-1.2)	1.1 (1.0-1.2)	1.2 (0.9-1.3)	0.777
GGT (IU/L) (n=688)	35.0 (24.0-55.0)	45.0 (26.0-81.0)	46.5 (25.0-64.0)	49.0 (24.0-122.0)	0.071
High GGT (n=688)	245 (43.4)	51 (56.0)	13 (59.1)	6 (54.5)	0.071
AST (IU/L) (n=688)	23.0 (20.0-29.0)	26.0 (21.1-34.0)	26.5 (22.0-34.0)###	21.0 (20.0-28.0)	0.009
ALT (IU/L) (n=646)	22.0 (16.0-32.0)	23.0 (17.0-33.0)	21.0 (18.0-31.0)	18.5 (15.5-37.5)	0.799
AST/ALT ratio	1.1 (0.9-1.4)	1.2 (0.9-1.5)	1.3 (1.1-1.4)	1.3 (0.9-1.5)	0.413
Fibrosis-4 index (n=644)	0.9 (0.7-1.3)	1.0 (0.8-1.3)	1.1 (0.9-1.5)	1.3 (0.7-1.6)	0.063
Liver fibrosis (n, %)					0.124
No risk	413 (78.4)	66 (75.0)	14 (66.7)	4 (50.0)	
Intermediate risk	109 (20.7)	19 (21.6)	6 (28.6)	4 (50.0)	
High risk	5 (0.9)	3 (3.4)	1 (4.8)	0 (0)	
Red blood cells (x10 ¹² /L)	4.6 (4.3-4.9)	4.5 (4.2-4.9)	4.5 (4.2-4.6)	4.7 (4.5-5.1)	0.071
White blood cells (x10 ⁹ /L)	23.0 (18.3-28.0)	22.0 (17.0-28.0)	26.0 (16.0-31.9)	25.0 (19.0-26.0)	0.550
Platelet count (x10 ⁹ /L)	276.0 (234.5-322.5)	276.5 (235.0-333.5)	271.0 (244.0-335.0)	261.0 (217.0-325.0)	0.956
Haematocrit (volume %)	0.4 (0.4-0.4)	0.4 (0.4-0.4)	0.4 (0.4-0.4)	0.4 (0.4-0.5)	0.433
Haemoglobin (g/dL)	13.5 (12.7-14.3)	13.3 (12.3-14.5)	13.5 (13.3-14.4)	13.7 (12.9-15.8)	0.390
Anaemia, n (%)	77 (13.6)	22 (23.9)	2 (9.1)	2 (18.2)	0.063

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318 Data is presented as median (25th-75th percentiles) or count and percentages. Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; uACR, urinary albumin-to-creatinine ratio; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; HbA1c, glycated haemoglobin; GGT, gamma-glutamyl transferase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; eGFR, estimated glomerular filtration rate; uACR, urinary albumin-to-creatinine ratio. Keys: *p=0.030 (CKD stage vs. no CKD; CKD stage

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3 323 3 vs. CKD stage 1); **p=0.007 (no CKD vs. CKD stage 1); ***p=0.039 (no CKD vs. CKD stage 2); #p=0.010 (no CKD vs. CKD stage
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5 324 1); ##p=0.013 (no CKD vs. CKD stage 3); ###p=0.042 (CKD stage 3 vs. CKD stage 2).
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For peer review only

340 DISCUSSION

341 To our knowledge, this is the first study to show that by utilizing an opportunistic approach, CKD
342 can be detected early, allowing for timely referral for specialized testing to confirm diagnosis and
343 subsequent care. This was achieved through leveraging the information already collected in an
344 existing screening programme that targeted individuals at high-risk for T2DM and included a few
345 additional kidney-related biochemical markers to the variables for testing. The yield of screen-
346 detected cases was high for a low investment which cost ZAR 237.80 (USD 14.59) per person and
347 highlights the potential cost-effectiveness of such a strategy.

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349 By including a minimal number of markers of kidney function (namely serum and urinary
350 creatinine, and urinary albumin) to the scope of markers already collected, we found that 18.1%
351 of those at high-risk for developing T2DM had CKD with the majority (73.6%) having mild CKD
352 (CKD stage 1). The CKD burden, at 22.7%, was even higher in participants with newly diagnosed
353 T2DM, which underscores the need for frequent screening of individuals at high-risk for T2DM
354 to avoid T2DM presenting with complications at diagnosis. Therefore, using T2DM as a gateway
355 for CKD screening through existing screening programmes is justified as such an approach,
356 together with diagnosing new T2DM, simultaneously identified those with complications i.e.,
357 CKD. The newly diagnosed T2DM may receive comprehensive care with tight control of both
358 their T2DM and CKD. This intensification of treatment could contribute to a delay in CKD
359 progression and consequently help reduce the risk of developing end-stage kidney disease (ESKD)
360 or CVD-related complications³⁰. Further support for CKD screening in individuals at high-risk
361 for T2DM was the substantial CKD burden in prediabetes (17.6%). Notably, if screening for CKD
362 was initiated only after the development of T2DM, the identification of CKD in individuals with
363 prediabetes, which generally fall below the threshold for disease management in clinical practice,
364 would have been missed. This would then have been a lost opportunity to identify and manage
365 CKD early and delay progression of the disease in this high-risk group.

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367 Our study also highlights the importance of screening for albuminuria as 91.2% of those with CKD
368 would have gone undetected if CKD were based on eGFR alone. Guidelines recommend
369 albuminuria testing using ACR, like we did in our study, however this is not always possible in
370 many low-resource settings. In these instances, low-cost semiquantitative methods, like urinary

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3 371 dipsticks, can be used to measure albuminuria with subsequent confirmation of positive dipstick
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5 372 result with a quantitative laboratory test to confirm CKD diagnosis ²⁰. Or repeated dipstick
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7 373 assessments can be employed to reduce the possibility of false-negative results as this could delay
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9 374 the timely diagnosis and management of CKD.

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12 376 Given that this is the first study to report the prevalence of CKD in people at high-risk for
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14 377 developing T2DM, based on the ADRS, the prevalence estimates cannot be directly compared to
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16 378 other studies as no similar data have been published. Nevertheless, at a similar median age (52 vs.
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18 379 53 years), the prevalence of CKD in those with prediabetes in our study was comparable to that
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20 380 reported in a large representative sample in the United States of America (17.6% vs. 17.7%,
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22 381 respectively) ³¹. Also, albeit an older population (median age of 68 years) with a higher prevalence
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24 382 of advanced CKD (stage 3-5), a South African study found that the prevalence of CKD in those
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26 383 with prediabetes was 19.8% ³². The similarly high CKD prevalence in prediabetes across several
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28 384 studies suggests that perhaps there should be regular CKD screening for all individuals with
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30 385 prediabetes.

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33 387 A likely contributor to the substantial CKD burden in this study is the high prevalence of
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35 388 hypertension, which at 55% is higher than the 44%-46% reported for South Africa ³³. While the
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37 389 high reported prevalence of hypertension is consequent to the score used to identify high-risk
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39 390 individuals, a larger proportion of the participants with hypertension had CKD compared to those
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41 391 with normal blood pressure (19.8% vs. 16.1%, respectively). The prevalence of CKD may be
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43 392 related to the delayed detection of hypertension or the suboptimal control of blood pressure in
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45 393 treated hypertension, as reported in the current study and in several South African studies ^{33, 34}.
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47 394 Indeed, a high proportion of participants with treated but uncontrolled hypertension had CKD
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49 395 (31.1%) in this study as did participants with newly detected hypertension (20.3%). This further
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51 396 highlights the benefit of screening high-risk individuals for CKD. Notably, adequate blood
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53 397 pressure control is fundamental to slowing the progression of CKD ^{35, 36} and timeous treatment
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55 398 with anti-hypertensive medication can improve both kidney and cardiovascular outcomes ^{37, 38}
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57 399 thereby preventing the progression to ESKD and reducing the risk of all-cause and cardiovascular
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59 400 mortality ^{37, 39, 40}.

