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Prevalence of and risk factors for chronic kidney disease of unknown aetiology in India: secondary data analysis of three population-based cross-sectional studies

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1 **TITLE PAGE**

2 **Title:** Prevalence of and risk factors for chronic kidney disease of unknown aetiology in India: secondary data
3 analysis of three population-based cross-sectional studies

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26 ABSTRACT

27 **Objectives:** To assess whether chronic kidney disease of unknown aetiology (CKDu) is present in India and to
28 identify risk factors for it using population-based data and standardised methods.

29 **Design:** Secondary data analysis of three population-based cross-sectional studies conducted between 2010-
30 2014.

31 **Setting:** Urban and rural areas of Northern India (states of Delhi and Haryana) and Southern India (states of
32 Tamil Nadu and Andhra Pradesh)

33 **Participants:** 12,500 individuals without diabetes, hypertension or heavy proteinuria

34 **Outcome measures:** Mean estimated the glomerular filtration rate (eGFR) and the prevalence of eGFR below
35 60ml/min per 1.73m² (eGFR<60) in individuals without diabetes, hypertension or heavy proteinuria (proxy
36 definition of CKDu).

37 **Results:** The mean eGFR was 105.0±17.8 ml/min per 1.73m². The prevalence of eGFR<60 was 1.6%
38 (95%CI=1.4-1.7), but this figure varied markedly between areas, being highest in rural areas of Southern Indian
39 [4.8% (3.8-5.8)]. In Northern India, older age was the only risk factor associated with lower mean eGFR and
40 eGFR<60 [regression coefficient (95%CI)=-0.94 (0.97 - 0.91); OR (95%CI)=1.10 (1.08-1.11)]. In Southern
41 India, risk factors for lower mean eGFR and eGFR<60 were residence in a rural area [-7.78 (-8.69 - -6.86); 4.95
42 (2.61-9.39)], older age [-0.90 (-0.93 - -0.86); 1.06 (1.04-1.08)] and less education [-0.94 (-1.32 - -0.56); 0.67
43 (0.50-0.90) for each five years at school].

44 **Conclusions:** CKDu is present in India and is not confined to Central America and Sri Lanka. Identified risk
45 factors are consistent with risk factors previously reported for CKDu in Central America and Sri Lanka.

46 KEYWORDS

47 Epidemiology; Chronic kidney disease; Chronic kidney disease of unknown aetiology;; India; Rural population

48 ARTICLE SUMMARY

49 Strengths and limitations of this study

- 50 • The use of a random selection of population-based participants allows the estimation of CKDu
51 prevalence in the general population.

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2
3 52 • A large sample size including participants from different areas of India (urban and rural, and Northern
4 53 and Southern India) increases the representativeness of our results.
5
6 54 • The use of standardized definitions of CKDu facilitates international comparisons of CKDu prevalence
7 and risk factors.
8 55
9
10 56 • The prevalence of eGFR<60 observed in this study is likely to be underestimated; however, this is
11 unlikely to have biased the internal comparisons conducted in this study.
12 57
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14

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67 INTRODUCTION

68 High prevalence of CKDu has mainly been reported in the last decades amongst the working age populations of
69 agricultural communities of tropical/subtropical regions, specifically in Central America and Sri Lanka (C
70 Wesseling et al. 2013; Correa-Rotter, Wesseling, and Johnson 2014; Jayatilake et al. 2013). In Nicaragua and El
71 Salvador, the estimated prevalence of estimated glomerular filtration rate (eGFR; the clinical measure of kidney
72 function) below 60ml/min per 1.73m² (eGFR<60), in the absence of diabetes and hypertension, was 10-20%
73 (Lebov et al. 2015; Peraza et al. 2012; Torres et al. 2010). It has been suggested that CKDu may also be highly
74 prevalent in other low and middle income countries (LMICs), including India (Seck et al. 2014; Barsoum 2013;
75 El Minshawy, Ghabrah, and El Bassuoni 2014; Rajapurkar et al. 2012; Reddy and Gunasekar 2013). However, it
76 is not clear in which other regions of the world CKDu occurs, whether the underlying aetiology is the same in
77 different regions and what the risk factors are. Currently, there is no consensus but factors such as heat stress,
78 strenuous work, climatic conditions, agrochemical use, heavy metal exposure and infections have been
79 suggested as risk factors (Jayasumana et al. 2015; C Wesseling et al. 2013; Catharina Wesseling et al. 2015;
80 Garcia-Garcia, Jha, and World Kidney Day Steering Committee 2015; Robey 2014).

81 Data on CKDu from India are scarce. The recent report of verbal autopsy data from India suggests CKD of all
82 causes is a growing problem. However, it does not provide accurate population-based data on CKDu (Jha and
83 Modi 2017; Dare et al. 2017). Existing reports indicate that CKDu may be common but it is difficult to be
84 definite about this because of the absence of population-based studies using standardised and comparable
85 methods. Data from the Indian CKD Registry, a hospital based registry of incident cases of CKD between 2006-
86 2010, found that CKDu was the second commonest form of CKD after diabetic nephropathy (Rajapurkar et al.
87 2012). However, this is restricted to referred cases and therefore may not be representative of the general
88 population. There are also sporadic reports of high numbers of CKDu cases among agricultural communities of
89 the South Eastern Indian states of Andhra Pradesh and Odisha (reviewed by Chatterjee (Chatterjee 1026) and
90 Ganguli (Ganguli 2016)). However, population-based data have not been reported for India.

91 We conducted a secondary analysis of representative sample surveys conducted in India between 2010-2014.
92 Given the absence of a clear case definition for CKDu it is necessary to make a presumptive diagnosis based on
93 measures/estimates of GFR in the absence of known risk factors for kidney disease. We therefore here report
94 both the distribution eGFR and prevalence of eGFR below 60ml/min per 1.73m² (eGFR<60), and the risk factors

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3 95 associated with these outcomes, in a population restricted to those without known risk factors for CKD, i.e.
4 96 diabetes, hypertension or heavy proteinuria (a marker of primary glomerular disease).

7 97 **METHODS**

10 98 **Study population**

13 99 We used cross-sectional data from three population-based studies conducted in India: the “Centre for
14 100 Cardiometabolic Risk Reduction in South Asia” cohort study (CARRS study) (Nair et al. 2012), the
15 101 “Implementing a Comprehensive Diabetes Prevention and Management Program” study (UDAY study) (Mohan
16 102 et al. 2017) and the “prevalence of coronary heart disease repeat survey” study funded by the Indian Council of
17 103 Medical Research (ICMR-CHD study) (Prabhakaran et al. 2017). Details on study design and selection of
18 104 participants from the CARRS, UDAY and ICMR-CHD studies have been previously described (Nair et al. 2012;
19 105 Prabhakaran et al. 2017; Mohan et al. 2017) and are summarized in Table 1. Participants from CARRS, UDAY
20 106 and ICMR-CHD studies provided informed consent prior to participation. The three studies obtained ethical
21 107 clearance from the corresponding institutions.

22 108 For the current analyses, we excluded participants with missing information on serum creatinine, sex and age, as
23 109 these variables were necessary to estimate eGFR. As the focus of our study was CKDu, we excluded participants
24 110 with known risk factors for CKD (i.e. diabetes and hypertension) or evidence of primary glomerular disease (as
25 111 assessed by heavy proteinuria) or with missing information for these risk factors. We also excluded participants
26 112 with missing information on basic co-variables (education) for all the analyses conducted. A study flowchart is
27 113 presented in Figure 1. We classified participants as having: diabetes, if plasma fasting glucose was ≥ 126 mg/dl,
28 114 or glycated haemoglobin A1c (HbA1c) was $\geq 6.5\%$, or the participant self-reported diabetes and was on oral
29 115 hypoglycaemic medication; hypertension, if systolic blood pressure was ≥ 140 mm Hg, or diastolic blood
30 116 pressure was ≥ 90 mm Hg, or the participant self-reported hypertension and was on antihypertensive medication;
31 117 and heavy proteinuria, if the albumin/creatinine ratio (ACR) in urine was ≥ 300 mg/g. We used the CKD-EPI
32 118 equation to estimate GFR (eGFR) (Levey et al. 2009).

33 119 **Data collection and laboratory analyses**

34 120 Data collection was conducted between October 2010 and December 2014. All three studies used a standardized
35 121 questionnaire to collect data on age, sex, completed years of education (0, ≤ 5 , $>5-\leq 10$, >10), alcohol intake

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3 122 (ever, never) and dietary habits (vegetarian yes, no). Body mass index (BMI, kg/m²) was calculated and
4 123 categorized (≤ 18.5 : underweight; >18.5 - ≤ 25 : normal weight; >25 - ≤ 30 : overweight; >30 : obese), fat free mass
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6 124 was derived from bioelectric impedance analysis (BIA) and blood pressure was measured using an electronic
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8 125 sphygmomanometer, as previously reported (Nair et al. 2012; Anand et al. 2015). A fasting venous blood sample
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10 126 was used to measure glucose levels, HbA1c and serum creatinine levels and urine sample to measure
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12 127 albuminuria and creatinuria (Nair et al. 2012). Glucose levels were measured using hexokinase/kinetic methods,
13
14 128 HbA1c using high-performance liquid chromatography, and the serum creatinine using the rate-blanked and
15
16 129 compensated kinetic Jaffe method, traceable to isotope dilution mass spectrometry (Nair et al. 2012).

18 130 **Statistical analyses**

21 131 We reported mean eGFR and prevalence eGFR <60 according to different characteristics of the study
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23 132 populations. UDAY and CARRS studies did not involve fully random population samples (since sampling was
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25 133 based on households, with one participant per household) and the proportions of study participants with
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27 134 particular outcomes (e.g. eGFR <60), will not be exactly the same (but very similar) to what would have been
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29 135 obtained with genuine random population samples; thus in this paper we refer to the prevalence in the study
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31 136 participants, not overall population prevalence estimates. We used linear regression models to estimate the
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33 137 associations between potential risk factors and eGFR and logistic regression models to estimate the associations
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35 138 between potential risk factors and eGFR <60 . We also repeated the analyses separately for males and females.
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37 139 Variables associated with eGFR in the basic analyses (adjusted for age and sex) were considered for the multiple
38
39 140 regression analysis. In the final multiple regression model, we included all variables that were of a priori interest
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41 141 and/or had shown independent associations with eGFR. We then checked for multicollinearity for each variable
42
43 142 in the multiple regression analyses in comparison with the basic analyses (Greenland et al. 2016). 6% of
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45 143 participants had missing values for education, 4% for BMI and 11% for fat free mass. For BMI and fat free mass,
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47 144 we excluded participants with missing values to compare models non-adjusted and adjusted for these variables.
48
49 145 We calculated prevalence ratios of eGFR <60 by age-group for rural and urban population. Finally, we estimated
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51 146 potential interactions between urban (versus rural) residence and latitude (Northern India (i.e. states of Delhi and
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53 147 Haryana) versus Southern India (states of Tamil Nadu and Andhra Pradesh)). We conducted all analyses using
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55 148 Stata version 14 (StataCorp, College Station, TX, USA).

56 149 **Patient and Public Involvement**

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3 150 Patients were not involved in the design of this analysis.

4 5 151 **RESULTS**

6 7 8 152 **Characteristics of study participants**

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11 153 12,500 people were eligible for the current analyses (Figure 1). Table 2 summarizes the socio-demographic and
12 154 anthropometric characteristics of the 12,500 study participants included in this analysis (the same information
13 155 including participants with known risk factors for CKD (n=24,774) in supplementary material Table S1). The
14 156 mean (standard deviation (\pm SD)) age of participants was 41.5 \pm 11.6 years. 88% (4,805/5,434) of the male
15 157 population was formally employed; 76% (5,346/7,066) of women worked on house duties (i.e. housewives).
16 158 The mean BMI was 24 \pm 5.0 kg/m² and mean fat free mass was 42 \pm 15 kg/m². The mean fasting plasma glucose
17 159 was 91.9 \pm 12.3 mg/dl and the mean HbA1c was 5.5 \pm 0.4 %. The mean systolic and diastolic blood pressures were
18 160 114 \pm 12 mm Hg and 74 \pm 9 mm Hg, respectively. The median (inter quartile range, IQR) albumin/creatinine ratio
19 161 (ACR) was 2.4 (4.3) mg/g (after exclusion of those with ACR>300mg/g, n=1,208).

20 21 22 162 **Mean eGFR and prevalence of eGFR<60**

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24
25 163 The mean eGFR was 105.0 \pm 17.8 ml/min per 1.73m². The mean eGFR was lower at increasing ages, in males, in
26 164 inhabitants from rural areas and in those from Northern India, in participants with no formal education, and in
27 165 participants who reported tobacco consumption, alcohol intake and being vegetarian (Table 2). We observed
28 166 differences in mean eGFR depending on the area, being 104.5 \pm 17.6 in urban areas of Northern India, 100.3 \pm 16.2
29 167 in rural areas of Northern India, 110.9 \pm 15.7 in urban areas of Southern India and 97.4 \pm 19.8 in the rural area of
30 168 Southern India.

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32
33 169 The prevalence of eGFR<60 among the study population was 1.6% (95% confidence interval (95% CI)=1.4% -
34 170 1.9%). 17% (95% CI=16% - 17%) of study participants had eGFR \geq 60-<90 ml/min per 1.73m² and 82% [95%
35 171 confidence interval (95% CI)=81% - 82%] had eGFR \geq 90 ml/min per 1.73m². The prevalences of different
36 172 categories of eGFR differed by formal education, tobacco consumption, alcohol intake and vegetarianism (Table
37 173 2). Also, we observed marked differences in the prevalence of eGFR<60 depending on the area, being 1.4 %
38 174 (95% CI=1.1 - 1.8) in urban areas of Northern India, 1.9 (95% CI=1.4% - 2.6%) in rural areas of Northern
39 175 India, 0.43% (95% CI =0.03% - 0.07%) in urban areas of Southern India and 4.8 % (95% CI= 3.9% - 5.9%) in

176 the rural area of Southern India. The prevalence ratio of eGFR<60 for rural versus urban residence was higher
177 for participants <50 years than for older groups (Figure 2).

178 **Risk factors for lower eGFR and eGFR<60**

179 As expected, age was an important risk factor for reduced eGFR: eGFR was 0.93 ml/min per 1.73 m² (95%CI=-
180 0.95 - -0.91, model adjusted for sex) lower for each additional year of age. Additionally, being male, living in a
181 rural setting, living in Southern India and consuming alcohol were associated with decreased mean eGFR (Table
182 3). Similarly, the odds of eGFR<60 also increased by each year of age [OR adjusted for sex (95%CI)=1.1 (1.1 -
183 1.1)] and being male, living in a rural setting, living in Southern India and consuming alcohol were also
184 associated with eGFR<60 (Table 3). Risk factors for decreased mean eGFR and for eGFR<60 were similar for
185 men and women (supplementary material, Table S2).

186 In the multiple regression analyses, decreased mean eGFR remained associated with older age, being male and
187 living in a rural setting and alcohol consumption (Table 4). Risk of eGFR<60 remained associated with older
188 age, being male and living in a rural setting and having no formal education remained associated with increased
189 risk of eGFR<60 (Table 4). We adjusted all the multiple regression models for fat free mass and vegetarianism
190 to assess the possibility that differences observed between urban and rural participants were due to differences in
191 diet and/or body composition. These adjustments had little effect on the results (Table 4).

192 We observed an interaction between the effects of latitude (North/South) and urban/rural residence in association
193 with reduced eGFR (p-value for interaction<0.001). The mean eGFR was lower in rural settings in both
194 Northern and Southern India (controlling for age, sex, education and alcohol intake). However, this decrease was
195 much more marked in Southern India. In Northern India, age was the only other risk factor associated with
196 reduced eGFR, whereas in Southern India, lower level of formal education was also a risk factor for reduced
197 eGFR (Table 5). We also observed an interaction between the effects of latitude (North/South) and urban/rural
198 residence in association with eGFR<60 (p-value likelihood-ratio test for interaction<0.001). In Northern India,
199 eGFR<60 was not associated with urban/rural residence, and older age was the only factor associated with
200 eGFR<60. In Southern India, rural residence was the strongest risk factor for eGFR<60 but older age and lower
201 level of formal education also increased the risk of eGFR<60 (Table 5).

202 **Sensitivity analyses**

203 We performed a sensitivity analysis including those with ACR>300 (but without hypertension or diabetes, n=33)
204 as we were concerned that those with CKDu might develop proteinuria at more advanced CKD stages. However,
205 this did not alter the mean eGFR (mean eGFR among the overall study population=105.0±17.8, mean eGFR in
206 this sensitivity analysis =105.0±17.8), nor the estimated prevalence of eGFR<60 (prevalence among the overall
207 study population=1.6%; prevalence in this sensitivity analysis =1.7%). The findings on risk factors were also
208 similar to the findings from the primary analyses (supplementary material, Table S3).

209 Given concerns about potentially different thresholds to define diabetes and high blood pressure in different
210 ethnic groups (Herman 2009; Modesti et al. 2016), we performed a further sensitivity analysis including fasting
211 plasma glucose, HbA1c and systolic blood pressure in the multivariate model (even though there is evidence for
212 both causation and reverse causation between these factors and CKD (Verhave et al. 2005)). Systolic blood
213 pressure and fasting plasma glucose were associated with reduced eGFR in this non diabetic population, but
214 inclusion of these variables did not alter the coefficients for the associations with other risk factors observed in
215 the primary analysis (supplementary material, Table S4). HbA1c was associated with eGFR<60 in this non
216 diabetic population but inclusion of this variable did not alter the OR for other risk factors observed in the
217 primary analysis (supplementary material, Table S4). Therefore, although the relationship between sub-clinical
218 diabetes and impaired kidney function requires further prospective investigation, there is no evidence that the
219 excess risk of low eGFR (i.e. lower mean eGFR and higher prevalence of eGFR<60) in rural Southern India is
220 associated with either impaired fasting glucose or higher blood pressure.

221 DISCUSSION

222 We report the distribution of eGFR in people without diabetes, hypertension or heavy proteinuria and estimate
223 the prevalence of CKDu in our study population, including participants from urban and rural settings. We found
224 that the rural population from Southern India (Vishakhapatnam district) had the highest risk of low eGFR (lower
225 mean eGFR and higher prevalence of eGFR<60). In Southern India, rural residence, older age and lower
226 education were risk factors for decreased eGFR, and there was also some evidence for higher risks in males. In
227 Northern India, older age was the only risk factor for low eGFR. This is the first population-based evidence,
228 using standardised methods, which indicates that CKDu is present in India and is not confined to Central
229 America and Sri Lanka.