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3 402 Elevated GGT and the FIB-4 index, which are commonly used markers of liver injury and non-
4 403 alcoholic fatty liver disease (NAFLD) ⁴¹, have been linked to increased CKD risk in various
5 404 populations ⁴²⁻⁴⁵. In our study, 56.5% of the participants with CKD presented with higher-than-
6 405 normal GGT levels, compared to 43.4% of participants without CKD. Also, a significant
7 406 proportion of people with CKD presented with intermediate and high risk for advanced liver
8 407 fibrosis, based on the FIB-4 index, compared to those without CKD (28.2% vs. 21.6%). Early
9 408 recognition and interventions directed at reducing the risk of liver injury among individuals with
10 409 CKD could reduce CKD progression.
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19 411 Anaemia was prevalent in our study population (14.9% of total sample), with nearly twice as many
20 412 participants with CKD having anaemia compared to those without CKD, as shown in other studies
21 413 as well ^{46, 47}. Although the overall prevalence of anaemia in this study was not uncommon for
22 414 South Africa ⁴⁸, the prevalence in participants with CKD is concerning. While erythropoiesis
23 415 stimulating agents and iron supplementation to treat anaemia are unlikely to be prescribed to
24 416 people in the early stages of CKD, anaemia can accelerate the decline in kidney function by
25 417 causing kidney haemodynamic alterations and tissue hypoxia ⁸. It is strongly predictive of all-
26 418 cause and cardiovascular mortality ^{49, 50}, and should thus be closely monitored.
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34 420 Although lifestyle interventions addressing unhealthy diets, physical inactivity, tobacco smoking
35 421 and alcohol misuse are advocated to reduce the growing global burden of non-communicable
36 422 diseases ^{51, 52}, little is known about the impact of reducing unhealthy lifestyle behaviours on kidney
37 423 health. The SA-DPP intervention, implemented in individuals with prediabetes, will provide a
38 424 unique opportunity to examine the effects of improving lifestyle behaviours on changes in CKD
39 425 status.
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46 427 This is the first study to show that utilizing an opportunistic approach, through leveraging the
47 428 information already collected in an existing screening programme is advantageous to screen for
48 429 CKD. However, our study does have limitations. The SA-DPP study included participants at high-
49 430 risk of T2DM and our findings might not be reproducible across other non-communicable diseases
50 431 screening programmes. The small number of participants identified with CKD in this study
51 432 reduced the statistical power of our analyses when stratifying by CKD stage. Based on the self-
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3 433 selection approaches used to recruit participants, the disproportionate greater number of females,
4 434 the varying socioeconomic status, lifestyle behaviours and disease prevalence (hypertension and
5 435 T2DM) across provinces and by urban-rural residence in South Africa³³, our study findings cannot
6
7 436 be generalised. Another limitation is that CKD was defined based on a single time-point serum
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9 437 and urinary creatinine and albumin assessment and not on repeated measurements, at least three
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11 438 months apart, as per KDIGO guidelines²⁰. However, a strength of our study is that both eGFR and
12
13 439 albuminuria were used to define CKD, unlike most other population-based CKD prevalence
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15 440 studies in South Africa and Africa in general which rely on eGFR only for CKD classification.
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17 441 Finally, as for all studies using eGFR to characterize CKD, instead of the gold standard of
18
19 442 measured GFR, the over- or under-estimation of the estimate cannot be excluded.
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22 444 **CONCLUSION**

23
24 445 The fact that almost one in five participants identified as high-risk for T2DM had CKD underscores
25
26 446 the value of including markers of kidney function in existing disease screening programmes. Our
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28 447 findings provide support for key stakeholders and policy makers to adapt current strategies for
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30 448 hypertension and T2DM screening to include screening for CKD. Indeed, by utilizing an
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32 449 opportunistic approach to screen high-risk individuals, those with early-stage CKD can be
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34 450 identified and appropriately managed to reduce disease progression. Existing cardiovascular or
35
36 451 non-communicable disease screening programmes should perhaps explore including markers for
37
38 452 CKD evaluations to maximise limited resources without compromising on effectiveness.
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40 453

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49
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51
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5 465 **Competing interest:** No competing interest to declare

6 466
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8 467 **Patient consent for publication:** Not required

9 468
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11 469 **Ethics approval:** Ethical clearance was obtained by the Research Ethics Committee of the South
12 African Medical Research Council (SAMRC) (approval no. EC018-7/2015).
13 470
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15 472 **Data availability statement:** The dataset depicted in this manuscript are available from the
16 corresponding author on reasonable request.
17 473
18 474

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493 **Figure legends**

494 **Figure 1:** Prevalence (%) of chronic kidney disease overall and by glucose and blood pressure
495 categories. Data presented as percentages. Abbreviations: T2DM, type 2 diabetes mellitus; HPT,
496 hypertension; BP, blood pressure

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498 **Figure 2:** Stages of chronic kidney disease according to estimated glomerular filtration rate and
499 albuminuria following Kidney Disease Improving Global Outcomes (KDIGO) classification.
500 Displayed are number of patients (%) within each category. The colour code indicates risk category
501 according to KDIGO ²⁰: green "low risk", yellow "moderate risk", orange "high risk" and red "very
502 high risk"

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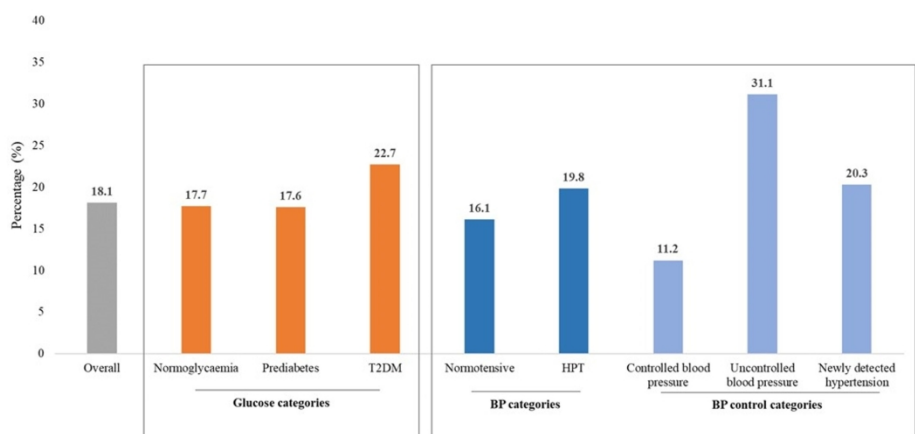


Figure 1: Prevalence (%) of chronic kidney disease overall and by glucose and blood pressure categories. Data presented as percentages. Abbreviations: T2DM, type 2 diabetes mellitus; HPT, hypertension; BP, blood pressure

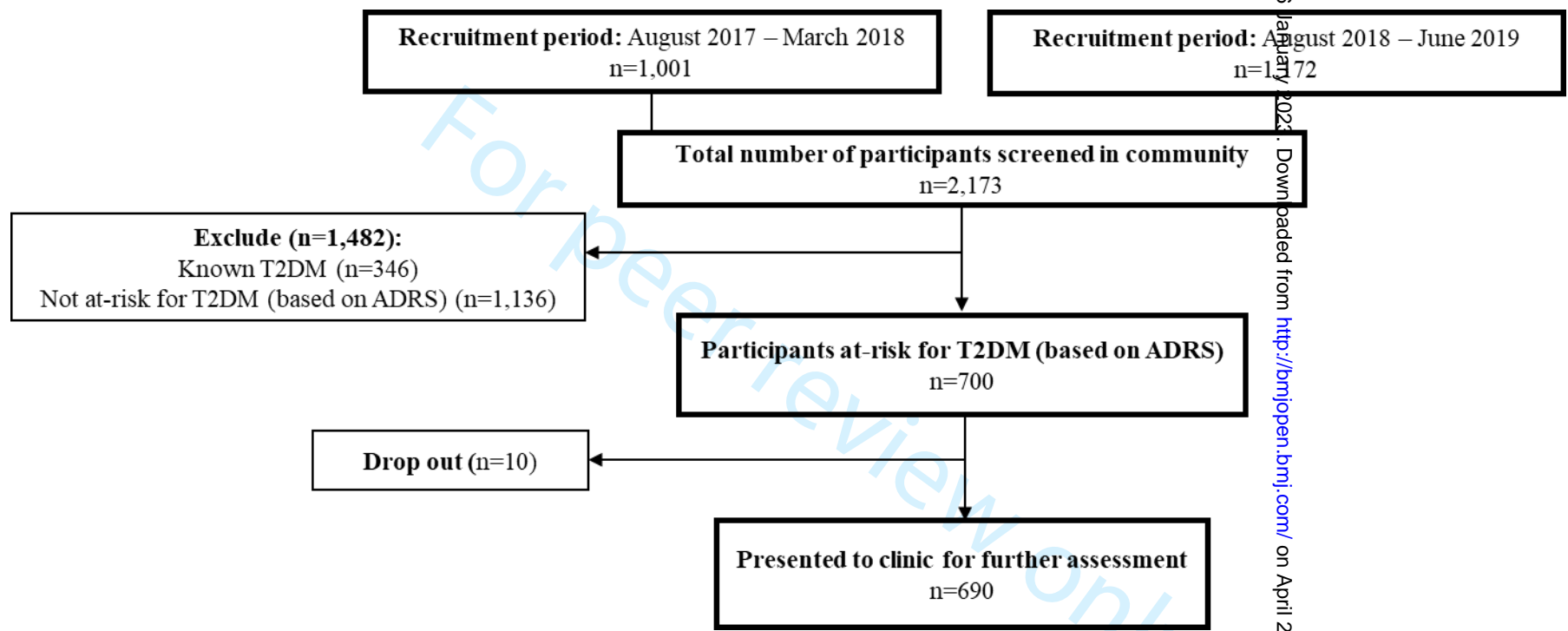
190x96mm (330 x 330 DPI)