230 As in Central America, the risk of low eGFR was higher in rural settings than in urban settings. This is in
231 concordance with a previous study from Hyderabad (India), that has provided evidence of a higher risk of low
232 eGFR in a rural population compared to urban-migrant and urban population (Bailey et al. 2013), and with
233 various studies from other LMICs that have provided evidence of clusters of CKDu among the rural population
234 (Correa-Rotter, Wesseling, and Johnson 2014; Jayatilake et al. 2013). Exposure to some of the suggested
235 potential risk factors for CKDu such as agricultural work and agrochemical exposure, amongst others (Lunyera
236 et al. 2016), may be greater in rural settings. Such exposures may also differ between Southern and Northern
237 India, and potentially explain the differences observed between these areas. The associations between urban/rural
238 residence and lower mean eGFR was much more marked in Southern India than in Northern India, and the
239 associations between urban/rural residence and eGFR<60 was only observed in Southern India. The higher
240 prevalence ratio (for eGFR<60) in the working age population compared to older age groups is consistent with
241 the hypothesis that decreased in eGFR could be potentially explained by occupational exposures. The suggestive
242 sex differences may also support this hypothesis. However, we did not have detailed data on occupation that
243 allowed us to explore these associations in greater detail.

244 The higher risk of low eGFR in Southern India (Chennai and Vishakhapatnam districts) observed in our study is
245 consistent with the clusters of CKDu cases previously reported in the Southern Indian states of Andhra Pradesh
246 and Odisha (Chatterjee 1026; Ganguli 2016; Reddy and Gunasekar 2013). Visakhapatnam district (state of
247 Andhra Pradesh) and Chennai district (state of Tamil Nadu) have a similar climate than these areas where
248 CKDu clusters have previously reported (Peel, Finlayson, and McMahon 2007). In these districts, mean
249 temperatures range from 18 °C to 37 °C and rainfall occurs mainly between June and December (Norwegian
250 Meteorological Institute and the Norwegian Broadcasting Corporation n.d.). On the other hand, sites from
251 Northern India included in the study (Delhi (state of Delhi), Sonipat and Faridabad (Haryana state)), have a
252 different climate. In these districts mean temperature ranges from 8 °C to 39 °C and precipitation occurs mainly
253 between July and August (Norwegian Meteorological Institute and the Norwegian Broadcasting Corporation
254 n.d.). A previous study conducted in Costa Rica found a spatial correlation between rates of CKD mortality and
255 temperature and rainfall (Catharina Wesseling et al. 2015).

256 About 5% of the rural population of Vishakhapatnam (Andhra Pradesh, Southern India) without diabetes,
257 hypertension or proteinuria had eGFR<60. This figure is almost as high as the prevalence observed in the USA
258 (i.e. 6.7%) including people with diabetes, hypertension or proteinuria (Levey and Coresh 2012). Moreover, the

estimates of GFR in our study are likely to be underestimated. The CKD-EPI equation has been standardised for the white and Afro-American population (Levey et al. 2009), but its validity for other ethnic groups has been questioned (Eastwood et al. 2010; Teo et al. 2011). Previous studies using CKD-EPI equation to estimate GFR in Indian populations reported mean eGFR values similar to the mean eGFR reported in our study (i.e. 104.9 ± 25.52 ml/min/1.73 m²) (Singh et al. 2013). However, two studies conducted among healthy kidney donors in India (population similar to those included in this analysis) have reported mean (measured) GFR between 81.4 and 95.5 ml/min per 1.73 m² (Barai et al. 2005; Srinivas et al. 2008), suggesting that the CKD-EPI equation substantially overestimates eGFR in the Indian population. Therefore, the prevalence of eGFR<60 observed in this study is likely to be substantially underestimated (although this is unlikely to have biased the internal comparisons, e.g. between urban and rural settings). The use of a conservative definition of the population susceptible to CKDu, may have also underestimated the prevalence of eGFR<60 in our study, as the population with diabetes, hypertension or glomerular disease may also have reduced eGFR due to other ('unknown') causes. To estimate the actual prevalence of reduced eGFR, future studies should include validated methods to estimate GFR in the Indian population. We were concerned that the validity of CKD-EPI among the Indian population may be also compromised by differences in muscular mass and meat consumption between population groups within India. We adjusted the analyses for fat free mass and vegetarianism, but this did not alter the results, suggesting no confounding effect by these variables.

Our study has at least three potential limitations. First, we only had one measure of eGFR, and therefore we could not differentiate acute kidney injury (AKI) from CKD. This is a common limitation in epidemiological studies, as it is challenging to obtain more than one measure of eGFR at least 3 months apart in large population-based investigations. Therefore, we may have misclassified some cases of AKI as reduced eGFR, and therefore overestimate the prevalence of this condition. Nevertheless, there is no a priori reason to think that potential misclassification was different according to the evaluated risks factors. Second, the three population-based studies included in this analysis used different sampling strategies. CARRS and UDAY studies included only one man and one woman from all the eligible participants of selected households, whereas ICMR-CHD included all eligible adults from each selected household. This could have slightly biased our results (including our prevalence estimates) if risk factors potentially associated with CKDu were different between households inhabited only by a man and a women or by extended families. Third, information on other potential risk factors for CKDu, such as infections by leptospora or hantavirus infection, or use of nonsteroidal anti-inflammatory drugs (NSAIDs) was not available.

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3 289 The main strengths of the study are the use of a random selection of population-based participants and a large
4
5 290 sample size including participants from different areas of India (urban and rural, and Northern and Southern
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7 291 India). Moreover, we used the definitions proposed in DRGREE study (Caplin et al. 2017), that aims to allow
8
9 292 international comparisons of CKDu prevalence and help in the description of risk factors and in identifying the
10
11 293 causes and mechanisms leading to CKDu.

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13 294 In conclusion, our findings indicate that reduced eGFR, consistent with the definition of CKDu, is common in
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15 295 rural settings of Southern India (Vishakhapatnam district). This results support the hypothesis that the epidemic
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17 296 of CKDu, initially described in agricultural communities of Central America and Sri Lanka, may be common in
18
19 297 other rural communities of tropical/subtropical countries. This has important implications for global health, since
20
21 298 it indicates that CKDu may have a substantial public health burden globally that has been previously
22
23 299 unrecognised. Population-based studies in other tropical/subtropical countries are required to assess the global
24
25 300 patterns of burden of disease from CKDu (Caplin et al. 2017).

301 **AUTHOR CONTRIBUTIONS AND ACKNOWLEDGEMENTS**

302 CO-G, BC, NP and DP designed the analysis; RS, SM, PPA, DK and SG let the collection of the original data;
303
304 all authors participated in interpretation and discussion of results; CO-G, BC and NP drafted the manuscript. All
305
306 authors contributed to critical reading of the report, provided comments and suggested revisions, and approved
307
308 the final version for publication.

309
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311 **CONFLICTS OF INTERESTS**

312
313 The authors declare that they have no competing interests

314 **DATA SHARING STATEMENT**

315
316 The datasets used and/or analysed during the current study are available from Public Health Foundation of India
317
318 (PHFI) on reasonable request. Interested investigators should contact PHFI. Computing code can be obtained
319
320 from the corresponding author.

321

314 REFERENCES

- 315 Anand, Shuchi, Roopa Shivashankar, Mohammed K Ali, Dimple Kondal, B Binukumar, Maria E Montez-rath,
316 Vamadevan S Ajay, et al. 2015. "Prevalence of Chronic Kidney Disease in Two Major Indian Cities and
317 Projections for Associated Cardiovascular Disease." *Kidney International* 88 (1). Nature Publishing
318 Group:178–85. <https://doi.org/10.1038/ki.2015.58>.
- 319 Bailey, Phillippa K, Charles R V Tomson, Sanjay Kinra, Shah Ebrahim, K V Radhakrishna, Hannah Kuper,
320 Dorothea Nitsch, and Yoav Ben-shlomo. 2013. "The Effect of Rural-to-Urban Migration on Renal
321 Function in an Indian Population : Cross-Sectional Data from the Hyderabad Arm of the Indian Migration
322 Study."
- 323 Barai, Sukanta, G P Bandopadhyaya, C D Patel, Manish Rathi, R Kumar, D Bhowmik, S Gambhir, N Gopendro
324 Singh, A Malhotra, and K D Gupta. 2005. "Do Healthy Potential Kidney Donors in India Have an Average
325 Glomerular Filtration Rate of 81.4 ML/min?" *Nephron. Physiology* 101 (1):p21-6.
326 <https://doi.org/10.1159/000086038>.
- 327 Barsoum, Rashad S. 2013. "Burden of Chronic Kidney Disease: North Africa." *Kidney International*
328 *Supplements* 3 (2):164–66. <https://doi.org/10.1038/kisup.2013.5>.
- 329 Caplin, Ben, Kristina Jakobsson, Jason Glaser, Dorothea Nitsch, Vivekanand Jha, Ajay Singh, Ricardo Correa-
330 Rotter, and Neil Pearce. 2017. "International Collaboration for the Epidemiology of eGFR in Low and
331 Middle Income Populations - Rationale and Core Protocol for the Disadvantaged Populations eGFR
332 Epidemiology Study (DEGREE)." *BMC Nephrology* 18 (1):1. <https://doi.org/10.1186/s12882-016-0417-1>.
- 333 Chatterjee, Rhitu. 1026. "Occupational Hazard." *Science*, 1026.
- 334 Correa-Rotter, Ricardo, Catharina Wesseling, and Richard J Johnson. 2014. "CKD of Unknown Origin in
335 Central America: The Case for a Mesoamerican Nephropathy." *American Journal of Kidney Diseases :
336 The Official Journal of the National Kidney Foundation* 63 (3):506–20.
337 <https://doi.org/10.1053/j.ajkd.2013.10.062>.
- 338 Dare, Anna J, Sze Hang Fu, Jayadeep Patra, Peter S Rodriguez, J S Thakur, Prabhat Jha, J Coresh, et al. 2017.
339 "Renal Failure Deaths and Their Risk Factors in India 2001–13: Nationally Representative Estimates from
340 the Million Death Study." *The Lancet Global Health* 5 (1). The Author(s). Published by Elsevier Ltd. This
341 is an Open Access article under the CC BY license:e89–95. [https://doi.org/10.1016/S2214-
342 109X\(16\)30308-4](https://doi.org/10.1016/S2214-109X(16)30308-4).
- 343 Eastwood, J. B., S. M. Kerry, J. Plange-Rhule, F. B. Micah, S. Antwi, F. G. Boa, D. Banerjee, and F. P.
344 Cappuccio. 2010. "Assessment of GFR by Four Methods in Adults in Ashanti, Ghana: The Need for an
345 eGFR Equation for Lean African Populations." *Nephrology Dialysis Transplantation* 25 (7):2178–87.
346 <https://doi.org/10.1093/ndt/gfp765>.
- 347 Ganguli, Anirban. 2016. "Uddanam Nephropathy/Regional Nephropathy in India: Preliminary Findings and a
348 Plea for Further Research." *American Journal of Kidney Diseases*. National Kidney Foundation, Inc., 2–6.
349 <https://doi.org/10.1053/j.ajkd.2016.04.012>.
- 350 Garcia-Garcia, Guillermo, Vivekanand Jha, and World Kidney Day Steering Committee. 2015. "Environmental
351 and Occupational Factors in CKD." *Occupational and Environmental Medicine* 72 (3):238.
352 <https://doi.org/10.1136/oemed-2015-102859>.
- 353 Greenland, Sander, Rhian Daniel, Neil Pearce, Sander Greenland, Rhian Daniel, and Neil Pearce. 2016.
354 "Outcome Modelling Strategies in Epidemiology: Traditional Methods and Basic Alternatives."
355 *International Journal of Epidemiology*, no. April:1–11. <https://doi.org/10.1093/ije/dyw040>.
- 356 Herman, William H. 2009. "Do Race and Ethnicity Impact Hemoglobin A1c Independent of Glycemia?" *Journal*
357 *of Diabetes Science and Technology* 3 (4):656–60. <https://doi.org/10.1177/193229680900300406>.
- 358 Jayasumana, Channa, Priyani Paranagama, Suneth Agampodi, Chinthaka Wijewardane, Sarath Gunatilake, and
359 Sisira Siribaddana. 2015. "Drinking Well Water and Occupational Exposure to Herbicides Is Associated
360 with Chronic Kidney Disease, in Padavi-Sripura, Sri Lanka." *Environmental Health : A Global Access*
361 *Science Source* 14 (1):6. <https://doi.org/10.1186/1476-069X-14-6>.
- 362 Jayatilake, Nihal, Shanthi Mendis, Palitha Maheepala, and Firdosi R Mehta. 2013. "Chronic Kidney Disease of
363 Uncertain Aetiology: Prevalence and Causative Factors in a Developing Country." *BMC Nephrology* 14
364 (1). BMC Nephrology:180. <https://doi.org/10.1186/1471-2369-14-180>.
- 365 Jha, Vivekanand, and Gopesh Modi. 2017. "Uncovering the Rising Kidney Failure Deaths in India." *The Lancet*

- 366 *Global Health* 5 (1). The Author(s). Published by Elsevier Ltd. This is an Open Access article under the
367 CC BY-NC-ND license:e14–15. [https://doi.org/10.1016/S2214-109X\(16\)30299-6](https://doi.org/10.1016/S2214-109X(16)30299-6).
- 368 Lebov, Jill F, Eliette Valladares, Rodolfo Pena, Edgar M Pena, Scott L Sanoff, Efrén Castellón Cisneros,
369 Romulo E Colindres, Douglas R Morgan, and Susan L Hogan. 2015. “A Population-Based Study of
370 Prevalence and Risk Factors of Chronic Kidney Disease in Leon, Nicaragua.” *Canadian Journal of Kidney
371 Health and Disease* 2. ???6. <https://doi.org/10.1186/s40697-015-0041-1>.
- 372 Levey, Andrew S., and Josef Coresh. 2012. “Chronic Kidney Disease.” *The Lancet* 379 (9811). Elsevier
373 Ltd:165–80. [https://doi.org/10.1016/S0140-6736\(11\)60178-5](https://doi.org/10.1016/S0140-6736(11)60178-5).
- 374 Levey, Andrew S, Lesley A Stevens, Christopher H Schmid, Yaping Lucy Zhang, Alejandro F Castro, Harold I
375 Feldman, John W Kusek, et al. 2009. “A New Equation to Estimate Glomerular Filtration Rate.” *Annals of
376 Internal Medicine* 150 (9):604–12. <http://www.ncbi.nlm.nih.gov/pubmed/19414839>.
- 377 Lunyera, Joseph, Dinushika Mohottige, Megan von Isenburg, Marc Jeuland, Uptal D. Patel, and John W.
378 Stanifer. 2016. “CKD of Uncertain Etiology: A Systematic Review.” *Clinical Journal of the American
379 Society of Nephrology* 11 (3):379–85. <https://doi.org/10.2215/CJN.07500715>.
- 380 Minshawy, Osama El, Tawfik Ghabrah, and Eman El Bassuoni. 2014. “End-Stage Renal Disease in Tabuk Area,
381 Saudi Arabia: An Epidemiological Study.” *Saudi Journal of Kidney Diseases and Transplantation : An
382 Official Publication of the Saudi Center for Organ Transplantation, Saudi Arabia* 25 (1):192–95.
383 <http://www.ncbi.nlm.nih.gov/pubmed/24434411>.
- 384 Modesti, Pietro Amedeo, Gianpaolo Reboldi, Francesco P Cappuccio, Charles Agyemang, Giuseppe Remuzzi,
385 Stefano Rapi, Eleonora Perruolo, and Gianfranco Parati. 2016. “Panethnic Differences in Blood Pressure
386 in Europe: A Systematic Review and Meta-Analysis.” *PLoS One* 11 (1):e0147601.
387 <https://doi.org/10.1371/journal.pone.0147601>.
- 388 Mohan, S, P; Jarhyan, S; Ghosh, SV; Nikhil, R; Gupta, R; Rana, C; Malhotra, et al. 2017. “UDAY: Protocol of
389 a Comprehensive Diabetes and Hypertension Prevention and Management Program in India.” *BMJ Open*.
390 In Press.
- 391 Nair, Manisha, Mohammed K Ali, Vamadevan S Ajay, Roopa Shivashankar, Viswanathan Mohan, Rajendra
392 Pradeepa, Mohan Deepa, et al. 2012. “CARRS Surveillance Study: Design and Methods to Assess Burdens
393 from Multiple Perspectives.” *BMC Public Health* 12 (1). BMC Public Health:701.
394 <https://doi.org/10.1186/1471-2458-12-701>.
- 395 Norwegian Meteorological Institute and the Norwegian Broadcasting Corporation. n.d. “Yr.” Accessed January
396 19, 2018. <https://www.yr.no>.
- 397 Peel, M. C., B. L. Finlayson, and T. A. McMahon. 2007. “Updated World Map of the Köppen-Geiger Climate
398 Classification.” *Hydrology and Earth System Sciences* 11:1633–1644.
- 399 Peraza, Sandra, Catharina Wesseling, Aurora Aragon, Ricardo Leiva, Ramón Antonio García-Trabanino, Cecilia
400 Torres, Kristina Jakobsson, Carl Gustaf Elinder, and Christer Hogstedt. 2012. “Decreased Kidney Function
401 among Agricultural Workers in El Salvador.” *American Journal of Kidney Diseases : The Official Journal
402 of the National Kidney Foundation* 59 (4):531–40. <https://doi.org/10.1053/j.ajkd.2011.11.039>.
- 403 Prabhakaran, Dorairaj, Ambuj Roy, Pradeep A. Praveen, Lakshmy Ramakrishnan, Ruby Gupta, Ritvik
404 Amarchand, Dimple Kondal, et al. 2017. “20-Year Trend of Cardiovascular Disease Risk Factors.” *Global
405 Heart*. <https://doi.org/10.1016/j.gheart.2016.11.004>.
- 406 Rajapurkar, Mohan M, George T John, Ashok L Kirpalani, Georgi Abraham, Sanjay K Agarwal, Alan F
407 Almeida, Sishir Gang, et al. 2012. “What Do We Know about Chronic Kidney Disease in India: First
408 Report of the Indian CKD Registry.” *BMC Nephrology* 13 (1):10. <https://doi.org/10.1186/1471-2369-13-10>.
- 410 Reddy, D. V., and A. Gunasekar. 2013. “Chronic Kidney Disease in Two Coastal Districts of Andhra Pradesh,
411 India: Role of Drinking Water.” *Environmental Geochemistry and Health* 35 (4):439–54.
412 <https://doi.org/10.1007/s10653-012-9506-7>.
- 413 Robey, R Brooks. 2014. “Cyclical Dehydration-Induced Renal Injury and Mesoamerican Nephropathy: As
414 Sweet by Any Other Name?” *Kidney International* 86 (2):226–29. <https://doi.org/10.1038/ki.2014.47>.
- 415 Seck, Sidy Mohamed, Dominique Doupa, Lamine Gueye, and Charles Abdou Dia. 2014. “Prevalence of Chronic
416 Kidney Disease and Associated Factors in Senegalese Populations: A Community-Based Study in Saint-
417 Louis.” *Nephro-Urology Monthly* 6 (5):e19085. <https://doi.org/10.5812/numonthly.19085>.
- 418 Singh, Ajay K., Youssef MK Farag, Bharati V. Mittal, Kuyilan Karai Subramanian, Sai Ram Keithi Reddy,

- 1
2
3 419 Vidya N. Acharya, Alan F. Almeida, et al. 2013. "Epidemiology and Risk Factors of Chronic Kidney
4 420 Disease in India – Results from the SEEK (Screening and Early Evaluation of Kidney Disease) Study."
5 421 *BMC Nephrology* 14 (1). BMC Nephrology:114. <https://doi.org/10.1186/1471-2369-14-114>.
- 6 422 Srinivas, Sanjay, Rajeev A Annigeri, Muthu Krishna Mani, Budithi Subba Rao, Prakash C Kowdle, and
7 423 Rajagopalan Seshadri. 2008. "Estimation of Glomerular Filtration Rate in South Asian Healthy Adult
8 424 Kidney Donors." *Nephrology (Carlton, Vic.)* 13 (5):440–46. <https://doi.org/10.1111/j.1440->
9 425 1797.2008.00967.x.
- 10 426 Teo, Boon Wee, Hui Xu, Danhua Wang, Jialiang Li, Arvind Kumar Sinha, Borys Shuter, Sunil Sethi, and Evan J
11 427 C Lee. 2011. "GFR Estimating Equations in a Multiethnic Asian Population." *American Journal of Kidney*
12 428 *Diseases : The Official Journal of the National Kidney Foundation* 58 (1):56–63.
13 429 <https://doi.org/10.1053/j.ajkd.2011.02.393>.
- 14 430 Torres, Cecilia, Aurora Aragón, Marvin González, Indiana López, Kristina Jakobsson, Carl-Gustaf Elinder,
15 431 Ingvar Lundberg, and Catharina Wesseling. 2010. "Decreased Kidney Function of Unknown Cause in
16 432 Nicaragua: A Community-Based Survey." *American Journal of Kidney Diseases : The Official Journal of*
17 433 *the National Kidney Foundation* 55 (3):485–96. <https://doi.org/10.1053/j.ajkd.2009.12.012>.
- 18 434 Verhave, Jacobien C., Hans L. Hillege, Johannes G M Burgerhof, Ron T. Gansevoort, Dick De Zeeuw, and Paul
19 435 E. De Jong. 2005. "The Association between Atherosclerotic Risk Factors and Renal Function in the
20 436 General Population." *Kidney International* 67 (5):1967–73. <https://doi.org/10.1111/j.1523->
21 437 1755.2005.00296.x.
- 22 438 Wesseling, C, J Crowe, C Hogstedt, K Jakobsson, R Lucas, and D Wegman. 2013. "Mesoamerican
23 439 Nephropathy: Report from the First International Research Workshop on MeN." Heredia, Costa Rica.
24 440 [http://www.regionalnephropathy.org/wp-content/uploads/2013/04/Technical-Report-for-Website-](http://www.regionalnephropathy.org/wp-content/uploads/2013/04/Technical-Report-for-Website-Final.pdf)
25 441 [Final.pdf](http://www.regionalnephropathy.org/wp-content/uploads/2013/04/Technical-Report-for-Website-Final.pdf).
- 26 442 Wesseling, Catharina, Berna van Wendel de Joode, Jennifer Crowe, Ralf Rittner, Negin A Sanati, Christer
27 443 Hogstedt, and Kristina Jakobsson. 2015. "Mesoamerican Nephropathy: Geographical Distribution and
28 444 Time Trends of Chronic Kidney Disease Mortality between 1970 and 2012 in Costa Rica." *Occupational*
29 445 *and Environmental Medicine* 72 (10):714–21. <https://doi.org/10.1136/oemed-2014-102799>.
- 30 446 World Health Organization. 2015. "STEPS Manual." 2015.
- 31
32 447
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449 TABLES

450 Table 1. Design and methods of the three studies included in the current analysis

	CARRS		UDAY				ICMR-CHD	
Latitude (North/South)	North	South	North		South		North	
Residence (Urban/Rural)	Urban		Urban	Rural	Urban	Rural	Urban	Rural
District (and State)	Delhi (state of Delhi)	Chennai (state of Tamil Nadu)	Sonapat (state of Haryana)		Vishakhapatnam (state of Andhra Pradesh)		National Capital Territory of Delhi (state of Delhi)	Faridabad (state of Haryana)
Household sampling	Multistage cluster random (wards - census enumeration blocks - households)		Multistage cluster random (Census Enumeration blocks (urban) or villages (rural) - households)				Multistage cluster random (wards - census enumeration blocks - households)	Simple cluster random (based on Health and Demographic Surveillance System)
Individual sampling	1 man and 1 woman from each household (selected by Kish method, (World Health Organization. 2015).)		1 man and 1 woman from each household (selected by Kish method, (World Health Organization. 2015).)				All adults	
Age groups included	≥ 20		≥ 30				≥ 30	
Exclusion criteria	Pregnant, bedridden and participants who were unable to comprehend the questionnaires due cognitive deficiencies were excluded							
Study period	October 2010 - November 2011		July 2014 - December 2014				August 2010 - January 2012	
Laboratory^a	PHFI ^b	MDRF ^c	PHFI ^b				PHFI ^b	

451 ^a Study laboratories participated in Randox International Quality Assurance Scheme (RIQAS) for clinical
 452 chemistry and HbA1c during the entire study periods. ^b Public Health Foundation of India; ^c Madras Diabetes
 453 Research Foundation

454 **Table 2.** Sociodemographic and anthropometric characteristics of study participants (population without
455 diabetes, hypertension or heavy proteinuria)

Variable	n (%) ^a n=12,500	eGFR mean (SD)	eGFR categories, n(%) ^b		
			≥90	90-60	<60
Socio-demographic					
Age (years)					
<39	6121 (49)	113.8 (14.6)	5656 (92)	443 (7)	22 (0)
40-49	3476 (28)	102.5 (14.2)	2864 (82)	572 (16)	40 (1)
50-59	1706 (14)	93.9 (14.3)	1163 (68)	503 (29)	40 (2)
60-69	893 (7)	85.3 (16.2)	463 (52)	368 (41)	62 (7)
≥70	304 (2)	77.5 (15.1)	62 (20)	201 (66)	41 (13)
Sex					
Female	7066 (57)	107.9 (17.1)	6039 (85)	945 (13)	82 (1)
Male	5434 (43)	101.3 (17.9)	4169 (77)	1142 (21)	123 (2)
Education (number completed years)					
0	2820 (23)	100.7 (19.0)	2165 (77)	551 (20)	104 (4)
≤5	1709 (14)	105.9 (17.3)	1412 (83)	273 (16)	24 (1)
6-≤10	4817 (39)	107.2 (16.8)	4095 (85)	675 (14)	47 (1)
> 10	3154 (25)	105.0 (17.5)	2536 (80)	588 (19)	30 (1)
Area ^c					
Urban	8494 (68)	107.8 (16.1)	7247 (85)	1171 (14)	76 (1)
Rural	4006 (32)	99.0 (18.0)	2961 (74)	916 (23)	129 (3)
Latitude ^d					
North	6263 (50)	103.0 (17.2)	4967 (79)	1197 (19)	99 (2)
South	6237 (50)	107.0 (18.1)	5241 (84)	890 (14)	106 (2)
Life-style factors					
Current tobacco consumption					
No	9357 (75)	106.8 (17.3)	7836 (84)	1406 (15)	115 (1)
Yes	3143 (25)	99.8 (18.1)	2372 (75)	681 (22)	90 (3)
Alcohol consumption ever					
No	10094 (81)	105.9 (17.4)	8362 (83)	1589 (16)	143 (1)
Yes	2406 (19)	101.1 (18.5)	1846 (77)	498 (21)	62 (3)
Vegetarian					

No	7972 (64)	107.0 (18.0)	6690 (84)	1154 (14)	128 (2)
Yes	4528 (36)	101.6 (16.6)	3518 (78)	933 (21)	77 (2)
Biological factors					
Body mass index (kg/m ²)					
Underweight (≤ 18.5)	5879 (47)	104.2 (17.9)	4734 (81)	1029 (18)	116 (2)
Normal ($>18.5 - \leq 25$)	1576 (13)	104.7 (19.3)	1283 (81)	257 (16)	36 (2)
Overweight ($>25 - \leq 30$)	3313 (27)	105.0 (16.9)	2710 (82)	568 (17)	35 (1)
Obese (>30)	1150 (9)	105.5 (16.4)	948 (82)	194 (17)	8 (1)
Missing data	582 (5)		533 (92)	39 (7)	10 (2)
Fat free mass (kg/m ²)					
1 st tertile (≤ 37)	3746 (30)	106.6 (18.1)	3146 (84)	532 (14)	68 (2)
2 nd tertile ($>37 - <45$)	3801 (30)	105.9 (17.2)	3145 (83)	601 (16)	55 (1)
3 rd tertile (≤ 45)	3834 (31)	102.1 (17.0)	2981 (78)	801 (21)	52 (1)
Missing data	1119 (9)		936 (84)	153 (14)	30 (3)

456 ^a Percentages in columns; ^b percentages in rows; ^c Urban areas include Delhi, Chennai and Sonipat district.

457 Rural areas include Sonipat, Vishakhapatnam and Faridabad districts; ^d North areas include Delhi, Sonipat

458 and Faridabad district. South areas include Chennai and Vishakhapatnam districts.

459 **Table 3.** Associations between sociodemographic and anthropometric characteristics and eGFR and
 460 eGFR<60

	eGFR	eGFR<60
Variable	Coefficient (95% CI) ^a	OR (95% CI) ^a
Age (years) ^b		
<39		1
40-49	-11 (-12 - -10)	3.1 (1.9 - 5.3)
50-59	-19 (-20 - -19)	6.4 (3.8 - 10)
60-69	-28 (-29 - -27)	20 (12 - 32)
>=70	-35 (-37 - -33)	39 (23 - 67)
Sex ^c		
Female		1
Male	-3.5 (- 4.0 - -3.1)	1.3 (0.99 - 1.8)
Education (number of completed years)		
0		1
≤5	1.9 (1.1 - 2.8)	0.41 (0.26 - 0.65)
6-≤10	1.3 (0.6 - 1.9)	0.36 (0.25 - 0.53)
> 10	-1.9 (-2.6 - -1.1)	0.40 (0.26 - 0.62)
Area ^d		
Urban		1
Rural	-3.8 (-4.4 - -3.3)	2.4 (1.8 - 3.2)
Latitude ^e		
North		1
South	0.86 (0.37 - 1.3)	1.5 (1.2 - 2.1)
Current tobacco consumption		
No		1
Yes	0.38 (-0.26 - 1.0)	1.4 (1.0 - 1.9)
Alcohol consumption ever		
No		1
Yes	-0.81 (-1.5 - -0.08)	1.6 (1.09 - 2.3)
Vegetarian		
No		1
Yes	-0.99 (-1.5 - -0.47)	0.65 (0.48 - 0.88)

Body mass index (kg/m ²) ^g		
Underweight (≤ 18.5)	3.0 (2.2 - 3.7)	0.81 (0.55 - 1.2)
Normal ($>18.5 - \leq 25$)		1
Overweight ($>25 - \leq 30$)	-0.75 (-1.3 - -0.16)	0.7 (0.46 - 1.0)
Obese (>30)	-0.71 (-1.6 - 0.17)	0.47 (0.23 - 0.98)
Fat free mass (kg/m ²) ^g		
1 st tertile (≤ 37)		1
2 nd tertile ($>37 - <45$)	-0.91 (-1.5 - -0.28)	0.69 (0.47 - 1.0)
3 rd tertile (≤ 45)	-3.9 (-4.8 - -3.0)	0.49 (0.31 - 0.80)

461 ^a Adjusted for age and sex; ^b Adjusted just for sex; ^c Adjusted just for age; ^d Urban areas include Delhi,
 462 Chennai and Sonipat district. Rural areas include Sonipat, Vishakhapatnam and Faridabad districts; ^e
 463 North areas include Delhi, Sonipat and Faridabad district. South areas include Chennai and
 464 Vishakhapatnam districts.

465 **Table 4.** Multiple regression analyses of sociodemographic characteristics associated with eGFR and eGFR<6). Models adjusting for all variables, plus models further
466 adjusted for fat free mass and vegetarianism.

Variable	eGFR Coefficient (95% CI)			eGFR<60 OR (95% CI)		
	Model 1 ^a	Model 2 ^b	Model 3 ^c	Model 1 ^a	Model 2 ^b	Model 3 ^c
Area ^d						
Urban				1	1	1
Rural	-4.6 (-5.1 - -4.0)	-3.9 (-4.5 - -3.4)	-4.1 (-4.7 - -3.5)	2.0 (1.4 - 2.8)	1.6 (1.1 - 2.3)	1.6 (1.1 - 2.4)
Latitude ^e						
North				1	1	1
South	0.31 (-0.18 - 0.80)	-0.10 (-0.61 - 0.41)	0.26 (-0.37 - 0.89)	1.3 (1.0 - 1.8)	1.60 (1.1 - 2.2)	1.33 (0.86 - 2.0)
Education (number of completed years)						
0				1	1	1
≤5	0.93 (0.01 - 1.8)	1.2 (0.30 - 2.0)	1.2 (0.32 - 2.0)	0.50 (0.31 - 0.80)	0.44 (0.26 - 0.74)	0.45 (0.26 - 0.75)
6-≤10	0.31 (-0.18 - 0.80)	0.21 (-0.49 - 0.91)	0.21 (-0.50 - 0.92)	0.50 (0.34 - 0.75)	0.38 (0.24 - 0.60)	0.39 (0.25 - 0.62)
> 10	-4.0 (-4.6 - -3.0)	-3.8 (-4.6 - -3.0)	-3.8 (-4.6 - -230)	0.68 (0.42 - 1.11)	0.61 (0.36 - 1.0)	0.6 (0.38 - 1.1)

Alcohol consumption ever

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No				1	1	1
Yes	-0.85 (-1.6 - -0.11)	-0.69 (-1.5 - 0.08)	-0.63 (-1.4 - 0.15)	1.3 (0.88 - 1.9)	1.2 (0.78 - 1.8)	1.1 (0.76 - 1.7)
Sex						
Female				1	1	1
Male	-2.8 (-2.2 - -3.4)	3.0 (2.4 - 3.6)	2.5 (1.9 - 3.2)	0.72 (0.50 - 1.0)	0.67 (0.45 - 1.0)	0.67 (0.43 - 1.0)
Age (years)	-0.91 (-0.93 - -0.89)	-0.91 (-0.93 - -0.89)	-0.91 (-0.94 - -0.89)	1.1 (1.1 - 1.1)	1.1 (1.1 - 1.1)	1.1 (1.1 - 1.1)
Fat free mass (kg/m ²)			-0.04 (-0.06 - -0.02)			1.0 (0.98 - 1.0)
Vegetarian						
No						1
Yes			0.66 (-0.03 - 1.3)			0.74 (0.47 - 1.2)

467 ^a Model 1: Variables mutually adjusted, n=12,500; ^b Model 2: Variables mutually adjusted. Model excluding missing on fat free mass, n=11,381; ^c Model 3: Variables
 468 mutually adjusted. Model includes further adjustment for fat free mass and vegetarianism, n=11,381. ^d Urban areas include Delhi, Chennai and Sonipat district. Rural areas
 469 include Sonipat, Vishakhapatnam and Faridabad districts; ^e North areas include Delhi, Sonipat and Faridabad district. South areas include Chennai and Vishakhapatnam
 470 districts.

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471 **Table 5.** Multivariate analysis of sociodemographic characteristics associated with eGFR and with
 472 eGFR<60 according to latitude ^a

Variables	eGFR (n=12,500)		eGFR<60(n=12,500)	
	North (n=6263) ^a	South (n= 6237) ^a	North (n=6263) ^a	South (n= 6237) ^a
	Coefficient (95% CI)	Coefficient (95% CI)	OR (95% CI)	OR (95% CI)
Area ^b				
Urban				
Rural	-1.4 (-2.1 - -0.70)	-7.9 (-8.8 - -7.0)	1	1
Education (number of completed years)			0.88 (0.57 - 1.4)	4.7 (2.5 - 8.8)
0				
≤5	-1.3 (-2.6 - -0.05)	1.0 (-0.06 - 2.2)	1	1
6-≤10	-3.5 (-4.5 - -2.5)	0.28 (-0.74 - 1.3)	1.2 (0.57 - 2.3)	0.40 (0.20 - 0.80)
> 10	-6.9 (-8.0 - -5.9)	-2.8 (-4.0 - -1.7)	1.3 (0.74 - 2.4)	0.35 (0.16 - 0.74)
Alcohol consumption				
ever			1.3 (0.69 - 2.6)	0.61 (0.24 - 1.6)
No				
Yes	-0.54 (-1.5 - 0.47)	-0.06 (-1.1 - 0.99)	1	1
Sex			1.1 (0.62 - 1.9)	1.3 (0.74 - 2.2)
Female				
Male	0.17 (-0.63 - 0.96)	5.4 (4.5 - 6.3)	1	1
Age (years)	-0.93 (-0.96 - -0.90)	-0.90 (-0.93 - -0.86)	1.0 (0.63 - 1.7)	0.63 (0.36 - 1.1)

473 ^{**} Likelihood ratio test for linear trend <0.05, OR (95% CI)=0.67 (0.50-0.90). ^aNorth areas include Delhi,
 474 Sonipat and Faridabad district. South areas include Chennai and Vishakhapatnam districts. ^bUrban areas
 475 include Delhi, Chennai and Sonipat district. Rural areas include Sonipat, Vishakhapatnam and Faridabad
 476 districts

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3 479 **FIGURES LEGENDS**

4
5 480 **Figure 1** Study flowchart

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7 481 **Figure 2** Prevalence ratio of eGFR<60 by age group between rural and urban areas

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3 482 **SUPPLEMENTARY MATERIAL**

4
5 483 **Content**

6
7 484 **Table S1.** Sociodemographic and anthropometric characteristics of overall study participants (prior to
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9 485 exclusion of population with diabetes, hypertension and proteinuria)

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11
12 486 **Table S2.** Associations between sociodemographic and anthropometric characteristics and estimated
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14 487 glomerular filtration rate (eGFR) and eGFR<60 by sex

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16
17 488 **Table S3.** Multiple regression analysis of sociodemographic and anthropometric characteristics
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19 489 associated with eGFR and eGFR<60 including study participants with proteinuria (but without diabetes or
20
21 490 hypertension)

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24 491 **Table S4.** Multiple regression analysis of sociodemographic and anthropometric characteristics
25
26 492 associated with eGFR and eGFR<60 including fasting plasma glucose, HbA1c and systolic blood
27
28 493 pressure

494 **Table S1.** Sociodemographic and anthropometric characteristics of overall study participants (prior to
 495 exclusion of population with diabetes, hypertension and proteinuria)