CKD stages	eGFR (ml/min/1.73m ²)	Albuminuria			Total
		A1	A2	A3	
		(<3 mg/mmol)	(3-30 mg/mmol)	(>30 mg/mmol)	
G1	≥90	565 (86.0%)	67 (10.2%)	25 (3.8%)	657 (95.2%)
G2	60–89	0 (0%)	15 (68.2%)	7 (31.8%)	22 (3.2%)
G3 (a and b)	<60	4 (36.4%)	4 (36.4%)	3 (27.3%)	11 (1.6%)
Total		569 (82.5%)	86 (12.5%)	35 (5.1%)	690 (100%)

Figure 2: Stages of chronic kidney disease according to estimated glomerular filtration rate and albuminuria following Kidney Disease Improving Global Outcomes (KDIGO) classification. Displayed are number of patients (%) within each category. The colour code indicates risk category according to KDIGO 20: green "low risk", yellow "moderate risk", orange "high risk" and red "very high risk"

196x42mm (300 x 300 DPI)

Addendum A: Flow diagram of recruitment process over two phases



Abbreviations: T2DM, type 2 diabetes mellitus; ADRS, African Diabetes Risk Score

STROBE Statement—Checklist of items that should be included in reports of *cross-sectional studies*

	Item No	Recommendation	Page No
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-8
Bias	9	Describe any efforts to address potential sources of bias	NA
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	8
		(b) Describe any methods used to examine subgroups and interactions	8
		(c) Explain how missing data were addressed	8
		(d) If applicable, describe analytical methods taking account of sampling strategy	NA
		(e) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	Addendum A
		(c) Consider use of a flow diagram	Addendum A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	5-8

		(b) Indicate number of participants with missing data for each variable of interest	10-11 and 13-14
Outcome data	15*	Report numbers of outcome events or summary measures	10-11 and 13-14
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	NA
		(b) Report category boundaries when continuous variables were categorized	7-8
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	16
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	18-19
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	19
Generalisability	21	Discuss the generalisability (external validity) of the study results	19
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	19

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

LEVERAGING THE SOUTH AFRICAN DIABETES PREVENTION PROGRAMME TO SCREEN FOR CHRONIC KIDNEY DISEASE – AN OBSERVATIONAL STUDY

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1 LEVERAGING THE SOUTH AFRICAN DIABETES 2 PREVENTION PROGRAMME TO SCREEN FOR CHRONIC 3 KIDNEY DISEASE – AN OBSERVATIONAL STUDY

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16 Word count: 3,779

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18 Keywords: chronic kidney disease; screening; Africa

31 Abstract

32 **Objective:** To evaluate the viability of leveraging an existing screening programme (the South
33 African Diabetes Prevention Programme [SA-DPP]) to screen for chronic kidney disease (CKD),
34 by assessing the yield of CKD cases among those participating in the programme.

35 **Design:** Observational study conducted between 2017 and 2019.

36 **Setting:** 16 resource-poor communities in Cape Town, South Africa.

37 **Participants:** 690 participants, aged between 25 and 65 years, identified as at high-risk for type 2
38 diabetes mellitus (T2DM) by the African Diabetes Risk Score.

39 **Primary outcome measure:** The prevalence of CKD among those participating in the SA-DPP.

40 **Results:** Of the 2,173 individuals screened in the community, 690 participants underwent further
41 testing. Of these participants, 9.6% (n=66) and 18.1% (n=125) had screen-detected T2DM and
42 CKD (defined as an estimated glomerular filtration rate of <60 ml/min/1.73m² (eGFR) and/or
43 albumin-to-creatinine ratio >3 mg/mmol), respectively. Of those with CKD, 73.6% (n=92), 17.6%
44 (n=22) and 8.8% (n=11) presented with stages 1, 2 and 3, respectively. Of the participants with an
45 eGFR <60 ml/min/1.73m², 36.4% had no albuminuria, and of those with normal kidney function
46 (eGFR ≥ 90 ml/min/1.73m²), 10.2% and 3.8% had albuminuria stage 2 and 3, respectively. Of those
47 with T2DM and hypertension, 22.7% and 19.8% had CKD, respectively.

48 **Conclusion:** The fact that almost one in five participants identified as high-risk for T2DM had
49 CKD underscores the value of including markers of kidney function in an existing screening
50 programme. By utilizing an opportunistic approach to screen high-risk individuals, those with
51 CKD can be identified and appropriately treated to reduce disease progression.

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61 Strengths and limitations of this study

- 62 • The strength of our study is that both estimated glomerular filtration rate (eGFR) and
63 albuminuria were used to define CKD, unlike most other population-based CKD
64 prevalence studies in South Africa and Africa in general which rely on eGFR only.
- 65 • Due to the self-selection approach of recruitment and the disproportionate female
66 participation, our study findings may not be generalisable.
- 67 • The small proportion of participants with chronic kidney disease (CKD) in this study
68 resulted in reduced statistical power when analysis was stratifying by CKD stage.
- 69 • CKD was defined based on a single time-point serum and urinary creatinine and albumin
70 assessment and not on repeated measurements, at least three months apart, as per
71 guidelines.

91 INTRODUCTION

92 Chronic kidney disease (CKD) is a leading cause of morbidity and mortality globally ¹, affecting
93 more than 840 million individuals worldwide ². The increasing burden of CKD is demonstrated by
94 its ascent in ranking among the global causes of disability-adjusted life years (DALYs), rising
95 from 29th in 1990 to 18th in 2019 overall, and from 14th to 8th in the older aged groups (aged ≥ 50
96 years) ³. However, despite being a global problem, the prevalence of CKD is increasing most
97 rapidly in low-and-middle income countries (LMICs) where the burden of disease is more
98 pronounced ⁴. This is worrisome as the health care systems in most LMICs are already under
99 pressure, and options for kidney replacement therapy are not frequently available or affordable ⁵.
100 ⁶. Given the inequity in access to healthcare services, which disproportionately affects
101 disadvantaged populations, and the costs of kidney replacement therapies, early detection of CKD
102 followed by low-cost treatments should be encouraged ⁷.

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104 Early-stage CKD presents with no or non-specific symptoms and is commonly diagnosed
105 opportunistically from screening tests for other diseases, or when the disease has progressed, and
106 symptoms appear ⁸. Therefore, screening for CKD plays an important role in early detection, as
107 implementing treatment on diagnosis can slow the rate of kidney function loss and reduce
108 morbidity and mortality ^{9,10}. However, there is often a strong argument against community-based
109 CKD screening due to the potential harm arising from screening and the cost-implications of such
110 an undertaking. According to a recent study, community-based CKD screening is unlikely to be
111 effective or cost-effective anywhere in the world ¹¹. In contrast, community-based screening for
112 CKD risk factors like hypertension and type 2 diabetes mellitus (T2DM) are deemed effective.
113 Community-based screening programmes for hypertension and T2DM provide an opportunity to
114 incorporate screening for CKD. Certainly, using the screening of hypertension and T2DM, which
115 are common risk factors for CKD, as a gateway for CKD screening in clinical settings will involve
116 minimal additional costs. Furthermore, (1) the yield of screen-detected cases is likely to be high,
117 considering the high prevalence and incidence of CKD in the presence of these risk factors; (2)
118 awareness of the presence of CKD with hypertension or T2DM can prompt the intensification or
119 modification of treatments to enhance kidney protection and prevent CKD progression; and (3) a
120 large proportion of people with CKD likely have a combination of sub-optimal risk factors with
121 raised levels of blood pressure and/or glucose that fall below the threshold for disease

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3 122 classification. These individuals with prediabetes and/or prehypertension are not generally
4 123 targeted for CKD screening in routine practice but may already have CKD. The opportunistic
5 124 incorporation of CKD testing in hypertension or T2DM screening programmes can therefore
6 125 identify CKD that may otherwise be missed if only those with established hypertension or T2DM
7 126 are screened for the condition.
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13 128 The aim of this study was to evaluate the viability of CKD screening when incorporated into an
14 129 existing disease screening programme. The yield of CKD cases in the South African Diabetes
15 130 Prevention Programme (SA-DPP) was determined by assessing markers of kidney function (serum
16 131 and urinary creatinine levels and urinary albumin) among participants at high-risk for T2DM.
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22 133 **MATERIAL AND METHODS**