496

Variable	n (%) n=12 500	eGFR		eGFR categories, n(%)**			
		mean (SD)	p-value [§]	≥90	90-60	<60	p-value ^{§§}
Socio-demographic factors							
Age (years)							
<39	9007 (36)	112.9 (14.9)	<0.001	8248 (92)	716 (8)	43 (0)	<0.001
40-49	6924 (28)	101.9 (14.8)		5617 (81)	1215 (18)	92 (1)	
50-59	4524 (18)	92.9 (15.2)		2997 (66)	1378 (30)	149 (3)	
60-69	3045 (12)	82.8 (17.1)		1410 (46)	1315 (43)	320 (11)	
≥70	1274 (5)	72.0 (17.3)		164 (13)	806 (63)	304 (24)	
Sex							
Female	13433 (54)	102.6 (19.5)		10404 (77)	2585 (19)	444 (3)	<0.001
Male	11341 (46)	97.7 (19.3)	0.33	8032 (71)	2845 (25)	464 (4)	
Education (number of years)							
0	4794 (19)	97.7 (20.2)	<0.001	3458 (72)	1075 (22)	261 (5)	<0.001
5	3194 (13)	101.7 (19.4)		2456 (77)	625 (20)	113 (4)	
10	8855 (36)	103.2 (18.9)		6995 (79)	1620 (18)	240 (3)	
> 10	6358 (26)	100.0 (19.2)		4638 (73)	1538 (24)	182 (3)	
Missing data	1573 (6)			889 (57)	572 (36)	112 (7)	
Area ^e							
Urban	17732 (72)	102 (19.5)	0.03	13577 (77)	3602 (20)	553 (3)	<0.001
Rural	7042 (28)	96.3 (19.1)		4859 (69)	1828 (26)	355 (5)	
Latitude ^f							
North	13570 (55)	98.1 (19.1)	<0.001	9599 (71)	3439 (25)	532 (4)	<0.001
South	11204 (45)	103.1 (19.7)		8837 (79)	1991 (18)	376 (3)	
Life-style factors							
Current smoking							
No	18402 (74)	101.5 (19.6)	0.01	13920 (76)	3838 (21)	644 (3)	<0.001
Yes	6372 (26)	97.1 (19.1)		4516 (71)	1592 (25)	264 (4)	
Alcohol consumption ever							
No	19588 (79)	100.9 (19.6)	0.01	14671 (75)	4203 (21)	714 (4)	0.01
Yes	5186 (21)	98.5 (19.1)		3765 (73)	1227 (24)	194 (4)	
Vegetarian							
No	15043 (61)	102.7 (19.7)	<0.001	11721 (78)	2835 (19)	487 (3)	<0.001
Yes	9731 (39)	96.8 (18.9)		6715 (69)	2595 (27)	421 (4)	
Biological factors							
Body mass index (kg/m ²)							
Underweight (≤18.5)	10297 (42)	100.1 (19.6)	<0.001	7626 (74)	2284 (22)	387 (4)	0.01
Normal (>18.5 - ≤25)	2403 (10)	101.58 (20.5)		1838 (76)	471 (20)	94 (4)	
Overweight (>25 - ≤30)	7221 (29)	99.9 (18.8)		5309 (74)	1680 (23)	232 (3)	
Obese (>30)	3286 (13)	99.3 (19.2)		2392 (73)	766 (23)	128 (4)	
Missing data	1567 (6)			1271 (81)	229 (15)	67 (4)	
Fat free mass (kg/m ²)							
1 st tertile (≤37)	7141 (29)	101.9 (20.1)	<0.001	5481 (77)	1381 (19)	279 (4)	<0.001

2 nd tertile (>37 - <45)	7141 (29)	101.3 (19.1)	5419 (76)	1487 (21)	235 (3)
3 rd tertile (≤45)	7141 (29)	98.3 (18.6)	5110 (72)	1797 (25)	234 (3)
Missing data	3351 (14)		2426 (72)	765 (23)	160 (5)

497

498 ^a Percentages in columns; ^b percentages in rows; ^c Bartlett's test for equal variance; ^d Chi-square test; ^e

499 Urban areas include Delhi, Chennai and Sonipat district. Rural areas include Sonipat, Vishakhapatnam

500 and Faridabad districts; ^f North areas include Delhi, Sonipat and Faridabad district. South areas include

501 Chennai and Vishakhapatnam districts.

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502 **Table S2.** Associations between sociodemographic and anthropometric characteristics and estimated glomerular filtration rate (eGFR) and eGFR<60 by sex

Variable	Men, n=5 434			Women, n=7 066		
	n (%)	eGFR	eGFR<60	n (%)	eGFR	eGFR<60
		Coefficient (95% CI) ^a	OR (95% CI) ^a		Coefficient (95% CI) ^a	OR (95% CI) ^a
Age (years) ^b						
<39	2335 (43)			3786 (54)		
40-49	1568 (29)	-9.0 (-10 - -8.0)	2.4 (1.2 - 4.6)	1908 (27)	-12 (-13 --12)	4.5 (1.9 - 10)
50-59	843 (16)	-17 (-18 - -16)	3.8 (1.9 - 7.7)	863 (12)	-21 (-22 --20)	12 (5.2 - 27)
60-69	479 (9)	-25 (-27 - -24)	13 (7.0 - 24)	414 (6)	-30 (-31 --29)	33 (15 - 73)
>=70	209 (4)	-34 (-36 - -32)	31 (16 - 59)	95 (1)	-35 (-38 --32)	43 (16 - 118)
Education (number of completed years)						
0	823 (15)		1	1997 (28)		1
≤5	703 (13)	3.3 (1.8 - 4.7)	0.24 (0.13 - 0.46)	1006 (14)	0.73 (-0.27 -1.7)	0.81 (0.42 - 1.6)
6-≤10	2363 (43)	1.7 (0.51 - 2.8)	0.31 (0.20 - 0.48)	2454 (35)	0.67 (-0.13 -1.5)	0.43 (0.21 - 0.9)
> 10	1545 (28)	-1.3 (-2.6 - -0.10)	0.27 (0.15 - 0.47)	1609 (23)	-2.4 (-3.3 --1.5)	0.76 (0.40 - 1.5)
Area ^c	3583 (66)					
Urban	1851 (34)		1	4911 (70)		1
Rural		-4.0 (-4.8 - -3.2)	2.7 (1.8 - 4.0)	2155 (30)	-3.7 (-4.4 --3.0)	2.0 (1.3 - 3.1)
Latitude ^d						
North	2861 (53)		1	3402 (48)		1
South	2573 (47)	-1.5 (-2.3 - -0.74)	1.8 (1.2 - 2.6)	3664 (52)	2.6 (2.0 -3.2)	1.3 (0.83 - 2.0)
Current tobacco consumption						
No	2804 (52)		1	6553 (93)		1
Yes	2630 (48)	1.1 (0.36 - 1.9)	1.3 (0.91 - 1.9)	513 (7)	-1.9 (-3.1 --0.73)	1.5 (0.87 - 2.7)
Alcohol consumption ever						
No	3035 (56)		1	7059 (100)		1

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6	Yes	2399 (44)	-0.71 (-1.5 - 0.06)	1.6 (1.08 - 2.3)	7 (0)	-9.3 (-19 -0.4)	1.0 (1.0 - 1.0)
7	Vegetarian						
8	No	3576 (66)		1	4396 (62)		1
9	Yes	1858 (34)	0.65 (-0.18 - 1.5)	0.61 (0.41 - 0.90)	2670 (38)	-2.1 (-2.7 --1.5)	0.70 (0.44 - 1.1)
10	Body mass index (kg/m2) ^e						
11							
12	Underweight (≤18.5)	2888 (56)		1	2991 (44)		1
13	Normal (>18.5 - ≤25)	812 (16)	4.0 (2.9 - 5.2)	0.69 (0.42 - 1.1)	764 (11)	1.6 (0.57 -2.6)	1.1 (0.57 - 2.0)
14	Overweight (>25 - ≤30)	1209 (23)	-1.7 (-2.7 - -0.73)	0.71 (0.42 - 1.2)	2104 (31)	-0.11 (-0.84 -0.62)	0.67 (0.38 - 1.2)
15	Obese (>30)	243 (5)	-0.71 (-2.6 - 1.2)	0.36 (0.09 - 1.5)	907 (13)	-0.64 (-1.6 -0.33)	0.55 (0.23 - 1.3)
16	Fat free mass (kg/m2) ^e						
17							
18	1st tertile (≤37)	361 (8)		1	3833 (58)		1
19	2nd tertile (>37 - <45)	1351 (28)	-0.42 (-2.1 - 1.2)	0.78 (0.44 - 1.4)	2535 (39)	-1.4 (-2.0 --0.74)	0.67 (0.38 - 1.2)
20	3rd tertile (≤45)	3093 (64)	-3.7 (-5.3 - -2.2)	0.50 (0.28 - 0.90)	208 (3)	-1.4 (-3.2 -0.45)	0.58 (0.08 - 4.2)

503 ^a Adjusted for age; ^b Not adjusted for age; ^c Urban areas include Delhi, Chennai and Sonipat district. Rural areas include Sonipat, Vishakhapatnam and Faridabad districts; ^d

504 North areas include Delhi, Sonipat and Faridabad district. South areas include Chennai and Vishakhapatnam districts; ^e Variables with missing values.

505 **Table S3.** Multiple regression analysis of sociodemographic characteristics associated with eGFR and eGFR<60
506 including study participants with proteinuria (but without diabetes or hypertension), n=12533

507

Variable	eGFR	eGFR<60
	Coefficient (95% CI) ^a	OR (95% CI) ^a
Area [†]		
Urban		1
Rural	-4.6 (-5.1 - -4.0)	1.9 (1.4 - 2.7)
Latitude [‡]		
North		1
South	0.29 (-0.21 - 0.78)	1.3 (0.98 - 1.8)
Education (number of years)		
0		1
5	0.83 (0 - 1.7)	0.55 (0.35 - 0.87)
10	0.04 (-0.64 - 0.72)	0.51 (0.35 - 0.76)
> 10	-3.8 (-4.6 - -3.0)	0.66 (0.4 - 1.1)
Alcohol consumption ever		
No		1
Yes	-0.78 (-1.5 - -0.05)	1.2 (0.85 - 1.8)
Sex		
Female		1
Male	-2.9 (-3.5 - -2.3)	1.4 (0.96 - 2.0)
Age	-0.91 (-0.93 - -0.89)	1.1 (1.1 - 1.1)

508 ^aVariables mutually adjusted, ^b Urban areas include Delhi, Chennai and Sonipat district. Rural areas include

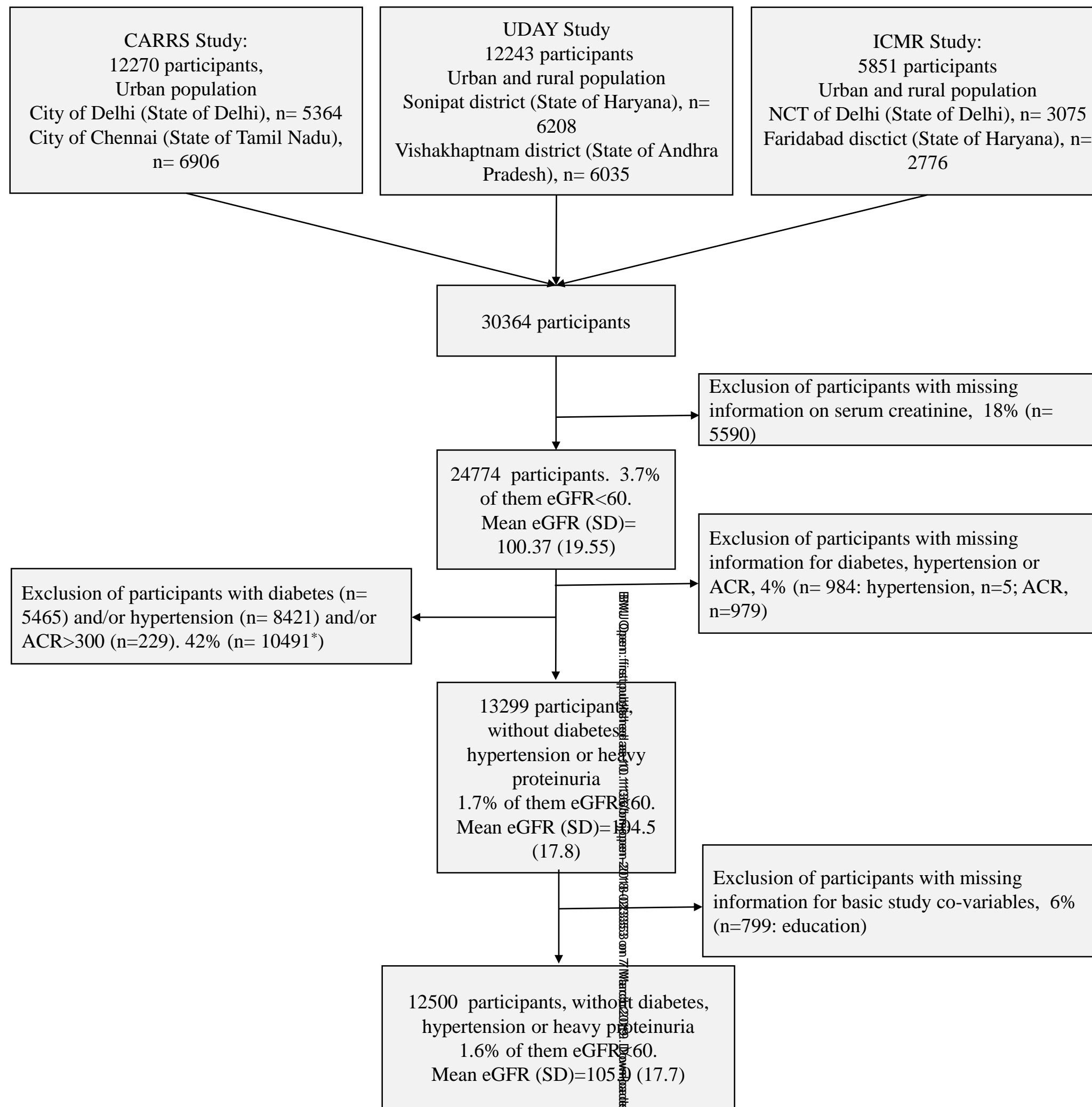
509 Sonipat, Vishakhapatnam and Faridabad districts; ^c North areas include Delhi, Sonipat and Faridabad district.

510 South areas include Chennai and Vishakhapatnam districts.

511 **Table S4.** Multiple regression analysis of sociodemographic characteristics associated with eGFR and eGFR<60
 512 including plasma fasting glucose, HbA1c and systolic blood pressure
 513

Variable	eGFR	eGFR<60
	Coefficient (95% CI) ^a	OR (95% CI) ^a
Area [†]		
Urban		1
Rural	-4.9 (-5.5 - -4.4)	2.3 (1.6 – 3.2)
Latitude [‡]		
North		1
South	0.23 (-0.26 - 0.72)	1.3 (0.95 - 1.8)
Education (number of years)		
0		1
5	1.0 (0.20 - 1.9)	0.49 (0.31 - 0.79)
10	0.19 (-0.49 - 0.87)	0.47 (0.31 - 0.71)
> 10	-3.5 (-4.3 - -2.8)	0.62 (0.40 - 1.0)
Alcohol consumption ever		
No		1
Yes	-0.72 (-1.4 - -0.01)	1.3 (0.90 - 1.9)
Sex		
Female		1
Male	-2.7 (-3.3 - -2.1)	1.5 (0.01 – 2.1)
Age	-0.89 (-0.92 - -0.87)	1.1 (1.1 – 1.1)
Systolic blood pressure (mm Hg)	-0.06 (-0.08 - -0.04)	1.0 (0.99 – 1.0)
Hb1Ac (%)	0.03 (-0.56 - 0.62)	1.9 (1.3 – 2.8)
Fasting plasma glucose (mg/dl)	-0.06 (-0.84 - -0.04)	1.0 (1.0 – 1.0)

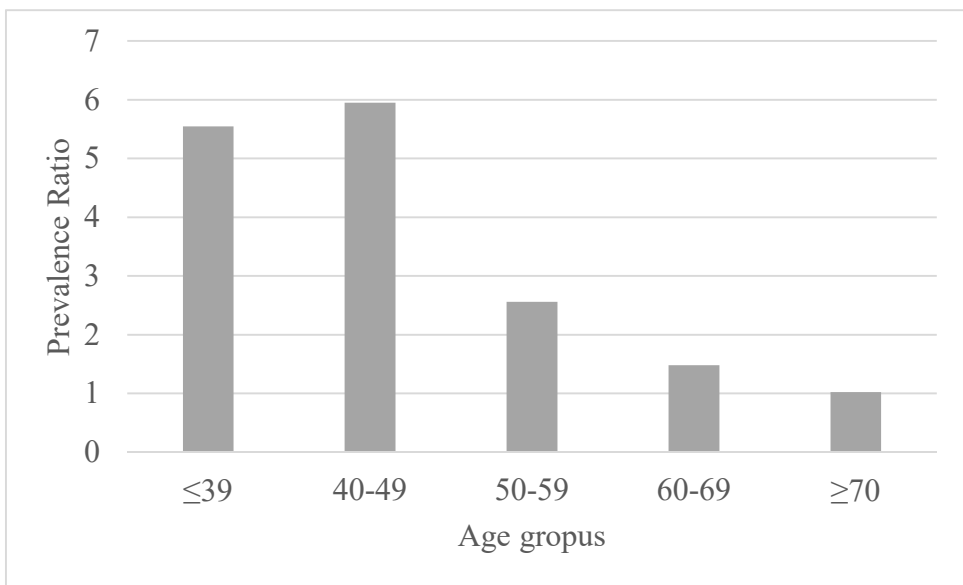
514 ^a Variables mutually adjusted, ^b Urban areas include Delhi, Chennai and Sonipat district. Rural areas include
 515 Sonipat, Vishakhapatnam and Faridabad districts; ^c North areas include Delhi, Sonipat and Faridabad district.
 516 South areas include Chennai and Vishakhapatnam districts.



* 2353 participants with diabetes only; 5185 participants with hypertension only; 35 participants with ACR>30 only; 2724 participants with diabetes, and hypertension; 35 participants with diabetes and ACR>30; 47 participants with hypertension and ACR>30; 112 participants with diabetes, hypertension and ACR>30.

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Supplementary material

Prevalence of and risk factors for chronic kidney disease of unknown aetiology in India: secondary data analysis of three population-based cross-sectional studies

Cristina O’Callaghan-Gordo, Roopa Shivashankar , Shuchi Anand, Shreeparna Ghosh , Jason Glaser, Ruby Gupta, Kristina Jakobsson, Dimple Kondal, Anand Krishnan, Sailesh Mohan, Viswanathan Mohan, Dorothea Nitsch, Praveen PA, Nikhil Tandon, K.M. Venkat Narayan, Neil Pearce Ben Caplin, Dorairaj Prabakharan

Content

Table 1. Sociodemographic and anthropometric characteristics of overall study participants (prior to exclusion of population with diabetes, hypertension and proteinuria)

Table 2. Associations between sociodemographic and anthropometric characteristics and estimated glomerular filtration rate (eGFR) and eGFR<60 by sex

Table 3. Multiple regression analysis of sociodemographic and anthropometric characteristics associated with eGFR and eGFR<60 including study participants with proteinuria (but without diabetes or hypertension)

Table 4. Multiple regression analysis of sociodemographic and anthropometric characteristics associated with eGFR and eGFR<60 including fasting plasma glucose, HbA1c and systolic blood pressure

Table 1. Sociodemographic and anthropometric characteristics of overall study participants (prior to exclusion of population with diabetes, hypertension and proteinuria)

Variable	n (%) n=12 500	eGFR		eGFR categories, n(%)**			
		mean (SD)	p-value [§]	≥90	90-60	<60	p-value ^{§§}
Socio-demographic factors							
Age (years)							
<39	9007 (36)	112.9 (14.9)	<0.001	8248 (92)	716 (8)	43 (0)	<0.001
40-49	6924 (28)	101.9 (14.8)		5617 (81)	1215 (18)	92 (1)	
50-59	4524 (18)	92.9 (15.2)		2997 (66)	1378 (30)	149 (3)	
60-69	3045 (12)	82.8 (17.1)		1410 (46)	1315 (43)	320 (11)	
≥=70	1274 (5)	72.0 (17.3)		164 (13)	806 (63)	304 (24)	
Sex							
Female	13433 (54)	102.6 (19.5)		10404 (77)	2585 (19)	444 (3)	<0.001
Male	11341 (46)	97.7 (19.3)	0.33	8032 (71)	2845 (25)	464 (4)	
Education (number of years)							
0	4794 (19)	97.7 (20.2)	<0.001	3458 (72)	1075 (22)	261 (5)	<0.001
5	3194 (13)	101.7 (19.4)		2456 (77)	625 (20)	113 (4)	
10	8855 (36)	103.2 (18.9)		6995 (79)	1620 (18)	240 (3)	
> 10	6358 (26)	100.0 (19.2)		4638 (73)	1538 (24)	182 (3)	
Missing data	1573 (6)			889 (57)	572 (36)	112 (7)	
Area ^e							
Urban	17732 (72)	102 (19.5)	0.03	13577 (77)	3602 (20)	553 (3)	<0.001
Rural	7042 (28)	96.3 (19.1)		4859 (69)	1828 (26)	355 (5)	
Latitude ^f							
North	13570 (55)	98.1 (19.1)	<0.001	9599 (71)	3439 (25)	532 (4)	<0.001
South	11204 (45)	103.1 (19.7)		8837 (79)	1991 (18)	376 (3)	
Life-style factors							
Current smoking							
No	18402 (74)	101.5 (19.6)	0.01	13920 (76)	3838 (21)	644 (3)	<0.001
Yes	6372 (26)	97.1 (19.1)		4516 (71)	1592 (25)	264 (4)	
Alcohol consumption ever							
No	19588 (79)	100.9 (19.6)	0.01	14671 (75)	4203 (21)	714 (4)	0.01
Yes	5186 (21)	98.5 (19.1)		3765 (73)	1227 (24)	194 (4)	
Vegetarian							
No	15043 (61)	102.7 (19.7)	<0.001	11721 (78)	2835 (19)	487 (3)	<0.001
Yes	9731 (39)	96.8 (18.9)		6715 (69)	2595 (27)	421 (4)	
Biological factors							
Body mass index (kg/m ²)							
Underweight (≤18.5)	10297 (42)	100.1 (19.6)	<0.001	7626 (74)	2284 (22)	387 (4)	0.01
Normal (>18.5 - ≤25)	2403 (10)	101.58 (20.5)		1838 (76)	471 (20)	94 (4)	
Overweight (>25 - ≤30)	7221 (29)	99.9 (18.8)		5309 (74)	1680 (23)	232 (3)	
Obese (>30)	3286 (13)	99.3 (19.2)		2392 (73)	766 (23)	128 (4)	
Missing data	1567 (6)			1271 (81)	229 (15)	67 (4)	
Fat free mass (kg/m ²)							
1 st tertile (≤37)	7141 (29)	101.9 (20.1)	<0.001	5481 (77)	1381 (19)	279 (4)	<0.001

2 nd tertile (>37 - <45)	7141 (29)	101.3 (19.1)	5419 (76)	1487 (21)	235 (3)
3 rd tertile (≤45)	7141 (29)	98.3 (18.6)	5110 (72)	1797 (25)	234 (3)
Missing data	3351 (14)		2426 (72)	765 (23)	160 (5)

^a Percentages in columns; ^b percentages in rows; ^c Bartlett's test for equal variance; ^d Chi-square test; ^e

Urban areas include Delhi, Chennai and Sonipat district. Rural areas include Sonipat, Vishakhapatnam and Faridabad districts; ^f North areas include Delhi, Sonipat and Faridabad district. South areas include Chennai and Vishakhapatnam districts.

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Table 2. Associations between sociodemographic and anthropometric characteristics and estimated glomerular filtration rate (eGFR) and eGFR<60 by sex

Variable	Men, n=5 434			Women, n=7 966		
	n (%)	eGFR Coefficient (95% CI) ^a	eGFR<60 OR (95% CI) ^a	n (%)	eGFR Coefficient (95% CI) ^a	eGFR<60 OR (95% CI) ^a
Age (years) ^b						
<39	2335 (43)			3786 (54)		
40-49	1568 (29)	-9.0 (-10 - -8.0)	2.4 (1.2 - 4.6)	1908 (27)	-12 (-13 --12)	4.5 (1.9 - 10)
50-59	843 (16)	-17 (-18 - -16)	3.8 (1.9 - 7.7)	863 (12)	-21 (-22 --20)	12 (5.2 - 27)
60-69	479 (9)	-25 (-27 - -24)	13 (7.0 - 24)	414 (6)	-30 (-31 --29)	33 (15 - 73)
>=70	209 (4)	-34 (-36 - -32)	31 (16 - 59)	95 (1)	-35 (-38 --32)	43 (16 - 118)
Education (number of completed years)						
0	823 (15)		1	1997 (28)		1
≤5	703 (13)	3.3 (1.8 - 4.7)	0.24 (0.13 - 0.46)	1006 (14)	0.73 (-0.27 -1.7)	0.81 (0.42 - 1.6)
6-≤10	2363 (43)	1.7 (0.51 - 2.8)	0.31 (0.20 - 0.48)	2454 (35)	0.67 (-0.13 -1.5)	0.43 (0.21 - 0.9)
> 10	1545 (28)	-1.3 (-2.6 - -0.10)	0.27 (0.15 - 0.47)	1609 (23)	-2.4 (-3.3 --1.5)	0.76 (0.40 - 1.5)
Area ^c	3583 (66)					
Urban	1851 (34)		1	4911 (70)		1
Rural		-4.0 (-4.8 - -3.2)	2.7 (1.8 - 4.0)	2155 (30)	-3.7 (-4.4 --3.0)	2.0 (1.3 - 3.1)
Latitude ^d						
North	2861 (53)		1	3402 (48)		1
South	2573 (47)	-1.5 (-2.3 - -0.74)	1.8 (1.2 - 2.6)	3664 (52)	2.6 (2.0 -3.2)	1.3 (0.83 - 2.0)
Current tobacco consumption						
No	2804 (52)		1	6553 (93)		1
Yes	2630 (48)	1.1 (0.36 - 1.9)	1.3 (0.91 - 1.9)	513 (7)	-1.9 (-3.1 --0.73)	1.5 (0.87 - 2.7)
Alcohol consumption ever						
No	3035 (56)		1	7059 (100)		1

1							
2							
3							
4	Yes	2399 (44)	-0.71 (-1.5 - 0.06)	1.6 (1.08 - 2.3)	7 (0)	-9.3 (-19 -0.4)	1.0 (1.0 - 1.0)
5	Vegetarian						
6	No	3576 (66)		1	4396 (62)		1
7	Yes	1858 (34)	0.65 (-0.18 - 1.5)	0.61 (0.41 - 0.90)	2670 (38)	-2.1 (-2.7 --1.5)	0.70 (0.44 - 1.1)
8	Body mass index (kg/m2) ^e						
9	Underweight (≤ 18.5)	2888 (56)		1	2991 (44)		1
10	Normal ($>18.5 - \leq 25$)	812 (16)	4.0 (2.9 - 5.2)	0.69 (0.42 - 1.1)	764 (11)	1.6 (0.57 - 2.6)	1.1 (0.57 - 2.0)
11	Overweight ($>25 - \leq 30$)	1209 (23)	-1.7 (-2.7 - -0.73)	0.71 (0.42 - 1.2)	2104 (31)	-0.11 (-0.84 - 0.62)	0.67 (0.38 - 1.2)
12	Obese (>30)	243 (5)	-0.71 (-2.6 - 1.2)	0.36 (0.09 - 1.5)	907 (13)	-0.64 (-1.6 - 0.33)	0.55 (0.23 - 1.3)
13	Fat free mass (kg/m2) ^e						
14	1st tertile (≤ 37)	361 (8)		1	3833 (58)		1
15	2nd tertile ($>37 - <45$)	1351 (28)	-0.42 (-2.1 - 1.2)	0.78 (0.44 - 1.4)	2535 (39)	-1.4 (-2.0 --0.74)	0.67 (0.38 - 1.2)
16	3rd tertile (≤ 45)	3093 (64)	-3.7 (-5.3 - -2.2)	0.50 (0.28 - 0.90)	208 (3)	-1.4 (-3.2 - 0.45)	0.58 (0.08 - 4.2)

^a Adjusted for age; ^b Not adjusted for age; ^c Urban areas include Delhi, Chennai and Sonipat district. Rural areas include Sonapat, Vishakhapatnam and Faridabad districts; ^d

North areas include Delhi, Sonipat and Faridabad district. South areas include Chennai and Vishakhapatnam districts; ^e Variables with missing values.

Table 3. Multiple regression analysis of sociodemographic characteristics associated with eGFR and eGFR<60 including study participants with proteinuria (but without diabetes or hypertension), n=12533

Variable	eGFR	eGFR<60
	Coefficient (95%CI)*	OR (95%CI)*
Area [¥]		
Urban		1
Rural	-4.6 (-5.1 - -4.0)	1.9 (1.4 - 2.7)
Latitude [‡]		
North		1
South	0.29 (-0.21 - 0.78)	1.3 (0.98 - 1.8)
Education (number of years)		
0		1
5	0.83 (0 - 1.7)	0.55 (0.35 - 0.87)
10	0.04 (-0.64 - 0.72)	0.51 (0.35 - 0.76)
> 10	-3.8 (-4.6 - -3.0)	0.66 (0.4 - 1.1)
Alcohol consumption ever		
No		1
Yes	-0.78 (-1.5 - -0.05)	1.2 (0.85 - 1.8)
Sex		
Female		1
Male	-2.9 (-3.5 - -2.3)	1.4 (0.96 - 2.0)
Age	-0.91 (-0.93 - -0.89)	1.1 (1.1 - 1.1)

^aVariables mutually adjusted, ^b Urban areas include Delhi, Chennai and Sonipat district. Rural areas include Sonipat, Vishakhapatnam and Faridabad districts; ^c North areas include Delhi, Sonipat and Faridabad district. South areas include Chennai and Vishakhapatnam districts.

Table 4. Multiple regression analysis of sociodemographic characteristics associated with eGFR and eGFR<60 including plasma fasting glucose, HbA1c and systolic blood pressure

Variable	eGFR	eGFR<60
	Coefficient (95%CI)*	OR (95%CI)*
Area [‡]		
Urban		1
Rural	-4.9 (-5.5 - -4.4)	2.3 (1.6 – 3.2)
Latitude [‡]		
North		1
South	0.23 (-0.26 - 0.72)	1.3 (0.95 - 1.8)
Education (number of years)		
0		1
5	1.0 (0.20 - 1.9)	0.49 (0.31 - 0.79)
10	0.19 (-0.49 - 0.87)	0.47 (0.31 - 0.71)
> 10	-3.5 (-4.3 - -2.8)	0.62 (0.40 - 1.0)
Alcohol consumption ever		
No		1
Yes	-0.72 (-1.4 - -0.01)	1.3 (0.90 - 1.9)
Sex		
Female		1
Male	-2.7 (-3.3 - -2.1)	1.5 (0.01 – 2.1)
Age	-0.89 (-0.92 - -0.87)	1.1 (1.1 – 1.1)
Systolic blood pressure (mm Hg)	-0.06 (-0.08 - -0.04)	1.0 (0.99 – 1.0)
Hb1Ac (%)	0.03 (-0.56 - 0.62)	1.9 (1.3 – 2.8)
Fasting plasma glucose (mg/dl)	-0.06 (-0.84 - -0.04)	1.0 (1.0 – 1.0)

^a Variables mutually adjusted, ^b Urban areas include Delhi, Chennai and Sonipat district. Rural areas include Sonipat, Vishakhapatnam and Faridabad districts; ^c North areas include Delhi, Sonipat and Faridabad district. South areas include Chennai and Vishakhapatnam districts.

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Prevalence of and risk factors for chronic kidney disease of unknown aetiology in India: secondary data analysis of three population-based cross-sectional studies

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1 **TITLE PAGE**

2 **Title:** Prevalence of and risk factors for chronic kidney disease of unknown aetiology in India: secondary data
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26 ABSTRACT

27 **Objectives:** To assess whether chronic kidney disease of unknown aetiology (CKDu) is present in India and to
28 identify risk factors for it using population-based data and standardised methods.

29 **Design:** Secondary data analysis of three population-based cross-sectional studies conducted between 2010-
30 2014.

31 **Setting:** Urban and rural areas of Northern India (states of Delhi and Haryana) and Southern India (states of
32 Tamil Nadu and Andhra Pradesh)

33 **Participants:** 12,500 individuals without diabetes, hypertension or heavy proteinuria

34 **Outcome measures:** Mean estimated the glomerular filtration rate (eGFR) and the prevalence of eGFR below
35 60ml/min per 1.73m² (eGFR<60) in individuals without diabetes, hypertension or heavy proteinuria (proxy
36 definition of CKDu).

37 **Results:** The mean eGFR was 105.0±17.8 ml/min per 1.73m². The prevalence of eGFR<60 was 1.6%
38 (95%CI=1.4, 1.7), but this figure varied markedly between areas, being highest in rural areas of Southern Indian
39 [4.8% (3.8, 5.8)]. In Northern India, older age was the only risk factor associated with lower mean eGFR and
40 eGFR<60 [regression coefficient (95%CI)=-0.94 (0.97, 0.91); OR (95%CI)=1.10 (1.08, 1.11)]. In Southern
41 India, risk factors for lower mean eGFR and eGFR<60 respectively were residence in a rural area [-7.78 (-8.69, -
42 6.86); 4.95 (2.61, 9.39)], older age [-0.90 (-0.93, -0.86); 1.06 (1.04, 1.08)] and less education [-0.94 (-1.32, -
43 0.56); 0.67 (0.50, 0.90) for each five years at school].

44 **Conclusions:** CKDu is present in India and is not confined to Central America and Sri Lanka. Identified risk
45 factors are consistent with risk factors previously reported for CKDu in Central America and Sri Lanka.

46 KEYWORDS

47 Epidemiology; Chronic kidney disease; Chronic kidney disease of unknown aetiology; India; Rural population

48 ARTICLE SUMMARY

49 Strengths and limitations of this study

- 50 • The use of a random selection of population-based participants allows the estimation of CKDu
51 prevalence in the general population.

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3 52 • A large sample size including participants from different areas of India (urban and rural, and Northern
4 53 and Southern India) increases the representativeness of our results.
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6 54 • The use of standardized definitions of CKDu facilitates international comparisons of CKDu prevalence
7 and risk factors.
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10 56 • The prevalence of eGFR<60 observed in this study is likely to be underestimated; however, this is
11 unlikely to have biased the internal comparisons conducted in this study.
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67 INTRODUCTION

68 High prevalence of CKDu has mainly been reported in the last decades amongst the working age populations of
69 agricultural communities of tropical/subtropical regions, specifically in Central America and Sri Lanka [1–3]. In
70 Nicaragua and El Salvador, the estimated prevalence of estimated glomerular filtration rate (eGFR; the clinical
71 measure of kidney function) below 60ml/min per 1.73m² (eGFR<60), in the absence of diabetes and
72 hypertension, was 10-20% [4–6]. It has been suggested that CKDu may also be highly prevalent in other low and
73 middle income countries (LMICs), including India [7–11]. However, it is not clear in which other regions of the
74 world CKDu occurs, whether the underlying aetiology is the same in different regions and what the risk factors
75 are. Currently, there is no consensus but factors such as heat stress, strenuous work, climatic conditions,
76 agrochemical use, heavy metal exposure and infections have been suggested as risk factors [1,12–15].

77 Data on CKDu from India are scarce. The recent report of verbal autopsy data from India suggests CKD of all
78 causes is a growing problem. However, it does not provide accurate population-based data on CKDu [16,17].
79 Existing reports indicate that CKDu may be common but it is difficult to be definite about this because of the
80 absence of population-based studies using standardised and comparable methods. Data from the Indian CKD
81 Registry, a hospital based registry of incident cases of CKD between 2006-2010, found that CKDu was the
82 second commonest form of CKD after diabetic nephropathy [10]. However, this is restricted to referred cases
83 and therefore may not be representative of the general population. There are also sporadic reports of high
84 numbers of CKDu cases among agricultural communities of the South Eastern Indian states of Andhra Pradesh
85 and Odisha (reviewed by Chatterjee [18] and Ganguli [19]). However, population-based data have not been
86 reported for India.

87 We conducted a secondary analysis of representative sample surveys conducted in India between 2010-2014.
88 Given the absence of a clear case definition for CKDu it is necessary to make a presumptive diagnosis based on
89 measures/estimates of GFR in the absence of known risk factors for kidney disease. The overall aim of the
90 current study was to use a methodology which is comparable to previous studies elsewhere in the world
91 (particularly in Central America) to assess the extent to which reduced kidney function is a problem in India, and
92 which areas and subpopulations are most affected. We therefore: (i) assessed the distribution eGFR and
93 prevalence of eGFR below 60ml/min per 1.73m² (eGFR<60) in Indian populations restricted to those without
94 known risk factors for CKD, i.e. diabetes, hypertension or heavy proteinuria; ii) compared these outcomes in

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3 95 North and South India and in urban and rural populations; and (iii) identified the risk factors associated with
4 96 these outcomes.