23 134 **Study population and setting**

24 135 The SA-DPP is a “real-world” randomised implementation trial, of a structured lifestyle
25 136 intervention programme, adapted from programmes previously shown to be effective in Finland
26 137 ¹², Australia ¹³, and India ¹⁴. The SA-DPP uses an open-labelled cluster randomized control design,
27 138 conducted across 16 resource-poor communities in Cape Town, South Africa. Participants were
28 139 recruited by self-selection approaches, by raising awareness of the study with flyers distributed in
29 140 the community or through local councillors’ offices, churches, and schools. Interested participants
30 141 were invited to pre-determined venues in their community for community-based risk screening.
31 142 In the current study, baseline data were obtained from black and mixed ancestry participants, aged
32 143 between 25 and 65 years, who were at high-risk for T2DM ¹⁵. The data included in this study was
33 144 collected between 2017 and 2019 and the details have been previously described ¹⁵. The study was
34 145 conducted in accordance with the Declaration of Helsinki and approved by the by the Research
35 146 Ethics Committee of the South African Medical Research Council (SAMRC) (approval no.
36 147 EC018-7/2015).
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50 149 **Community-based screening to identify high-risk individuals**

51 150 For the community-based risk screening, the African Diabetes Risk Score (ADRS) ¹⁶, which is a
52 151 validated African screening tool comprising non-laboratory-based variables including age, waist
53 152 circumference (WC) and the presence of hypertension, was used to identify adults at high-risk for

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3 153 T2DM. Trained fieldworkers administered a brief questionnaire, which included age, gender,
4 154 population group, and measured anthropometry and blood pressure. Standard anthropometric
5 155 methods were used to measure weight, height, and WC¹⁷. Body weight (nearest 0.1 kg) was
6 156 measured with a calibrated Omron digital scale, with the participant in light clothing and without
7 157 shoes. A stadiometer was used to measure the participant height (nearest cm), with the participant
8 158 standing in an upright position, on a flat surface. Waist circumference was measured using a non-
9 159 elastic tape measure at the level of the umbilicus. Blood pressure measurements were taken in a
10 160 seated position after five minutes of rest. The systolic and diastolic blood pressures (SBP and DBP,
11 161 respectively) were recorded three times at 2-min intervals, using an appropriately sized cuff and
12 162 an automated blood pressure monitor (Omron 711, Omron Health Care, Hamburg, Germany). An
13 163 average of the last two readings was used in the analyses.
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15 165 **Clinic-based assessments of high-risk participants**

16 166 Participants deemed at high-risk, based on the ADRS, were invited for further clinical and
17 167 biochemical assessments. At the clinic, trained fieldworkers administered questionnaires to obtain
18 168 information on participant sociodemographic and personal and family medical history.
19 169 Anthropometric and blood pressure measurements were repeated using standardized techniques as
20 170 described above.
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22 172 As per the World Health Organization's (WHO) guidelines¹⁸, blood samples were collected after
23 173 a 10-hour overnight fast by a qualified nurse for the oral glucose tolerance test (OGTT). Following
24 174 the administration of 75 g anhydrous glucose dissolved in 250 ml, blood samples were taken two
25 175 hours later. Biochemical analyses were conducted at an ISO accredited laboratory (PathCare
26 176 Laboratories, Cape Town, SA). Plasma glucose was determined by the glucose oxidase method
27 177 (Glucose Analyzer 2, Beckman Instruments, Fullerton, CA, USA), serum insulin, determined by
28 178 a Microparticle Enzyme Immunoassay (AxSym Insulin Kit, Abbot, IL, USA) and glycated
29 179 haemoglobin (HbA1c) was analysed with high-performance liquid chromatography (Biorad
30 180 Variant Turbo, BioRad, Johannesburg, SA). Vitamin D (25(OH)D3) was measured using liquid
31 181 chromatography mass spectrometry and enzymatic colorimetric methods were used to measure
32 182 serum calcium, phosphate, aspartate aminotransferase (AST), alanine aminotransferase (ALT),
33 183 and gamma-glutamyl transferase (GGT). Full blood counts, including total red blood cells (RBC),
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3 184 total white blood cells (WBC), haemoglobin, haematocrit, and platelets were measured on a
4 185 Coulter LH 750 haematology analyser (Beckman Coulter, South Africa).

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8 187 For the current study, we utilized the blood and urine samples in the SA-DPP biobank to conduct
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10 188 secondary laboratory analyses. To determine the levels of serum and urinary creatinine, the
11 189 modified Jaffe-Kinetic method (calibrated to isotope dilution mass spectrometry standards)
12 190 (Beckman AU, Beckman Coulter, SA) was used, and the colorimetric (using bromocresol purple)
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14 191 method (Beckman AU, Beckman Coulter, SA) was used to determine the level of urine albumin.
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19 193 **Classification of kidney function and co-morbidities**

20 194 Kidney function was estimated using the serum creatinine-based CKD Epidemiology
21 195 Collaboration 2009 (CKD-EPI) equation¹⁹, with the race correction factor omitted. CKD was
22 196 defined as an estimated glomerular filtration rate (eGFR) of <60 ml/min/1.73 m² and/or urinary
23 197 albumin-to-creatinine ratio (uACR) >3 mg/mmol. CKD staging was based on the Kidney Disease
24 198 Improving Global Outcomes (KDIGO) guidelines²⁰ as, stage 1 (eGFR ≥ 90 ml/min/1.73m² and
25 199 uACR >3 mg/mmol), stage 2 (eGFR 60–89 ml/min/1.73m² and uACR >3 mg/mmol) and stage 3
26 200 (eGFR <60 ml/min/1.73m²). Albuminuria (stage 2) was defined as uACR between 3 and 30
27 201 mg/mmol and albuminuria (stage 3) as >30 mg/mmol²¹.

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31 203 Given that GFR declines with healthy aging without any overt signs of kidney damage, CKD was
32 204 also defined by an age-adapted definition, as an eGFR <75 ml/min/1.73m² for participants younger
33 205 than 40 years, eGFR <60 ml/min/1.73m² for participants aged between 40 and 65 years and eGFR
34 206 <45 ml/min/1.73m² for participants aged greater than 65 years²². Additionally, the age-
35 207 standardized prevalence of CKD was calculated, using the standard world population distribution
36 208 as projected by the World Health Organization for 2000–2025²³.

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38 210 Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared
39 211 (kg/m²). This was categorised as normal weight (BMI ≤ 24.9 kg/m²), overweight (BMI 25.0–29.9
40 212 kg/m²) and obese (BMI ≥ 30 kg/m²). Hypertension was defined as SBP ≥ 140 mmHg and/or DBP
41 213 ≥ 90 mmHg,²⁴ or taking anti-hypertensive medications. We further categorized our study
42 214 participants into four groups related to the level of blood pressure control, namely, 1) normotensive

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3 215 (defined as no use of anti-hypertensive medication and SBP/DBP <140/90mmHg), 2) treated and
4 216 controlled blood pressure (defined as use of anti-hypertensive medication and SBP/DBP
5 <140/90mmHg), 3) treated but uncontrolled blood pressure (defined as use of anti-hypertensive
6 217 medication but SBP/DBP \geq 140/90mmHg), 4) newly detected hypertension (defined as no use of
7 218 anti-hypertensive medication and SBP/DBP \geq 140/90mmHg). Normal and dysglycaemia
8 219 categories, based on the OGTT, were defined according to WHO criteria¹⁸ as: (1) normal glucose
9 220 tolerance [fasting glucose (FG) <6.1 mmol/L and 2-h glucose <7.8 mmol/L]; or (2) prediabetes
10 221 including impaired FG (IFG) [6.1 \leq FG<7.0 mmol/L and 2-h glucose <7.8 mmol/L], impaired
11 222 glucose tolerance (IGT) [FG <7.0 mmol/L and 7.8 \leq 2-h glucose<11.1 mmol/L]; and (3) T2DM
12 223 (FG \geq 7.0 mmol/L and/or 2-h glucose \geq 11.1 mmol/L). High GGT was defined as levels >38 IU/L,
13 224 and based on the laboratory (PathCare, South Africa) reference standards. Liver fibrosis was
14 225 classified based on the fibrosis-4 (FIB-4) index, where FIB-4 index was calculated using the
15 226 formula: [age (years) x AST (IU/L)] / [platelet (10⁹/L) x \sqrt ALT (IU/L)]²⁵. Low risk for advanced
16 227 fibrosis was defined a FIB-4 score <1.30, intermediate risk as a value between 1.30 and 2.67, and
17 228 high risk as FIB-4 >2.67²⁶. Anaemia was defined using the National Kidney Foundation Kidney
18 229 Disease Outcome Quality Initiative (K/DOQI) guidelines as haemoglobin level <13.5 g/dL for
19 230 men and <12 g/ dL for women²⁷.

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232 233 **Statistical analysis**

234 The SA-DPP sample size was calculated based on the following assumptions, 1) a cumulative
235 incident diabetes rate of 13.6% at 2–3 years, as observed in our Bellville South cohort²⁸, 2) an
236 expected relative risk of 0.51, which is the pooled effect estimate of efficacy trials comparing
237 lifestyle intervention to usual care in diabetes prevention studies²⁹, 3) an intra-cluster correlation
238 coefficient for fasting glucose of 0.02³⁰, 4) a significance level of 5% with a type II error risk of
239 20%, and 5) an estimated 36-months loss to follow-up of 20–25%.

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241 Due to the non-Gaussian distribution of most variables, the participant characteristics were
242 summarised as median (25th-75th percentile) or counts and percentages. Group comparisons were
243 analysed by chi-square tests, Wilcoxon rank-sum and Kruskal-Wallis tests. The Dunn's test was
244 used as nonparametric pairwise multiple-comparison post-hoc test when the Kruskal-Wallis test

245 was rejected. All statistical analyses were performed using STATA version 17 (Statcorp, College
246 Station, TX) and statistical significance was based on a p-value <0.05.

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248 **Patient and public involvement:** Participants and/or the public were not involved in the design,
249 or conduct, or reporting or dissemination plans of this research.

251 RESULTS

252 Of the 2,173 individuals screened in the community, 690 participants, deemed at high-risk of
253 T2DM based on the ADRS, presented at our research clinic for an OGTT and other assessments
254 (Supplementary File). The sociodemographic, clinical, and biochemical characteristics are
255 summarised by CKD status in Table 1. Among the 690 participants included in this study, 80.9%
256 were female, with a group median age of 52 years. Of these participants, 9.6% had screen-detected
257 T2DM and 18.1% had CKD, with 2.2% presenting with both CKD and T2DM. A similar CKD
258 prevalence rate was observed with age-adapted eGFR thresholds (18.1%); however, the age-
259 standardized prevalence of CKD was lower, at 14.6%. Furthermore, there were high rates of
260 obesity (77.1%), hypertension (55.0%), raised GGT levels (45.8%), intermediate risk of advanced
261 liver fibrosis (21.4%) and anaemia (14.2%) among participants in this study. There were no
262 significant differences in the sociodemographic and anthropometric variables between participants
263 with and without CKD. However, SBP (128.0 vs. 123.5 mmHg; p=0.004) and DBP (86.0 vs. 83.0
264 mmHg; p=0.014) were higher in participants with CKD compared to those without. Although
265 hypertension prevalence was not significantly different by CKD status (p=0.215), uncontrolled
266 hypertension on treatment was significantly higher in those with than without CKD (42.7% vs.
267 23.4%). The median levels of GGT (47.0 vs. 35.0 IU/L; p=0.008), AST (26.0 vs. 23.0 IU/L;
268 p=0.004), and FIB-4 index (1.0 vs. 0.9; p=0.016), were higher in participants with CKD compared
269 to those without CKD, while RBC count (4.5 vs. 4.6 x10¹²/L; p=0.046) was lower in CKD compared
270 to those with normal kidney function. The prevalence of high GGT (p=0.008) and anaemia
271 (p=0.042) were significantly higher in participants with CKD compared to those without CKD.
272 All other biochemical variable were similar between groups.

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276 **Table 1:** Sociodemographic, clinical, and biochemical characteristics presented in the overall sample and by CKD status

Sociodemographic variables	Total (n=690)	Without CKD (n=565)	CKD (n=125)	p-value
Age (years)	52 (45-59)	52 (45-59)	53 (45-60)	0.241
Gender (n,% female)	558 (80.9)	460 (81.4)	98 (78.4)	0.438
African Diabetes Risk Score	2.3 (1.7-3.4)	2.3 (1.7-3.4)	2.4 (1.7-3.4)	0.882
Anthropometry				
Weight (kg)	91.0 (79.6-103.6)	92.2 (80.4-104.6)	88.0 (76.2-101.3)	0.050
Waist circumference (cm)	102.7 (95.3-111.1)	103.4 (95.7-111.1)	101.3 (93.4-111.1)	0.242
Hip circumference (cm) (n=632)	112.6 (103.2-121.7)	113.0 (104.3-122.4)	111.3 (101.1-118.3)	0.067
Body mass index (kg/m ²)	35.6 (30.5-40.5)	35.7 (30.6-40.6)	33.9 (29.4-39.9)	0.185
Body mass index categories (n, %)				0.316
Normal	29 (4.2)	23 (4.1)	6 (4.8)	
Overweight	129 (18.7)	100 (17.7)	29 (23.2)	
Obese	532 (77.1)	442 (78.2)	90 (72.0)	
Blood pressure				
Systolic blood pressure (mmHg)	124.5 (113.5-137.0)	123.5 (113.5-135.0)	128.0 (116.0-145.5)	0.004
Diastolic blood pressure (mmHg)	83.0 (77.0-91.5)	83.0 (77.0-90.3)	86.0 (78.5-94.5)	0.014
Hypertension	379 (55.0)	304 (53.9)	75 (60.0)	0.215
Among participants with hypertension (n=379):				<0.0001
Treated and controlled BP	143 (37.7)	127 (41.8)	16 (21.3)	
Treated and uncontrolled BP	103 (27.2)	71 (23.4)	32 (42.7)	
Screen-detected HPT	133 (35.1)	106 (34.9)	27 (36.0)	
Biochemical				
Fasting blood glucose (mmol/L)	5.0 (4.6-5.5)	5.0 (4.6-5.5)	5.0 (4.6-5.6)	0.691
2-hour glucose (mmol/L) (n=688)	6.0 (4.9-7.4)	6.0 (4.9-7.3)	6.3 (5.1-7.6)	0.205
Glucose categories (n, %) (n=688)				0.600
Normoglycaemia	520 (75.6)	428 (76.0)	92 (73.6)	
Prediabetes (IFG/IGT)	102 (14.8)	84 (14.9)	18 (14.4)	
Type 2 diabetes	66 (9.6)	51 (9.1)	15 (12.0)	
HbA1c (%) (n=685)	5.8 (5.6-6.1)	5.8 (5.6-6.1)	5.9 (5.6-6.2)	0.740
Fasting insulin (IU/L)	8.8 (6.2-12.6)	8.5 (5.9-12.1)	11.1 (7.1-14.8)	0.144

Vitamin D (ng/mL)	6.1 (5.0-7.8)	6.0 (5.0-7.7)	6.2 (5.0-8.1)	0.222
Calcium (mmol/L) (n=688)	2.3 (2.3-2.4)	2.3 (2.3-2.4)	2.4 (2.3-2.4)	0.644
Phosphate (mmol/L) (n=688)	1.1 (1.0-1.2)	1.1 (1.0-1.2)	1.1 (1.0-1.2)	0.981
Gamma-glutamyl transferase (IU/L) (n=688)	36.0 (24.0-61.0)	35.0 (24.0-55.0)	47.0 (26.0-78.0)	0.008
High gamma-glutamyl transferase (n=688)	315 (45.8)	245 (43.4)	70 (6.5)	0.008
Aspartate aminotransferase (IU/L) (n=688)	24.0 (20.0-29.0)	23.0 (20.0-29.0)	26.0 (21.0-34.0)	0.004
Alanine aminotransferase (IU/L) (n=646)	22.0 (16.0-32.0)	22.0 (16.0-32.0)	22.0 (17.0-33.0)	0.372
AST/ALT ratio	1.1 (0.9-1.4)	1.1 (0.9-1.4)	1.2 (0.9-1.5)	0.110
Fibrosis-4 index (n=644)	0.9 (0.7-1.3)	0.9 (0.7-1.3)	1.0 (0.8-1.4)	0.016
Liver fibrosis (n, %)				0.065
No risk	497 (77.2)	413 (78.4)	84 (7.8)	
Intermediate risk	138 (21.4)	109 (20.7)	29 (2.8)	
High risk	9 (1.4)	5 (0.9)	4 (0.4)	
Red blood cells (x10 ¹² /L)	4.6 (4.2-4.9)	4.6 (4.3-4.9)	4.5 (4.2-4.8)	0.046
White blood cells (x10 ⁹ /L)	23.0 (18.0-28.0)	23.0 (18.3-28.0)	23.0 (17.0-28.0)	0.270
Platelet count (x10 ⁹ /L)	276 (235-325)	276.0 (234.5-322.5)	276.0 (233.0-333.0)	0.705
Haematocrit (volume %)	0.4 (0.4-0.4)	0.4 (0.4-0.4)	0.4 (0.4-0.4)	0.442
Haemoglobin (g/dL)	13.5 (12.6-14.3)	13.5 (12.7-14.3)	13.4 (12.4-14.4)	0.491
Anaemia, n (%)	103 (14.9)	77 (13.6)	26 (2.8)	0.042

Data is presented as median (25th-75th percentiles) or count and percentages. Abbreviations: CKD, chronic kidney disease; BP, blood pressure; HPT, hypertension; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; HbA1c, glycated haemoglobin; AST/ALT ratio, aspartate aminotransferase to alanine aminotransferase ratio.