7 97 **METHODS**

10 98 **Study population**

13 99 We used cross-sectional data from three population-based studies conducted in India: the “Centre for
14 100 Cardiometabolic Risk Reduction in South Asia” cohort study (CARRS study) [20], the “Implementing a
15 101 Comprehensive Diabetes Prevention and Management Program” study (UDAY study) [21] and the “prevalence
16 102 of coronary heart disease repeat survey” study funded by the Indian Council of Medical Research (ICMR-CHD
17 103 study) [22]. Details on study design and selection of participants from the CARRS, UDAY and ICMR-CHD
18 104 studies have been previously described [20–22] and are summarized in Table 1. Participants from CARRS,
19 105 UDAY and ICMR-CHD studies provided informed consent prior to participation. The three studies obtained
20 106 ethical clearance from the corresponding institutions.

107 **Table 1.** Design and methods of the three studies included in the current analysis

	CARRS		UDAY				ICMR-CHD	
Latitude (North/South)	North	South	North		South		North	
Residence (Urban/Rural)	Urban		Urban	Rural	Urban	Rural	Urban	Rural
District (and State)	Delhi (state of Delhi)	Chennai (state of Tamil Nadu)	Sonapat (state of Haryana)		Vishakhapatnam (state of Andhra Pradesh)		National Capital Territory of Delhi (state of Delhi)	Faridabad (state of Haryana)
Household sampling	Multistage cluster random (wards - census enumeration blocks - households)		Multistage cluster random (Census Enumeration blocks (urban) or villages (rural) - households)				Multistage cluster random (wards - census enumeration blocks - households)	Simple cluster random (based on Health and Demographic Surveillance System)
Individual sampling	1 man and 1 woman from each household (selected by Kish method, [23].) ^b		1 man and 1 woman from each household (selected by Kish method, [23].) ^b				All adults	
Age groups included	≥ 20		≥ 30				≥ 30	
Exclusion criteria	Pregnant, bedridden and participants who were unable to comprehend the questionnaires due cognitive deficiencies were excluded							
Study period	October 2010 - November 2011		July 2014 - December 2014				August 2010 - January 2012	
Laboratory^a	PHFI ^c	MDRF ^d	PHFI ^c				PHFI ^c	

108 ^a Study laboratories participated in Randox International Quality Assurance Scheme (RIQAS) for clinical
 109 chemistry and HbA1c during the entire study periods. ^b In households where only eligible men or only eligible
 110 women were present, we selected just one adult. ^c Public Health Foundation of India; ^d Madras Diabetes
 111 Research Foundation

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3 112 For the current analyses, we excluded participants with missing information on serum creatinine, as this variable
4 113 was necessary to estimate eGFR. As the focus of our study was CKDu, we excluded participants with known
5 114 risk factors for CKD (i.e. diabetes and hypertension) or evidence of primary glomerular disease (as assessed by
6 115 heavy proteinuria) or with missing information for these risk factors. We also excluded participants with missing
7 116 information on basic co-variables (education) for all the analyses conducted. A study flowchart is presented in
8 117 Figure 1. We classified participants as having: diabetes, if plasma fasting glucose was ≥ 126 mg/dl, or glycated
9 118 haemoglobin A1c (HbA1c) was $\geq 6.5\%$, or the participant self-reported diabetes; hypertension, if systolic blood
10 119 pressure was ≥ 140 mm Hg, or diastolic blood pressure was ≥ 90 mm Hg, or the participant self-reported
11 120 hypertension; and heavy proteinuria, if the albumin/creatinine ratio (ACR) in urine was ≥ 300 mg/g. We used the
12 121 CKD-EPI equation to estimate GFR (eGFR) [24].

122 **Data collection and laboratory analyses**

123 Data collection was conducted between October 2010 and December 2014. All three studies used a standardized
124 questionnaire to collect data on age, sex, completed years of education (0, ≤ 5 , $>5-\leq 10$, >10), alcohol intake
125 (ever, never) and dietary habits (vegetarian yes, no). Weight, height and body composition were measured using
126 stadiometers (SECA 214 in the three studies) and electronic bioimpedance measuring instruments (Tanita BC
127 418 in CARRS and ICMR-CHD studies, and Tanita BC 601 in UDAY study). Body mass index (BMI, kg/m^2)
128 was calculated and categorized (≤ 18.5 : underweight; $>18.5-\leq 25$: normal weight; $>25-\leq 30$: overweight; >30 :
129 obese) and fat free mass was derived from bioelectric impedance analysis (BIA). In CARRS and ICMR-CHD
130 studies, fat free mass (Kg) was directly measured as previously described [25], whereas in UDAY study, fat free
131 mass was estimated from the percentage of total body fat. To estimate total fat free mass from the percentage of
132 body fat, we calculated the amount of total body fat by multiplying the percentage of body fat by the weight of
133 the participant, and from that value we estimated the amount of fat free mass by subtracting the weight of total
134 body fat from the total weight of the participant. Blood pressure was measured using electronic
135 sphygmomanometers (OMRON (HEM-7080) in CARRS and ICMR-CHD studies, and OMRON (HEM 7200) in
136 UDAY study), as previously reported [20,26]. Stadiometers, electronic bioimpedance measuring instruments,
137 and electronic sphygmomanometers were calibrated before each study, and no re-calibration was needed during
138 the duration of different studies. A fasting venous blood sample was used to measure glucose levels, HbA1c and
139 serum creatinine levels and urine sample to measure albuminuria and creatinuria [20]. Glucose levels were
140 measured using hexokinase/kinetic methods, HbA1c using high-performance liquid chromatography, serum

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3 141 creatinine using the rate-blanked and compensated kinetic Jaffe method, traceable to isotope dilution mass
4 142 spectrometry, and albuminuria using immune turbidmetric method [20]. Samples from UDAY, ICMR-CHD, and
5 143 samples from CARRS from Delhi were analysed at Public Health Foundation of India (PHFI) laboratory and
6 144 samples from CARRS from Chennai were analysed at Madras Diabetes Research Foundation (MDRF)
7 145 laboratory. Both PHFI and MDRF laboratories used the same methodologies and protocols to analyse the
8 146 samples and participated in Randox International Quality Assurance Scheme (RIQAS) for clinical chemistry and
9 147 HbA1c during the entire study periods. Data from the three studies were homogenized and merged in a single
10 148 data set.

18 149 **Statistical analyses**

21 150 We reported mean eGFR and prevalence eGFR<60 according to different characteristics of the study
22 151 populations. UDAY and CARRS studies did not involve fully random population samples (since sampling was
23 152 based on households, with one participant per household) and the proportions of study participants with
24 153 particular outcomes (e.g. eGFR<60), will not be exactly the same (but very similar) to what would have been
25 154 obtained with genuine random population samples; thus in this paper we refer to the prevalence in the study
26 155 participants, not overall population prevalence estimates. We used linear regression models to estimate the
27 156 associations between potential risk factors and eGFR and logistic regression models to estimate the associations
28 157 between potential risk factors and eGFR<60. We also repeated the analyses separately for males and females.
29 158 Variables associated with eGFR in the basic analyses (adjusted for age and sex) were considered for the multiple
30 159 regression analysis. In the final multiple regression model, we included all variables that were of a priori interest
31 160 and/or had shown independent associations with eGFR. We then checked for multicollinearity for each variable
32 161 in the multiple regression analyses in comparison with the basic analyses [27]. 6% had missing values for basic
33 162 co-variables (i.e. education) and were excluded from the analysis. 4% and 11% of participants had missing
34 163 values for BMI and for fat free mass respectively. These participants were included in the main analysis, but we
35 164 excluded them to compare models non-adjusted and adjusted for these variables. We calculated prevalence ratios
36 165 of eGFR<60 by age-group for rural and urban areas. Urban areas were defined as “all places with a municipality,
37 166 corporation, cantonment board or notified town area committee, etc., and all other places which satisfied the
38 167 following criteria: a minimum population of 5,000; at least 75 per cent of the male main working population
39 168 engaged in non-agricultural pursuits; and a density of population of at least 400 persons per km²”, according to
40 169 the 2011 Census of India definition [28]. Finally, we estimated potential interactions between urban (versus

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3 170 rural) residence and latitude (Northern India (i.e. states of Delhi and Haryana) versus Southern India (states of
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5 171 Tamil Nadu and Andhra Pradesh). Classification of latitude was done in concordance with the classification of
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7 172 major geographical areas on India defined by the Indian Council of Medical Research [29], figure 1. We
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9 173 conducted all analyses using Stata version 14 (StataCorp, College Station, TX, USA).

11 174 **Patient and Public Involvement**

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14 175 Patients were not involved in the design of this analysis.

16 176 **RESULTS**

19 177 **Characteristics of study participants**

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22 178 12,500 people were eligible for the current analyses (Figure 2). Table 2 summarizes the socio-demographic and
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24 179 anthropometric characteristics of the 12,500 study participants included in this analysis (the same information
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26 180 including participants with known risk factors for CKD (n=24,774) in supplementary material Table S1). The
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28 181 mean (standard deviation (\pm SD)) age of participants was 41.5 \pm 11.6 years. 88% (4,805/5,434) of the male
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30 182 population was formally employed; 76% (5,346/7,066) of women worked on house duties (i.e. housewives).
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32 183 The mean BMI was 24 \pm 5.0 kg/m² and mean fat free mass was 42 \pm 15 kg/m². The mean fasting plasma glucose
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34 184 was 91.9 \pm 12.3 mg/dl and the mean HbA1c was 5.5 \pm 0.4 %. The mean systolic and diastolic blood pressures were
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36 185 114 \pm 12 mm Hg and 74 \pm 9 mm Hg, respectively. The median (inter quartile range, IQR) albumin/creatinine ratio
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38 186 (ACR) was 2.4 (4.3) mg/g (after exclusion of those with ACR>300mg/g, n=1,208).

39 187 **Mean eGFR and prevalence of eGFR<60**

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42 188 The mean eGFR was 105.0 \pm 17.8 ml/min per 1.73m². The mean eGFR was lower at increasing ages, in males, in
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44 189 inhabitants from rural areas and in those from Northern India, in participants with no formal education, and in
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46 190 participants who reported tobacco consumption, alcohol intake and being vegetarian (Table 2). We observed
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48 191 differences in mean eGFR depending on the area, being 104.5 \pm 17.6 in urban areas of Northern India, 100.3 \pm 16.2
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50 192 in rural areas of Northern India, 110.9 \pm 15.7 in urban areas of Southern India and 97.4 \pm 19.8 in the rural area of
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52 193 Southern India.

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54 194 The prevalence of eGFR<60 among the study population was 1.6% (95% confidence interval (95% CI)=1.4,
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56 195 1.9). Seventeen per cent (95% CI=16, 17) of study participants had eGFR \geq 60-<90 ml/min per 1.73m² and 82%

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3 196 [95% confidence interval (95% CI)=81, 82] had eGFR \geq 90 ml/min per 1.73m². The prevalences of different
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5 197 categories of eGFR differed by formal education, tobacco consumption, alcohol intake and vegetarianism (Table
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7 198 2). Also, we observed marked differences in the prevalence of eGFR<60 depending on the area, being 1.4 %
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9 199 (95% CI=1.1, 1.8) in urban areas of Northern India, 1.9 (95% CI=1.4, 2.6) in rural areas of Northern India,
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11 200 0.43% (95% CI =0.03, 0.07) in urban areas of Southern India and 4.8 % (95% CI= 3.9, 5.9) in the rural area of
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13 201 Southern India. The prevalence ratio of eGFR<60 for rural versus urban residence was higher for participants
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15 202 <50 years than for older groups (Figure 3).
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203 **Table 2.** Sociodemographic and anthropometric characteristics of study participants (population without
204 diabetes, hypertension or heavy proteinuria)

Variable	n (%) ^a n=12,500	eGFR mean (SD)	eGFR categories, n(%) ^b		
			≥90	90-60	<60
Socio-demographic					
Age (years)					
<39	6121 (49)	113.8 (14.6)	5656 (92)	443 (7)	22 (0)
40-49	3476 (28)	102.5 (14.2)	2864 (82)	572 (16)	40 (1)
50-59	1706 (14)	93.9 (14.3)	1163 (68)	503 (29)	40 (2)
60-69	893 (7)	85.3 (16.2)	463 (52)	368 (41)	62 (7)
≥70	304 (2)	77.5 (15.1)	62 (20)	201 (66)	41 (13)
Sex					
Female	7066 (57)	107.9 (17.1)	6039 (85)	945 (13)	82 (1)
Male	5434 (43)	101.3 (17.9)	4169 (77)	1142 (21)	123 (2)
Education (number completed years)					
0	2820 (23)	100.7 (19.0)	2165 (77)	551 (20)	104 (4)
≤5	1709 (14)	105.9 (17.3)	1412 (83)	273 (16)	24 (1)
6-≤10	4817 (39)	107.2 (16.8)	4095 (85)	675 (14)	47 (1)
> 10	3154 (25)	105.0 (17.5)	2536 (80)	588 (19)	30 (1)
Area ^c					
Urban	8494 (68)	107.8 (16.1)	7247 (85)	1171 (14)	76 (1)
Rural	4006 (32)	99.0 (18.0)	2961 (74)	916 (23)	129 (3)
Latitude ^d					
North	6263 (50)	103.0 (17.2)	4967 (79)	1197 (19)	99 (2)
South	6237 (50)	107.0 (18.1)	5241 (84)	890 (14)	106 (2)
Life-style factors					
Current tobacco consumption					
No	9357 (75)	106.8 (17.3)	7836 (84)	1406 (15)	115 (1)
Yes	3143 (25)	99.8 (18.1)	2372 (75)	681 (22)	90 (3)
Alcohol consumption ever					
No	10094 (81)	105.9 (17.4)	8362 (83)	1589 (16)	143 (1)
Yes	2406 (19)	101.1 (18.5)	1846 (77)	498 (21)	62 (3)
Vegetarian					

No	7972 (64)	107.0 (18.0)	6690 (84)	1154 (14)	128 (2)
Yes	4528 (36)	101.6 (16.6)	3518 (78)	933 (21)	77 (2)
Biological factors					
Body mass index (kg/m ²)					
Underweight (≤ 18.5)	5879 (47)	104.2 (17.9)	4734 (81)	1029 (18)	116 (2)
Normal ($>18.5 - \leq 25$)	1576 (13)	104.7 (19.3)	1283 (81)	257 (16)	36 (2)
Overweight ($>25 - \leq 30$)	3313 (27)	105.0 (16.9)	2710 (82)	568 (17)	35 (1)
Obese (>30)	1150 (9)	105.5 (16.4)	948 (82)	194 (17)	8 (1)
Missing data	582 (5)		533 (92)	39 (7)	10 (2)
Fat free mass (kg)					
1 st tertile (≤ 37)	3746 (30)	106.6 (18.1)	3146 (84)	532 (14)	68 (2)
2 nd tertile ($>37 - <45$)	3801 (30)	105.9 (17.2)	3145 (83)	601 (16)	55 (1)
3 rd tertile (≥ 45)	3834 (31)	102.1 (17.0)	2981 (78)	801 (21)	52 (1)
Missing data	1119 (9)		936 (84)	153 (14)	30 (3)

205 ^a Percentages in columns; ^b percentages in rows; ^c Urban areas include Delhi, Chennai and Sonipat district. Rural
 206 areas include Sonipat, Vishakhapatnam and Faridabad districts; ^d North areas include Delhi, Sonipat and
 207 Faridabad district. South areas include Chennai and Vishakhapatnam districts.

208 Risk factors for lower eGFR and eGFR<60

209 As expected, age was an important risk factor for reduced eGFR: eGFR was 9.30 ml/min per 1.73 m² (95%CI=-
210 9.51, -9.09, model adjusted for sex) lower for each additional 10 years of age. Additionally, being male, living in
211 a rural setting, and consuming alcohol were associated with decreased mean eGFR (Table 3). Similarly, the odds
212 of eGFR<60 also increased with age [OR per 10 years, adjusted for sex (95%CI)=2.34 (2.12, 2.59)] and being
213 male, living in a rural setting, living in Southern India and consuming alcohol were also associated with
214 eGFR<60 (Table 3). In general, risk factors for decreased mean eGFR and for eGFR<60 were similar for men
215 and women (supplementary material, Table S2), but few differences were observed. Regarding mean eGFR,
216 living in Southern India was associated with decreased mean eGFR in men and with increased mean eGFR in
217 women; tobacco consumption was associated with increased mean eGFR in men and with decreased mean eGFR
218 in women; vegetarianism was associated with decreased mean eGFR in women but not in men; and being
219 overweight was associated with decreased mean eGFR but in men but not in women. Regarding risk of
220 eGFR<60, living in Southern India was associated with increased risk of eGFR<60 in men but not in women.

221 **Table 3.** Associations between sociodemographic and anthropometric characteristics and eGFR and eGFR<60

	eGFR	eGFR<60
Variable	Coefficient (95 CI) ^a	OR (95 CI) ^a
Age (years) ^b		
<39	0.00 (ref)	1.00 (ref)
40-49	-11.08 (-11.68, -10.47)	3.15 (1.87, 5.32)
50-59	-19.43 (-20.20, -18.65)	6.41 (3.80, 10.83)
60-69	-27.84 (-28.86, -26.82)	19.68 (12.01, 32.26)
≥70	-35.04 (-36.71, -33.37)	39.23 (22.87, 67.23)
Sex ^c		
Female	0.00 (ref)	1.00 (ref)
Male	-3.55 (- 4.05, -3.06)	1.33 (0.99, 1.78)
Education (number of completed years)		
0	0.00 (ref)	1.00 (ref)
≤5	1.92 (1.09, 2.76)	0.41 (0.26, 0.65)
6-≤10	1.27 (0.61, 1.93)	0.36 (0.25, 0.53)
> 10	-1.86 (-2.59, -1.14)	0.40 (0.26, 0.62)
Area ^d		
Urban	0.00 (ref)	1.00 (ref)
Rural	-3.84 (-4.37, -3.32)	2.39 (1.78, 3.22)
Latitude ^e		
North	0.00 (ref)	1.00 (ref)
South	0.86 (0.37, 1.35)	1.55 (1.16, 2.07)
Current tobacco consumption		
No	0.00 (ref)	1.00 (ref)
Yes	0.38 (-0.26, 1.02)	1.39 (1.01, 1.91)
Alcohol consumption ever		
No	0.00 (ref)	1.00 (ref)
Yes	-0.81 (-1.55, -0.08)	1.57 (1.09, 2.27)

Vegetarian		
No	0.00 (ref)	1.00 (ref)
Yes	-0.99 (-1.50, -0.47)	0.65 (0.48, 0.88)
Body mass index (kg/m ²)		
Underweight (≤ 18.5)	2.96 (2.20, 3.73)	0.81 (0.55, 1.20)
Normal ($>18.5 - \leq 25$)	0.00 (ref)	1.00 (ref)
Overweight ($>25 - \leq 30$)	-0.75 (-1.34, -0.16)	0.68 (0.46, 1.01)
Obese (>30)	-0.71 (-1.59, 0.17)	0.47 (0.23, 0.98)
Fat free mass (kg)		
1st tertile (≤ 37)	0.00 (ref)	1.00 (ref)
2nd tertile ($>37 - <45$)	-0.91 (-1.54, -0.28)	0.69 (0.47, 1.03)
3rd tertile (≥ 45)	-3.90 (-4.77, -3.04)	0.49 (0.31, 0.80)

222 ^a Adjusted for age and sex; ^b Adjusted just for sex; ^c Adjusted just for age; ^d Urban areas include Delhi, Chennai
 223 and Sonipat district. Rural areas include Sonipat, Vishakhapatnam and Faridabad districts; ^e North areas include
 224 Delhi, Sonipat and Faridabad district. South areas include Chennai and Vishakhapatnam districts.

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3 225 In the multiple regression analyses, decreased mean eGFR remained associated with older age, being male and
4 226 living in a rural setting and alcohol consumption (Table 4). Risk of eGFR<60 remained associated with older
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6 227 age, being male and living in a rural setting and having no formal education remained associated with increased
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8 228 risk of eGFR<60 (Table 4). We adjusted all the multiple regression models for fat free mass and vegetarianism
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10 229 to assess the possibility that differences observed between urban and rural participants were due to differences in
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12 230 diet and/or body composition. These adjustments had little effect on the results (Table 4).
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231 **Table 4.** Multiple regression analyses of sociodemographic characteristics associated with eGFR and eGFR<6).

Variable	eGFR Coefficient (95% CI)			eGFR<60 OR (95% CI)		
	Model 1 ^a	Model 2 ^b	Model 3 ^c	Model 1 ^a	Model 2 ^b	Model 3 ^c
Area^d						
Urban	0.00 (ref)	0.00 (ref)	0.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Rural	-4.57 (-5.13, -4.02)	-3.94 (-4.53, -3.36)	-4.10 (-4.70, -3.51)	1.99 (1.43, 2.76)	1.61 (1.12, 2.30)	1.65 (1.14, 2.37)
Latitude^e						
North	0.00 (ref)	0.00 (ref)	0.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
South	0.31 (-0.18, 0.80)	-0.10 (-0.61, 0.41)	0.26 (-0.37, 0.89)	1.33 (0.98, 1.81)	1.60 (1.14, 2.32)	1.33 (0.86, 2.04)
Education (number of completed years)						
0	0.00 (ref)	0.00 (ref)	0.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
≤5	0.94 (0.01, 1.77)	1.16 (0.30, 2.02)	1.18 (0.32, 2.04)	0.50 (0.31, 0.80)	0.44 (0.26, 0.74)	0.45 (0.26, 0.75)
6-≤10	0.04 (-0.64, 0.72)	0.21 (-0.49, 0.91)	0.21 (-0.50, 0.92)	0.50 (0.34, 0.75)	0.38 (0.24, 0.60)	0.39 (0.25, 0.62)
> 10	-3.81 (-4.6, -3.0)	-3.81 (-4.60, -3.02)	-3.78 (-4.59, -2.97)	0.68 (0.42, 1.11)	0.61 (0.36, 1.03)	0.65 (0.38, 1.11)
Alcohol consumption ever						
No	0.00 (ref)	0.00 (ref)	0.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)

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Yes	-0.85 (-1.58, -0.12)	-0.69 (-1.47, 0.08)	-0.63 (-1.41, 0.15)	1.28 (0.88, 1.87)	1.18 (0.78, 1.79)	1.15 (0.76, 1.74)
Sex						
Female	0.00 (ref)	0.00 (ref)	0.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Male	-2.85 (-3.44, -2.25)	-3.00 (-3.62, -2.38)	-2.52 (-3.18, -1.86)	1.39 (0.96, 2.01)	1.49 (1.00, 2.21)	1.50 (0.97, 2.31)
Age (per 10 years)	-9.10 (-9.32, -8.88)	-9.09 (-9.32, -8.86)	-9.15 (-9.38, -8.91)	2.21 (1.98, 2.47)	2.25 (2.00, 2.55)	2.27 (2.00, 2.57)
Fat free mass (kg)			-0.04 (-0.06, -0.02)			1.0 (0.98, 1.02)
Vegetarian						
No			0.00 (ref)			1.00 (ref)
Yes			0.66 (-0.03, 1.35)			0.74 (0.47, 1.18)

^a Model 1 included the following variables: area, latitude, education, alcohol consumption, sex and age; n=12,500; ^b Model 2 included the same variables than model 1. Participants with missing information on fat free mass were excluded from the analysis, n=11,381; ^c Model 3 included the same variables than model 1 plus fat free mass and vegetarianism, n=11,381. ^d Urban areas include Delhi, Chennai and Sonipat district. Rural areas include Sonipat, Vishakhapatnam and Faridabad districts; ^e North areas include Delhi, Sonipat and Faridabad district. South areas include Chennai and Vishakhapatnam districts.

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3 236 We observed an interaction between the effects of latitude (North/South) and urban/rural residence in
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5 237 association with reduced eGFR (p-value for interaction<0.001). The mean eGFR was lower in rural
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7 238 settings in both Northern and Southern India (controlling for age, sex, education and alcohol intake).
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9 239 However, this decrease was much more marked in Southern India. In Northern India, rural residence,
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11 240 formal education (and duration) and age were the only other risk factor associated with reduced eGFR. In
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13 241 Southern India, being male was also a risk factor for reduced eGFR, whereas formal education was only a
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15 242 risk factor for reduced eGFR among those with more than 10 years of schooling (Table 5). We also
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17 243 observed an interaction between the effects of latitude (North/South) and urban/rural residence in
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19 244 association with eGFR<60 (p-value likelihood-ratio test for interaction<0.001). In Northern India,
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21 245 eGFR<60 was not associated with urban/rural residence, and older age was the only factor associated
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23 246 with eGFR<60. In Southern India, rural residence was the strongest risk factor for eGFR<60 but older age
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25 247 and lower years of formal education also increased the risk of eGFR<60 (Table 5).
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248 **Table 5.** Multivariate analysis of sociodemographic characteristics associated with eGFR and with
 249 eGFR<60 according to latitude ^a

Variables	eGFR (n=12,500)		eGFR<60(n=12,500)	
	North (n=6263) ^a	South (n= 6237) ^b	North (n=6263) ^a	South (n= 6237) ^b
	Coefficient (95% CI)	Coefficient (95% CI)	OR (95% CI)	OR (95% CI)
Area ^c				
Urban	0.00 (ref)	0.00 (ref)	1.00 (ref)	1.00 (ref)
Rural	-1.42 (-2.15, -0.70)	-7.90 (-8.81, -7.00)	0.88 (0.57, 1.37)	4.68 (2.50, 8.77)
Education (number of completed years)				
0	0.00 (ref)	0.00 (ref)	1.00 (ref)	1.00 (ref) ^{**}
≤5	-1.32 (-2.58, -0.05)	1.05 (-0.06, 2.16)	1.16 (0.57, 2.35)	0.40 (0.20, 0.80)
6-≤10	-3.50 (-4.48, -2.52)	0.28 (-0.74, 1.30)	1.34 (0.74, 2.41)	0.35 (0.16, 0.74)
> 10	-6.93 (-7.97, -5.89)	-2.85 (-4.03, -1.67)	1.34 (0.69, 2.58)	0.61 (0.24, 1.57)
Alcohol consumption ever				
No	0.00 (ref)	0.00 (ref)	1.00 (ref)	1.00 (ref)
Yes	-0.54 (-1.55, 0.47)	-0.06 (-1.11, 0.99)	1.09 (0.62, 1.92)	1.36 (0.74, 2.17)
Sex				
Female	0.00 (ref)	0.00 (ref)	1.00 (ref)	1.00 (ref)
Male	-0.17 (-0.96, 0.63)	-5.40 (-6.29, -4.51)	0.97 (0.59, 1.59)	1.58 (0.91, 2.75)
Age (per 10 years)	-9.26 (-9.55, -8.97)	-8.96 (-9.28, -8.64)	2.51 (2.15, 2.93)	2.10 (1.77, 2.50)

250 ^{**} Likelihood ratio test for linear trend <0.05, OR (95% CI)=0.68 (0.51, 0.91). ^a North areas include Delhi,
 251 Sonipat and Faridabad district. ^b South areas include Chennai and Vishakhapatnam districts. ^c Urban areas
 252 include Delhi, Chennai and Sonipat district. Rural areas include Sonipat, Vishakhapatnam and Faridabad
 253 districts

254 Sensitivity analyses

255 We performed a sensitivity analysis including those with ACR>300 (but without hypertension or
256 diabetes, n=33) as we were concerned that those with CKDu might develop proteinuria at more advanced
257 CKD stages. However, this did not alter the mean eGFR (mean eGFR among the overall study
258 population=105.0±17.8, mean eGFR in this sensitivity analysis =105.0±17.8), nor the estimated
259 prevalence of eGFR<60 (prevalence among the overall study population=1.6%; prevalence in this
260 sensitivity analysis =1.7%). The findings on risk factors were also similar to the findings from the
261 primary analyses (supplementary material, Table S3).

262 Given concerns about potentially different thresholds to define diabetes and high blood pressure in
263 different ethnic groups [30,31], we performed a further sensitivity analysis including fasting plasma
264 glucose, HbA1c and systolic blood pressure in the multivariate model (even though there is evidence for
265 both causation and reverse causation between these factors and CKD [32]). Systolic blood pressure and
266 fasting plasma glucose were associated with reduced eGFR in this non diabetic population, but inclusion
267 of these variables did not alter the coefficients for the associations with other risk factors observed in the
268 primary analysis (supplementary material, Table S4). HbA1c was associated with eGFR<60 in this non
269 diabetic population but inclusion of this variable did not alter the OR for other risk factors observed in the
270 primary analysis (supplementary material, Table S4). Therefore, although the relationship between sub-
271 clinical diabetes and impaired kidney function requires further prospective investigation, there is no
272 evidence that the excess risk of low eGFR (i.e. lower mean eGFR and higher prevalence of eGFR<60) in
273 rural Southern India is associated with either impaired fasting glucose or higher blood pressure.

274 DISCUSSION

275 We report the distribution of eGFR in people without diabetes, hypertension or heavy proteinuria and
276 estimate the prevalence of CKDu in our study population, including participants from urban and rural
277 settings. This is the first population-based evidence, using standardised methods, which indicates that
278 CKDu is present in India and is not confined to Central America and Sri Lanka. We found that the rural
279 population from Southern India (Vishakhapatnam district) had the highest risk of decreased eGFR (lower
280 mean eGFR and higher prevalence of eGFR<60). Risk factors of decreased eGFR were different between
281 Southern and Northern India. In Southern India, rural residence, older age and being male were risk

282 factors for both lower mean eGFR and eGFR<60; education was associated with decreased risk for
283 eGFR<60 but not with lower mean eGFR. In Northern India, older age was the only risk factor for both
284 lower mean eGFR and eGFR<60; rural residence and years of formal education were associated with
285 lower mean eGFR but not with eGFR<60. In summary, in Southern India, older age, being male and rural
286 residence were the main risk factors for decreased eGFR, whereas in Northern India older age was the
287 main risk factors for decreased eGFR.

288 As in Central America, the risk of low eGFR was higher in rural settings than in urban settings. This is in
289 concordance with a previous study from Hyderabad (India), that has provided evidence of a higher risk of
290 low eGFR in a rural population compared to urban-migrant and urban population [33], and with various
291 studies from other LMICs that have provided evidence of clusters of CKDu among the rural population
292 [2,3]. Exposure to some of the suggested potential risk factors for CKDu such as agricultural work and
293 agrochemical exposure, amongst others [34], may be greater in rural settings. Such exposures may also
294 differ between Southern and Northern India, and potentially explain the differences observed between
295 these areas. The associations between urban/rural residence and lower mean eGFR was much more
296 marked in Southern India than in Northern India, and the associations between urban/rural residence and
297 eGFR<60 was only observed in Southern India. The higher prevalence ratio (for eGFR<60) in the
298 working age population compared to older age groups is consistent with the hypothesis that decreased in
299 eGFR could be potentially explained by occupational exposures. The suggestive sex differences may also
300 support this hypothesis. However, we did not have detailed data on occupation that allowed us to explore
301 these associations in greater detail.

302 The higher risk of low eGFR in Southern India (Chennai and Vishakhapatnam districts) observed in our
303 study is consistent with the clusters of CKDu cases previously reported in the Southern Indian states of
304 Andhra Pradesh and Odisha [11,18,19]. Visakhapatnam district (state of Andhra Pradesh) and Chennai
305 district (state of Tamil Nadu) have a similar climate than these areas where CKDu clusters have
306 previously reported [35]. In these districts, mean temperatures range from 18 °C to 37 °C and rainfall
307 occurs mainly between June and December [36]. On the other hand, sites from Northern India included in
308 the study (Delhi (state of Delhi), Sonipat and Faridabad (Haryana state)), have a different climate. In
309 these districts mean temperature ranges from 8 °C to 39 °C and precipitation occurs mainly between July

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3 310 and August [36]. A previous study conducted in Costa Rica found a spatial correlation between rates of
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5 311 CKD mortality and temperature and rainfall [13].
6

7 312 About 5% of the rural population of Vishakhapatnam (Andhra Pradesh, Southern India) without diabetes,
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9 313 hypertension or proteinuria had eGFR<60. This figure is almost as high as the prevalence observed in the
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11 314 USA (i.e. 6.7%) including people with diabetes, hypertension or proteinuria [37]. Moreover, the estimates
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13 315 of GFR in our study are likely to be underestimated. The CKD-EPI equation has been standardised for the
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15 316 white and Afro-American population [24], but its validity for other ethnic groups has been questioned
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17 317 [38,39]. Previous studies using CKD-EPI equation to estimate GFR in Indian populations reported mean
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19 318 eGFR values similar to the mean eGFR reported in our study (i.e. 104.9 ± 25.52 ml/min/1.73 m²) [40].
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21 319 However, two studies conducted among healthy kidney donors in India (population similar to those
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23 320 included in this analysis) have reported mean (measured) GFR between 81.4 and 95.5 ml/min per 1.73 m²
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25 321 [41,42], suggesting that the CKD-EPI equation substantially overestimates eGFR in the Indian
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27 322 population. Therefore, the prevalence of eGFR<60 observed in this study is likely to be substantially
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29 323 underestimated (although this is unlikely to have biased the internal comparisons, e.g. between urban and
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31 324 rural settings). The use of a conservative definition of the population susceptible to CKDu, may have also
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33 325 underestimated the prevalence of eGFR<60 in our study, as the population with diabetes, hypertension or
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35 326 glomerular disease may also have reduced eGFR due to other ('unknown') causes. To estimate the actual
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37 327 prevalence of reduced eGFR, future studies should include validated methods to estimate GFR in the
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39 328 Indian population. We were concerned that the validity of CKD-EPI among the Indian population may be
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41 329 also compromised by differences in muscular mass and meat consumption between population groups
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43 330 within India. We adjusted the analyses for fat free mass and vegetarianism, but this did not alter the
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45 331 results, suggesting no confounding effect by these variables.

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47 332 Our study has at least three potential limitations. First, we only had one measure of eGFR, and therefore
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49 333 we could not differentiate acute kidney injury (AKI) from CKD. This is a common limitation in
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51 334 epidemiological studies, as it is challenging to obtain more than one measure of eGFR at least 3 months
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53 335 apart in large population-based investigations. Therefore, we may have misclassified some cases of AKI
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55 336 as reduced eGFR, and therefore overestimate the prevalence of this condition. Nevertheless, there is no a
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57 337 priori reason to think that potential misclassification was different according to the evaluated risks factors.
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59 338 Second, the three population-based studies included in this analysis used different sampling strategies.

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3 339 CARRS and UDAY studies included only one man and one woman from all the eligible participants of
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5 340 selected households, whereas ICMR-CHD included all eligible adults from each selected household. This
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7 341 could have slightly biased our results (including our prevalence estimates) if risk factors potentially
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9 342 associated with CKDu were different between households inhabited only by a man and a women or by
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11 343 extended families. Third, information on other potential risk factors for CKDu, such as infections by
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13 344 leptospora or hantavirus infection, or use of nonsteroidal anti-inflammatory drugs (NSAIDs) was not
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15 345 available.

16
17 346 The main strengths of the study are the use of a random selection of population-based participants and a
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19 347 large sample size including participants from different areas of India (urban and rural, and Northern and
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21 348 Southern India). Moreover, we used the definitions proposed in DRGREE study [43], that aims to allow
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23 349 international comparisons of CKDu prevalence and help in the description of risk factors and in
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25 350 identifying the causes and mechanisms leading to CKDu.

26
27 351 In conclusion, our findings indicate that reduced eGFR, consistent with the definition of CKDu, is
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29 352 common in rural settings of Southern India (Vishakhapatnam district). This results support the hypothesis
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31 353 that the epidemic of CKDu, initially described in agricultural communities of Central America and Sri
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33 354 Lanka, may be common in other rural communities of tropical/subtropical countries. This has important
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35 355 implications for global health, since it indicates that CKDu may have a substantial public health burden
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37 356 globally that has been previously unrecognised. Population-based studies in other tropical/subtropical
38
39 357 countries are required to assess the global patterns of burden of disease from CKDu [43].

40 358 **AUTHOR CONTRIBUTIONS AND ACKNOWLEDGEMENTS**

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42
43 359 CO-G, BC, NP and DP designed the work; RS, SA, SG, RG, AK, SM, VM, PPA, NT, and KMN
44
45 360 collected the data; CO-G and DK conducted the analysis of the data; CO-G, RS, SA, JG, KJ, DN, SM,
46
47 361 KMN, NP, BC, and DP interpreted the data of the work. CO-G, RS, BC, and NP drafted the manuscript;
48
49 362 RS, SA, SG, JG, RG, KJ, DK, AK, SM, VM, DN, PPA, NT, KMN, and DP revised the manuscript for
50
51 363 important intellectual content, provided comments and suggested revisions. All authors approved the final
52
53 364 version for publication.