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3 284 The prevalence of CKD in the overall sample and grouped by glucose and blood pressure
4 285 categories are shown in Figure 1. In those with prediabetes, T2DM, and hypertension, 17.6%,
5 286 22.7% and 19.8% had CKD, respectively. Of the participants with hypertension, the prevalence of
6 287 CKD was highest in those on anti-hypertensive treatment but with uncontrolled blood pressure
7 288 (31.1%), while 20.3% of those newly identified with hypertension and 11.2% of those on treatment
8 289 with controlled blood pressure had CKD.
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15 291 **Figure 1 to be included here**
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19 293 The stages of CKD according to eGFR and albuminuria following KDIGO classification are
20 294 presented in Figure 2. Of the 11 participants with an eGFR <60 ml/min/1.73m², four (36.4%) had
21 295 no albuminuria, with 36.4% (n=4) and 27.3% (n=3) presenting with moderate (uACR: 3-
22 296 30mg/mmol) and severe albuminuria (uACR: >30mg/mmol), respectively. Furthermore, of the
23 297 those with normal kidney function (eGFR ≥90 ml/min/1.73m²), 67 (10.2%) and 25 (3.8%) had
24 298 moderate and severe albuminuria, respectively.
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31 300 **Figure 2 to be included here**
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34 302 Table 2 describes the participant characteristics by CKD stage. The majority of individuals with
35 303 CKD presented with stage 1 CKD (73.6%), with 17.6% and 8.8% presenting with stage 2 and 3,
36 304 respectively. Participants with stage 3 CKD were older than those with normal kidney function
37 305 and stage 1 CKD (p=0.030 for both). Levels of AST were significantly higher with stage 2 CKD
38 306 compared with stage 3 CKD (p=0.042). SBP and DBP did not differ by stages of CKD but differed
39 307 between those with normal kidney function and those with CKD as follows: normal kidney
40 308 function vs. CKD stage 1 (SBP: p=0.007 and DBP: p=0.010), stage 2 (SBP: p=0.039) and stage 3
41 309 (DBP: p=0.013).
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315 **Table 2:** Sociodemographic, clinical, and biochemical characteristics in participants by CKD stages

Sociodemographic variables	No CKD (n=565)	Stage 1 (n=92)	Stage 2 (n=22)	Stage 3 (n=11)	p-value
Age (years)	52 (45-59)*	52 (45-59)*	56 (51-61)	57 (52-63)	0.029
Gender (n,% female)	460 (81.4)	75 (81.5)	15 (68.2)	8 (72.7)	0.408
African Diabetes Risk Score	2.3 (1.7-3.4)	2.4 (1.8-3.1)	2.2 (1.7-4.8)	2.8 (1.9-3.9)	0.865
Kidney function					
Serum creatinine (µmol/L)	57.0 (48.0-67.0)	54.0 (46.5-62.0)	78.5 (72.0-88.0)	122.0 (96.0-160.0)	0.0001
eGFR (ml/min/1.73m ²)	103.0 (95.0-114.0)	106.0 (98.0-117.5)	79.5 (75.0-83.0)	49.0 (32.0-57.0)	0.0001
uACR (mg/mmol)	0.6 (0.4-1.0)	6.0 (4.1-14.1)	6.5 (3.6-17.3)	3.9 (0.8-43.2)	0.0001
Anthropometry					
Weight (kg)	92.2 (80.4-104.6)	89.1 (77.8-101.7)	84.4 (70.6-95.3)	78.7 (63.2-102.4)	0.117
Waist circumference (cm)	103.4 (95.7-111.1)	101.6 (93.9-111.4)	97.2 (93.1-109.7)	100.6 (93.4-107.0)	0.497
Hip circumference (cm) (n=632)	113.0 (104.3-122.4)	112.7 (102.3-120.9)	110.4 (99.4-117.9)	108.6 (96.4-108.9)	0.085
BMI (kg/m ²)	35.7 (30.6-40.6)	34.7 (30.5-40.7)	31.6 (26.9-39.5)	31.9 (27.2-36.9)	0.121
BMI categories (n, %)					0.039
Normal	23 (4.1)	2 (2.2)	2 (9.1)	2 (18.2)	
Overweight	100 (17.7)	19 (20.7)	8 (36.4)	2 (18.2)	
Obese	442 (78.2)	71 (77.2)	12 (54.5)	7 (63.6)	
Blood pressure					
SBP (mmHg)	123.5 (113.5-135.0)	129.5 (115.0-145.5)**	126.5 (123.5-153.0)***	127.5 (106.5-156.0)	0.031
DBP (mmHg)	83.0 (77.0-90.3)	86.5 (78.3-94.0)#	80.8 (75.0-94.5)	90.5 (82.5-105.5)##	0.017
Hypertension	304 (53.9)	54 (58.7)	12 (54.5)	9 (81.8)	0.263
Among participants with hypertension (n=379):					0.010
Treated and controlled BP	127 (41.8)	10 (18.5)	3 (25.0)	3 (33.3)	
Treated and uncontrolled BP	71 (23.4)	23 (42.6)	5 (41.7)	4 (44.4)	
Screen-detected HPT	106 (34.9)	21 (38.9)	4 (33.3)	2 (22.2)	
Biochemical					
FBG (mmol/L)	5.0 (4.6-5.5)	5.0 (4.6-5.6)	4.9 (4.4-5.6)	4.8 (4.7-5.3)	0.886
2-hour glucose (mmol/L) (n=688)	6.0 (4.9-7.3)	6.3 (5.1-7.6)	6.3 (4.7-8.5)	6.4 (5.6-7.2)	0.624
Glucose categories (n, %) (n=688)					0.543
Normoglycaemia	428 (76.0)	70 (76.0)	13 (59.1)	9 (81.8)	

Prediabetes (IFG/IGT)	84 (14.9)	11 (12.0)	6 (27.3)	1 (9.1)	
Type 2 diabetes	51 (9.1)	11 (12.0)	3 (13.6)	1 (9.1)	
HbA1c (%) (n=685)	5.8 (5.6-6.1)	5.9 (5.6-6.2)	5.7 (5.3-6.2)	5.7 (5.6-6.2)	0.591
Fasting insulin (IU/L)	8.5 (5.9-12.1)	11.1 (6.4-15.5)	11.0 (8.7-13.2)	-	0.334
Vitamin D (ng/mL)	6.0 (5.0-7.7)	6.2 (5.0-7.8)	6.7 (5.9-8.1)	6.8 (5.2-10.6)	0.361
Calcium (mmol/L) (n=688)	2.3 (2.3-2.4)	2.3 (2.3-2.4)	2.4 (2.3-2.4)	2.3 (2.3-2.4)	0.794
Phosphate (mmol/L) (n=688)	1.1 (1.0-1.2)	1.1 (1.0-1.2)	1.1 (1.0-1.2)	1.2 (0.9-1.3)	0.777
GGT (IU/L) (n=688)	35.0 (24.0-55.0)	45.0 (26.0-81.0)	46.5 (25.0-64.0)	49.0 (24.0-122.0)	0.071
High GGT (n=688)	245 (43.4)	51 (56.0)	13 (59.1)	6 (54.5)	0.071
AST (IU/L) (n=688)	23.0 (20.0-29.0)	26.0 (21.1-34.0)	26.5 (22.0-34.0)###	21.0 (20.0-28.0)	0.009
ALT (IU/L) (n=646)	22.0 (16.0-32.0)	23.0 (17.0-33.0)	21.0 (18.0-31.0)	18.5 (15.5-37.5)	0.799
AST/ALT ratio	1.1 (0.9-1.4)	1.2 (0.9-1.5)	1.3 (1.1-1.4)	1.3 (0.9-1.5)	0.413
Fibrosis-4 index (n=644)	0.9 (0.7-1.3)	1.0 (0.8-1.3)	1.1 (0.9-1.5)	1.3 (0.7-1.6)	0.063
Liver fibrosis (n, %)					0.124
No risk	413 (78.4)	66 (75.0)	14 (66.7)	4 (50.0)	
Intermediate risk	109 (20.7)	19 (21.6)	6 (28.6)	4 (50.0)	
High risk	5 (0.9)	3 (3.4)	1 (4.8)	0 (0)	
Red blood cells (x10 ¹² /L)	4.6 (4.3-4.9)	4.5 (4.2-4.9)	4.5 (4.2-4.6)	4.7 (4.5-5.1)	0.071
White blood cells (x10 ⁹ /L)	23.0 (18.3-28.0)	22.0 (17.0-28.0)	26.0 (16.0-31.9)	25.0 (19.0-26.0)	0.550
Platelet count (x10 ⁹ /L)	276.0 (234.5-322.5)	276.5 (235.0-333.5)	271.0 (244.0-335.0)	261.0 (217.0-325.0)	0.956
Haematocrit (volume %)	0.4 (0.4-0.4)	0.4 (0.4-0.4)	0.4 (0.4-0.4)	0.4 (0.4-0.5)	0.433
Haemoglobin (g/dL)	13.5 (12.7-14.3)	13.3 (12.3-14.5)	13.5 (13.3-14.4)	13.7 (12.9-15.8)	0.390
Anaemia, n (%)	77 (13.6)	22 (23.9)	2 (9.1)	2 (18.2)	0.063

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317 Data is presented as median (25th-75th percentiles) or count and percentages. Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; uACR, urinary albumin-to-creatinine ratio; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; HbA1c, glycated haemoglobin; GGT, gamma-glutamyl transferase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; eGFR, estimated glomerular filtration rate; uACR, urinary albumin-to-creatinine ratio. Keys: *p=0.030 (CKD stage vs. no CKD; CKD stage

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3 322 3 vs. CKD stage 1); **p=0.007 (no CKD vs. CKD stage 1); ***p=0.039 (no CKD vs. CKD stage 2); #p=0.010 (no CKD vs. CKD stage
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5 323 1); ##p=0.013 (no CKD vs. CKD stage 3); ###p=0.042 (CKD stage 3 vs. CKD stage 2).
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339 DISCUSSION

340 To our knowledge, this is the first study to show that by utilizing an opportunistic approach, CKD
341 can be detected early, allowing for timely referral for specialized testing to confirm diagnosis and
342 subsequent care. This was achieved through leveraging the information already collected in an
343 existing screening programme that targeted individuals at high-risk for T2DM and included a few
344 additional kidney-related biochemical markers to the variables for testing. The yield of screen-
345 detected cases was high for a low investment which cost ZAR 237.80 (USD 14.59) per person and
346 highlights the potential cost-effectiveness of such a strategy.

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348 By including a minimal number of markers of kidney function (namely serum and urinary
349 creatinine, and urinary albumin) to the scope of markers already collected, we found that 18.1%
350 of those at high-risk for developing T2DM had CKD with the majority (73.6%) having mild CKD
351 (CKD stage 1). The CKD burden, at 22.7%, was even higher in participants with newly diagnosed
352 T2DM, which underscores the need for frequent screening of individuals at high-risk for T2DM
353 to avoid T2DM presenting with complications at diagnosis. Therefore, using T2DM as a gateway
354 for CKD screening through existing screening programmes is justified as such an approach,
355 together with diagnosing new T2DM, simultaneously identified those with complications i.e.,
356 CKD. The newly diagnosed T2DM may receive comprehensive care with tight control of both
357 their T2DM and CKD. This intensification of treatment could contribute to a delay in CKD
358 progression and consequently help reduce the risk of developing end-stage kidney disease (ESKD)
359 or CVD-related complications³¹. Further support for CKD screening in individuals at high-risk
360 for T2DM was the substantial CKD burden in prediabetes (17.6%). Notably, if screening for CKD
361 was initiated only after the development of T2DM, the identification of CKD in individuals with
362 prediabetes, which generally fall below the threshold for disease management in clinical practice,
363 would have been missed. This would then have been a lost opportunity to identify and manage
364 CKD early and delay progression of the disease in this high-risk group.

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366 Our study also highlights the importance of screening for albuminuria as 91.2% of those with CKD
367 would have gone undetected if CKD were based on eGFR alone. Guidelines recommend
368 albuminuria testing using ACR, like we did in our study, however this is not always possible in
369 many low-resource settings. In these instances, low-cost semiquantitative methods, like urinary

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3 370 dipsticks, can be used to measure albuminuria with subsequent confirmation of positive dipstick
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5 371 result with a quantitative laboratory test to confirm CKD diagnosis ²⁰. Or repeated dipstick
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7 372 assessments can be employed to reduce the possibility of false-negative results as this could delay
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9 373 the timely diagnosis and management of CKD.

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12 375 Given that this is the first study to report the prevalence of CKD in people at high-risk for
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14 376 developing T2DM, based on the ADRS, the prevalence estimates cannot be directly compared to
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16 377 other studies as no similar data have been published. Nevertheless, at a similar median age (52 vs.
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18 378 53 years), the prevalence of CKD in those with prediabetes in our study was comparable to that
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20 379 reported in a large representative sample in the United States of America (17.6% vs. 17.7%,
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22 380 respectively) ³². Also, albeit an older population (median age of 68 years) with a higher prevalence
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24 381 of advanced CKD (stage 3-5), a South African study found that the prevalence of CKD in those
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26 382 with prediabetes was 19.8% ³³. The similarly high CKD prevalence in prediabetes across several
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28 383 studies suggests that perhaps there should be regular CKD screening for all individuals with
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30 384 prediabetes.

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33 386 A likely contributor to the substantial CKD burden in this study is the high prevalence of
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35 387 hypertension, which at 55% is higher than the 44%-46% reported for South Africa ³⁴. While the
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37 388 high reported prevalence of hypertension is consequent to the score used to identify high-risk
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39 389 individuals, a larger proportion of the participants with hypertension had CKD compared to those
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41 390 with normal blood pressure (19.8% vs. 16.1%, respectively). The prevalence of CKD may be
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43 391 related to the delayed detection of hypertension or the suboptimal control of blood pressure in
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45 392 treated hypertension, as reported in the current study and in several South African studies ^{34, 35}.
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47 393 Indeed, a high proportion of participants with treated but uncontrolled hypertension had CKD
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49 394 (31.1%) in this study as did participants with newly detected hypertension (20.3%). This further
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51 395 highlights the benefit of screening high-risk individuals for CKD. Notably, adequate blood
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53 396 pressure control is fundamental to slowing the progression of CKD ^{36, 37} and timeous treatment
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55 397 with anti-hypertensive medication can improve both kidney and cardiovascular outcomes ^{38, 39}
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57 398 thereby preventing the progression to ESKD and reducing the risk of all-cause and cardiovascular
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59 399 mortality ^{38, 40, 41}.

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3 401 Elevated GGT and the FIB-4 index, which are commonly used markers of liver injury and non-
4 402 alcoholic fatty liver disease (NAFLD) ⁴², have been linked to increased CKD risk in various
5 403 populations ⁴³⁻⁴⁶. In our study, 56.5% of the participants with CKD presented with higher-than-
6 404 normal GGT levels, compared to 43.4% of participants without CKD. Also, a significant
7 405 proportion of people with CKD presented with intermediate and high risk for advanced liver
8 406 fibrosis, based on the FIB-4 index, compared to those without CKD (28.2% vs. 21.6%). Early
9 407 recognition and interventions directed at reducing the risk of liver injury among individuals with
10 408 CKD could reduce CKD progression.
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19 410 Anaemia was prevalent in our study population (14.9% of total sample), with nearly twice as many
20 411 participants with CKD having anaemia compared to those without CKD, as shown in other studies
21 412 as well ^{47, 48}. Although the overall prevalence of anaemia in this study was not uncommon for
22 413 South Africa ⁴⁹, the prevalence in participants with CKD is concerning. While erythropoiesis
23 414 stimulating agents and iron supplementation to treat anaemia are unlikely to be prescribed to
24 415 people in the early stages of CKD, anaemia can accelerate the decline in kidney function by
25 416 causing kidney haemodynamic alterations and tissue hypoxia ⁸. It is strongly predictive of all-
26 417 cause and cardiovascular mortality ^{50, 51}, and should thus be closely monitored.
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34 419 Although lifestyle interventions addressing unhealthy diets, physical inactivity, tobacco smoking
35 420 and alcohol misuse are advocated to reduce the growing global burden of non-communicable
36 421 diseases ^{52, 53}, little is known about the impact of reducing unhealthy lifestyle behaviours on kidney
37 422 health. The SA-DPP intervention, implemented in individuals with prediabetes, will provide a
38 423 unique opportunity to examine the effects of improving lifestyle behaviours on changes in CKD
39 424 status.
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46 426 This is the first study to show that utilizing an opportunistic approach, through leveraging the
47 427 information already collected in an existing screening programme is advantageous to screen for
48 428 CKD. However, our study does have limitations. The SA-DPP study included participants at high-
49 429 risk of T2DM and our findings might not be reproducible across other non-communicable diseases
50 430 screening programmes. The small number of participants identified with CKD in this study
51 431 reduced the statistical power of our analyses when stratifying by CKD stage. Based on the self-
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3 432 selection approaches used to recruit participants, the disproportionate greater number of females,
4 433 the varying socioeconomic status, lifestyle behaviours and disease prevalence (hypertension and
5 434 T2DM) across provinces and by urban-rural residence in South Africa ³⁴, our study findings cannot
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7 435 be generalised. Another limitation is that CKD was defined based on a single time-point serum
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9 436 and urinary creatinine and albumin assessment and not on repeated measurements, at least three
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11 437 months apart, as per KDIGO guidelines ²⁰. However, a strength of our study is that both eGFR and
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13 438 albuminuria were used to define CKD, unlike most other population-based CKD prevalence
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15 439 studies in South Africa and Africa in general which rely on eGFR only for CKD classification.
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17 440 Finally, as for all studies using eGFR to characterize CKD, instead of the gold standard of
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19 441 measured GFR, the over- or under-estimation of the estimate cannot be excluded.
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22 443 **CONCLUSION**

23
24 444 The fact that almost one in five participants identified as high-risk for T2DM had CKD underscores
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26 445 the value of including markers of kidney function in existing disease screening programmes. Our
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28 446 findings provide support for key stakeholders and policy makers to adapt current strategies for
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30 447 hypertension and T2DM screening to include screening for CKD. Indeed, by utilizing an
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32 448 opportunistic approach to screen high-risk individuals, those with early-stage CKD can be
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34 449 identified and appropriately managed to reduce disease progression. Existing cardiovascular or
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36 450 non-communicable disease screening programmes should perhaps explore including markers for
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38 451 CKD evaluations to maximise limited resources without compromising on effectiveness.
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7 465
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492 **Figure legends**

493 **Figure 1:** Prevalence (%) of chronic kidney disease overall and by glucose and blood pressure
494 categories. Data presented as percentages. Abbreviations: T2DM, type 2 diabetes mellitus; HPT,
495 hypertension; BP, blood pressure

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497 **Figure 2:** Stages of chronic kidney disease according to estimated glomerular filtration rate and
498 albuminuria following Kidney Disease Improving Global Outcomes (KDIGO) classification.
499 Displayed are number of patients (%) within each category. The colour code indicates risk category
500 according to KDIGO ²⁰: green "low risk", yellow "moderate risk", orange "high risk" and red "very
501 high risk"

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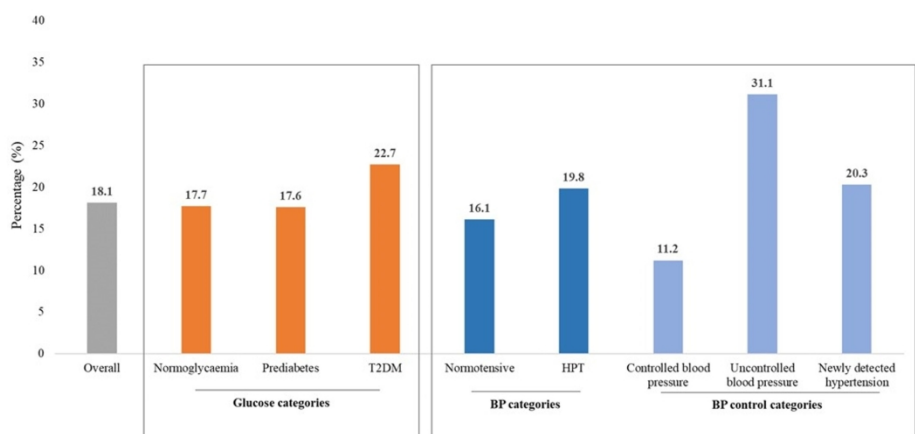


Figure 1: Prevalence (%) of chronic kidney disease overall and by glucose and blood pressure categories. Data presented as percentages. Abbreviations: T2DM, type 2 diabetes mellitus; HPT, hypertension; BP, blood pressure

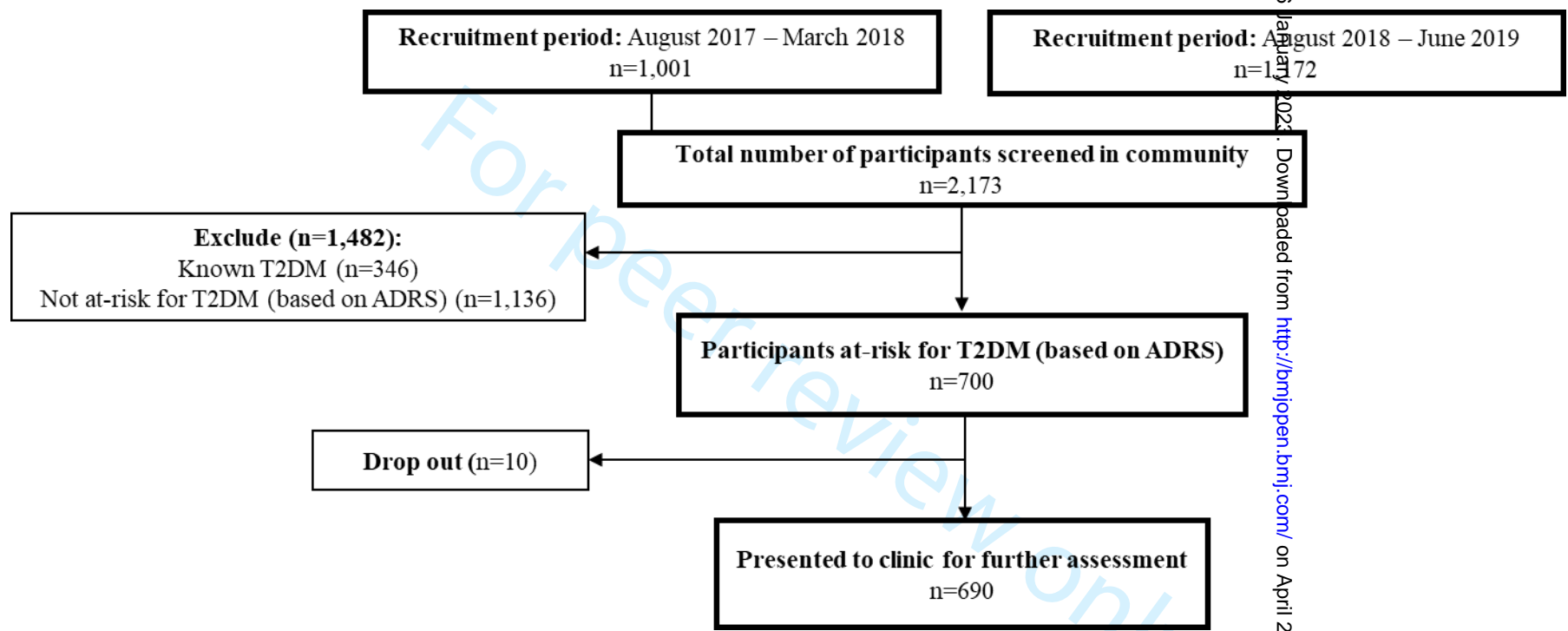
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CKD stages	eGFR (ml/min/1.73m ²)	Albuminuria			Total
		A1 (<3 mg/mmol)	A2 (3-30 mg/mmol)	A3 (>30 mg/mmol)	
G1	≥90	565 (86.0%)	67 (10.2%)	25 (3.8%)	657 (95.2%)
G2	60–89	0 (0%)	15 (68.2%)	7 (31.8%)	22 (3.2%)
G3 (a and b)	<60	4 (36.4%)	4 (36.4%)	3 (27.3%)	11 (1.6%)
Total		569 (82.5%)	86 (12.5%)	35 (5.1%)	690 (100%)

Figure 2: Stages of chronic kidney disease according to estimated glomerular filtration rate and albuminuria following Kidney Disease Improving Global Outcomes (KDIGO) classification. Displayed are number of patients (%) within each category. The colour code indicates risk category according to KDIGO 20: green "low risk", yellow "moderate risk", orange "high risk" and red "very high risk"

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Addendum A: Flow diagram of recruitment process over two phases



Abbreviations: T2DM, type 2 diabetes mellitus; ADRS, African Diabetes Risk Score

STROBE Statement—Checklist of items that should be included in reports of *cross-sectional studies*

	Item No	Recommendation	Page No
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-8
Bias	9	Describe any efforts to address potential sources of bias	NA
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	8
		(b) Describe any methods used to examine subgroups and interactions	8
		(c) Explain how missing data were addressed	8
		(d) If applicable, describe analytical methods taking account of sampling strategy	NA
		(e) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	Addendum A
		(c) Consider use of a flow diagram	Addendum A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	5-8

		(b) Indicate number of participants with missing data for each variable of interest	10-11 and 13-14
Outcome data	15*	Report numbers of outcome events or summary measures	10-11 and 13-14
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	NA
		(b) Report category boundaries when continuous variables were categorized	7-8
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	16
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	18-19
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	19
Generalisability	21	Discuss the generalisability (external validity) of the study results	19
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	19

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.