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3 366 **CONFLICTS OF INTERESTS**

4
5 367 The authors declare that they have no competing interests

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8 368 **DATA SHARING STATEMENT**

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11 369 The datasets used and/or analysed during the current study are available from Public Health Foundation
12 of India (PHFI) on reasonable request. Interested investigators should contact PHFI. Computing code can
13 370 be obtained from the corresponding author.
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372 REFERENCES

- 373 1 Wesseling C, Crowe J, Hogstedt C, *et al*. Mesoamerican Nephropathy: Report from the First
374 International Research Workshop on MeN. Heredia, Costa Rica: 2013.
- 375 2 Correa-Rotter R, Wesseling C, Johnson RJ. CKD of unknown origin in Central America: the case
376 for a Mesoamerican nephropathy. *Am J Kidney Dis* 2014;**63**:506–20.
377 doi:10.1053/j.ajkd.2013.10.062
- 378 3 Jayatilake N, Mendis S, Maheepala P, *et al*. Chronic kidney disease of uncertain aetiology:
379 Prevalence and causative factors in a developing country. *BMC Nephrol* 2013;**14**:1.
380 doi:10.1186/1471-2369-14-180
- 381 4 Lebov JF, Valladares E, Pena R, *et al*. A population-based study of prevalence and risk factors of
382 chronic kidney disease in Leon, Nicaragua. *Can J kidney Heal Dis* 2015;**2**:6. doi:10.1186/s40697-
383 015-0041-1
- 384 5 Peraza S, Wesseling C, Aragon A, *et al*. Decreased kidney function among agricultural workers
385 in El Salvador. *Am J Kidney Dis* 2012;**59**:531–40. doi:10.1053/j.ajkd.2011.11.039
- 386 6 Torres C, Aragón A, González M, *et al*. Decreased kidney function of unknown cause in
387 Nicaragua: a community-based survey. *Am J Kidney Dis* 2010;**55**:485–96.
388 doi:10.1053/j.ajkd.2009.12.012
- 389 7 Seck SM, Doupa D, Gueye L, *et al*. Prevalence of chronic kidney disease and associated factors
390 in senegalese populations: a community-based study in saint-louis. *Nephrourol Mon*
391 2014;**6**:e19085. doi:10.5812/numonthly.19085
- 392 8 Barsoum RS. Burden of chronic kidney disease: North Africa. *Kidney Int Suppl* 2013;**3**:164–6.
393 doi:10.1038/kisup.2013.5
- 394 9 El Minshawy O, Ghabrah T, El Bassuoni E. End-stage renal disease in Tabuk Area, Saudi Arabia:
395 an epidemiological study. *Saudi J Kidney Dis Transpl* 2014;**25**:192–5.
- 396 10 Rajapurkar MM, John GT, Kirpalani AL, *et al*. What do we know about chronic kidney disease in
397 India: First report of the Indian CKD registry. *BMC Nephrol* 2012;**13**. doi:10.1186/1471-2369-
398 13-10
- 399 11 Reddy D V., Gunasekar A. Chronic kidney disease in two coastal districts of Andhra Pradesh,
400 India: Role of drinking water. *Environ Geochem Health* 2013;**35**:439–54. doi:10.1007/s10653-
401 012-9506-7
- 402 12 Jayasumana C, Paranagama P, Agampodi S, *et al*. Drinking well water and occupational exposure
403 to Herbicides is associated with chronic kidney disease, in Padavi-Sripura, Sri Lanka -No section-
404 . *Environ Heal A Glob Access Sci Source* 2015;**14**. doi:10.1186/1476-069X-14-6
- 405 13 Wesseling C, Van Wendel De Joode B, Crowe J, *et al*. Mesoamerican nephropathy: Geographical
406 distribution and time trends of chronic kidney disease mortality between 1970 and 2012 in Costa
407 Rica. *Occup Environ Med* 2015;**72**:714–21. doi:10.1136/oemed-2014-102799
- 408 14 Garcia-Garcia G, Jha V, World Kidney Day Steering Committee. Environmental and
409 occupational factors in CKD. *Occup Environ Med* 2015;**72**:238. doi:10.1136/oemed-2015-102859
- 410 15 Robey RB. Cyclical dehydration-induced renal injury and Mesoamerican nephropathy: as sweet
411 by any other name? *Kidney Int* 2014;**86**:226–9. doi:10.1038/ki.2014.47
- 412 16 Jha V, Modi G. Uncovering the rising kidney failure deaths in India. *Lancet Glob Heal*
413 2017;**5**:e14–5. doi:10.1016/S2214-109X(16)30299-6
- 414 17 Dare AJ, Fu SH, Patra J, *et al*. Renal failure deaths and their risk factors in India 2001–13:
415 nationally representative estimates from the Million Death Study. *Lancet Glob Heal* 2017;**5**:e89–
416 95. doi:10.1016/S2214-109X(16)30308-4
- 417 18 Chatterjee R. Occupational Hazard. *Science (80-)* 1026;**352**:24–7.
- 418 19 Ganguli A. Uddanam Nephropathy/Regional Nephropathy in India: Preliminary Findings and a
419 Plea for Further Research. *Am J Kidney Dis* 2016;**68**:344–8. doi:10.1053/j.ajkd.2016.04.012
- 420 20 Nair M, Ali MK, Ajay VS, *et al*. CARRS Surveillance study: Design and methods to assess
421 burdens from multiple perspectives. *BMC Public Health* 2012;**12**:1. doi:10.1186/1471-2458-12-

- 1
2
3 422 701
- 4 423 21 Mohan S, Jarhyan P, Ghosh S, *et al.* UDAY: Protocol of a Comprehensive Diabetes and
5 424 Hypertension Prevention and Management Program in India. *BMJ open* 2018;**8**:e015919.
6 425 doi:e015919. doi: 10.1136/bmjopen-2017-015919
- 7 426 22 Prabhakaran D, Roy A, Praveen PA, *et al.* 20-Year Trend of Cardiovascular Disease Risk Factors.
8 427 *Glob Heart* Published Online First: 2017. doi:10.1016/j.gheart.2016.11.004
- 9 428 23 World Health Organization. STEPS Manual. 2015.
- 10 429 24 Levey AS, Stevens LA, Schmid CH, *et al.* A new equation to estimate glomerular filtration rate.
11 430 *Ann Intern Med* 2009;**150**:604–12.
- 12 431 25 Patel SA, Deepa M, Shivashankar R, *et al.* Comparison of multiple obesity indices for
13 432 cardiovascular disease risk classification in South Asian adults: The CARRS Study. *PLoS One*
14 433 2017;**12**:e0174251.
- 15 434 26 Anand S, Shivashankar R, Ali MK, *et al.* Prevalence of chronic kidney disease in two major
16 435 Indian cities and projections for associated cardiovascular disease. *Kidney Int* 2015;**88**:178–85.
17 436 doi:10.1038/ki.2015.58
- 18 437 27 Greenland S, Daniel R, Pearce N, *et al.* Outcome modelling strategies in epidemiology:
19 438 traditional methods and basic alternatives. *Int J Epidemiol* 2016;**1**:1–11. doi:10.1093/ije/dyw040
- 20 439 28 Census of India. 2011. <http://censusindia.gov.in/> (accessed 1 Aug 2018).
- 21 440 29 Longvah T, Ananthan R, Bhaskarachary K, *et al.* Indian Food Composition tables. Hyderabad:
22 441 2017.
- 23 442 30 Herman WH. Do race and ethnicity impact hemoglobin A1c independent of glycemia? *J Diabetes*
24 443 *Sci Technol* 2009;**3**:656–60. doi:10.1177/193229680900300406
- 25 444 31 Modesti PA, Rebaldi G, Cappuccio FP, *et al.* Panethnic Differences in Blood Pressure in Europe:
26 445 A Systematic Review and Meta-Analysis. *PLoS One* 2016;**11**:e0147601.
27 446 doi:10.1371/journal.pone.0147601
- 28 447 32 Verhave JC, Hillege HL, Burgerhof JGM, *et al.* The association between atherosclerotic risk
29 448 factors and renal function in the general population. *Kidney Int* 2005;**67**:1967–73.
30 449 doi:10.1111/j.1523-1755.2005.00296.x
- 31 450 33 Bailey PK, Tomson CRV, Kinra S, *et al.* The effect of rural-to-urban migration on renal function
32 451 in an Indian population: Cross-sectional data from the Hyderabad arm of the Indian Migration
33 452 Study. *BMC Nephrol* 2013;**14**. doi:10.1186/1471-2369-14-240
- 34 453 34 Lunyera J, Mohottige D, von Isenburg M, *et al.* CKD of uncertain etiology: A systematic review.
35 454 *Clin J Am Soc Nephrol* 2016;**11**:379–85. doi:10.2215/CJN.07500715
- 36 455 35 Peel MC, Finlayson BL, McMahon TA. Updated world map of the Koppen-Geiger climate
37 456 classification. *Hydrol Earth Syst Sci* 2007;**11**:1633–1644.
- 38 457 36 Norwegian Meteorological Institute and the Norwegian Broadcasting Corporation. Yr.
- 39 458 37 Levey AS, Coresh J. Chronic kidney disease. *Lancet* 2012;**379**:165–80. doi:10.1016/S0140-
40 459 6736(11)60178-5
- 41 460 38 Eastwood JB, Kerry SM, Plange-Rhule J, *et al.* Assessment of GFR by four methods in adults in
42 461 Ashanti, Ghana: the need for an eGFR equation for lean African populations. *Nephrol Dial*
43 462 *Transplant* 2010;**25**:2178–87. doi:10.1093/ndt/gfp765
- 44 463 39 Teo BW, Xu H, Wang D, *et al.* GFR estimating equations in a multiethnic Asian population. *Am*
45 464 *J Kidney Dis* 2011;**58**:56–63. doi:10.1053/j.ajkd.2011.02.393
- 46 465 40 Singh AK, Farag YMK, Mittal B V., *et al.* Epidemiology and risk factors of chronic kidney
47 466 disease in India - Results from the SEEK (Screening and Early Evaluation of Kidney Disease)
48 467 study. *BMC Nephrol* 2013;**14**:1. doi:10.1186/1471-2369-14-114
- 49 468 41 Barai S, Bandopadhyaya GP, Patel CD, *et al.* Do healthy potential kidney donors in India have
50 469 an average glomerular filtration rate of 81.4 ml/min? *Nephron - Physiol* 2005;**101**:21–6.
51 470 doi:10.1159/000086038
- 52 471 42 Srinivas S, Annigeri RA, Mani MK, *et al.* Estimation of glomerular filtration rate in South Asian
53 472 healthy adult kidney donors. *Nephrology* 2008;**13**:440–6. doi:10.1111/j.1440-1797.2008.00967.x

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473 43 Caplin B, Jakobsson K, Glaser J, *et al.* International Collaboration for the Epidemiology of eGFR
 474 in Low and Middle Income Populations - Rationale and core protocol for the Disadvantaged
 475 Populations eGFR Epidemiology Study (DEGREE). *BMC Nephrol* 2017;**18**:1–8.
 476 doi:10.1186/s12882-016-0417-1

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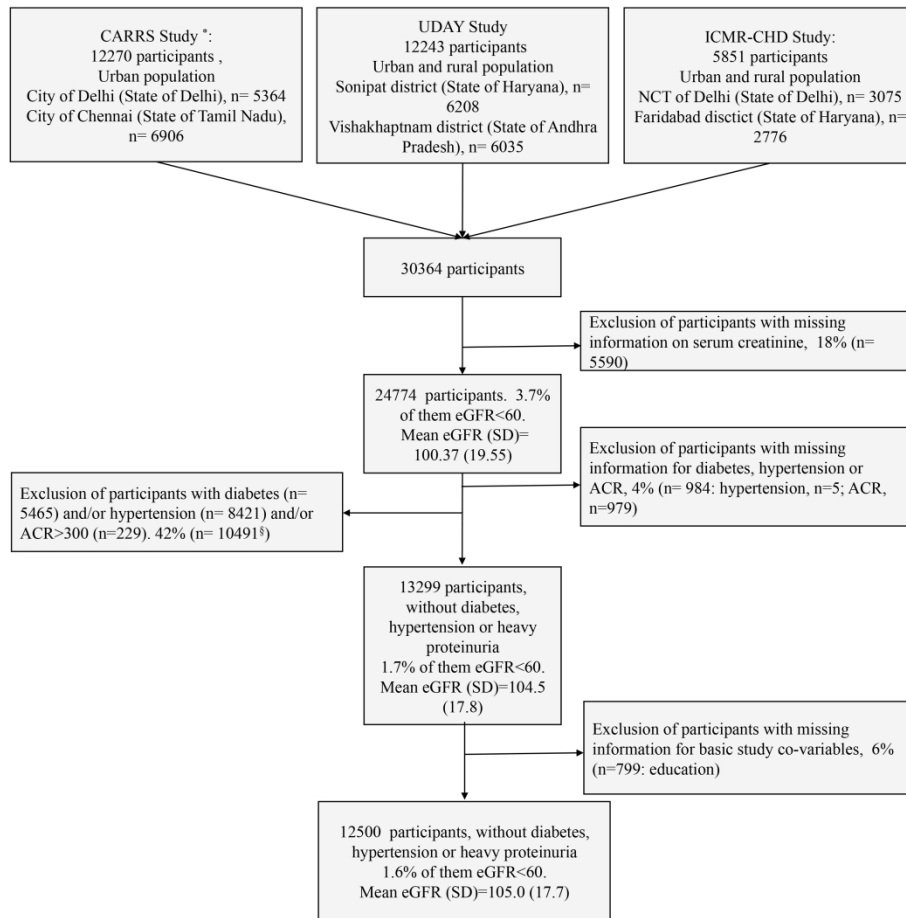
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3 477 **FIGURES LEGENDS**

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6 478 **Figure 1** Study areas

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8 479 **Figure 2** Study flowchart

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10 480 **Figure 3** Prevalence ratio of eGFR<60 by age group between rural and urban areas
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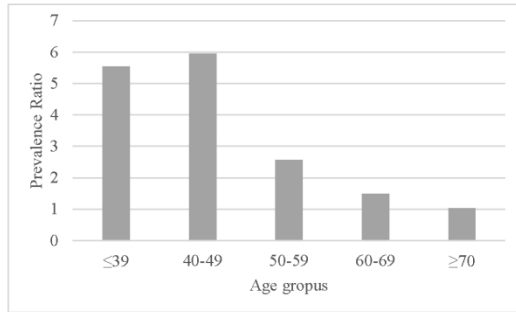


* The original sample size in the CARRS study is 12271, one transgender person was excluded for the current analysis; § 2353 participants with diabetes only; 5185 participants with hypertension only; 35 participants with ACR>30 only; 2724 participants with diabetes, and hypertension; 35 participants with diabetes and ACR>30; 47 participants with hypertension and ACR>30; 112 participants with diabetes, hypertension and ACR>30.

Study flowchart

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Prevalence ratio of eGFR<60 by age group between rural and urban areas

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3 **1 SUPPLEMENTARY MATERIAL**

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5 **2 Content**

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8 **3 Table S1.** Sociodemographic and anthropometric characteristics of overall study participants (prior to
9 exclusion of population with diabetes, hypertension and proteinuria)
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13 **4 Table S2.** Associations between sociodemographic and anthropometric characteristics and estimated
14 glomerular filtration rate (eGFR) and eGFR<60 by sex
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18 **5 Table S3.** Multiple regression analysis of sociodemographic and anthropometric characteristics associated
19 with eGFR and eGFR<60 including study participants with proteinuria (but without diabetes or
20 hypertension)
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25 **6 Table S4.** Multiple regression analysis of sociodemographic and anthropometric characteristics associated
26 with eGFR and eGFR<60 including fasting plasma glucose, HbA1c and systolic blood pressure
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Table S1. Sociodemographic and anthropometric characteristics of overall study participants (prior to exclusion of population with diabetes, hypertension and proteinuria)

Variable	n (%) ^a n=24774	eGFR categories, n(%) ^b			
		mean (SD)	≥90	90-60	<60
Socio-demographic factors					
Age (years)					
<39	9007 (36)	112.9 (14.9)	8248 (92)	716 (8)	43 (0)
40-49	6924 (28)	101.9 (14.8)	5617 (81)	1215 (18)	92 (1)
50-59	4524 (18)	92.9 (15.2)	2997 (66)	1378 (30)	149 (3)
60-69	3045 (12)	82.8 (17.1)	1410 (46)	1315 (43)	320 (11)
≥70	1274 (5)	72.0 (17.3)	164 (13)	806 (63)	304 (24)
Sex					
Female	13433 (54)	102.6 (19.5)	10404 (77)	2585 (19)	444 (3)
Male	11341 (46)	97.7 (19.3)	8032 (71)	2845 (25)	464 (4)
Education (number of years)					
0	4794 (19)	97.7 (20.2)	3458 (72)	1075 (22)	261 (5)
5	3194 (13)	101.7 (19.4)	2456 (77)	625 (20)	113 (4)
10	8855 (36)	103.2 (18.9)	6995 (79)	1620 (18)	240 (3)
> 10	6358 (26)	100.0 (19.2)	4638 (73)	1538 (24)	182 (3)
Missing data	1573 (6)		889 (57)	572 (36)	112 (7)
Area ^d					
Urban	17732 (72)	102 (19.5)	13577 (77)	3602 (20)	553 (3)
Rural	7042 (28)	96.3 (19.1)	4859 (69)	1828 (26)	355 (5)
Latitude ^e					
North	13570 (55)	98.1 (19.1)	9599 (71)	3439 (25)	532 (4)
South	11204 (45)	103.1 (19.7)	8837 (79)	1991 (18)	376 (3)
Life-style factors					
Current smoking					
No	18402 (74)	101.5 (19.6)	13920 (76)	3838 (21)	644 (3)
Yes	6372 (26)	97.1 (19.1)	4516 (71)	1592 (25)	264 (4)
Alcohol consumption ever					
No	19588 (79)	100.9 (19.6)	14671 (75)	4203 (21)	714 (4)
Yes	5186 (21)	98.5 (19.1)	3765 (73)	1227 (24)	194 (4)
Vegetarian					
No	15043 (61)	102.7 (19.7)	11721 (78)	2835 (19)	487 (3)
Yes	9731 (39)	96.8 (18.9)	6715 (69)	2595 (27)	421 (4)
Biological factors					
Body mass index (kg/m ²)					
Underweight (≤18.5)	10297 (42)	100.1 (19.6)	7626 (74)	2284 (22)	387 (4)
Normal (>18.5 - ≤25)	2403 (10)	101.58 (20.5)	1838 (76)	471 (20)	94 (4)
Overweight (>25 - ≤30)	7221 (29)	99.9 (18.8)	5309 (74)	1680 (23)	232 (3)
Obese (>30)	3286 (13)	99.3 (19.2)	2392 (73)	766 (23)	128 (4)
Missing data	1567 (6)		1271 (81)	229 (15)	67 (4)
Fat free mass (kg)					
1 st tertile (≤37)	7141 (29)	101.9 (20.1)	5481 (77)	1381 (19)	279 (4)
2 nd tertile (>37 - <45)	7141 (29)	101.3 (19.1)	5419 (76)	1487 (21)	235 (3)

3 rd tertile (≥ 45)	7141 (29)	98.3 (18.6)	5110 (72)	1797 (25)	234 (3)
Missing data	3351 (14)		2426 (72)	765 (23)	160 (5)

14 ^a Percentages in columns; ^b percentages in rows; ^d Urban areas include Delhi, Chennai and Sonipat district.

15 Rural areas include Sonipat, Vishakhapatnam and Faridabad districts; ^e North areas include Delhi, Sonipat

16 and Faridabad district. South areas include Chennai and Vishakhapatnam districts.

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17 **Table S2.** Associations between sociodemographic and anthropometric characteristics and estimated glomerular filtration rate (eGFR) and eGFR<60 by sex

Variable	Men, n=5 434			Women, n=7 066		
	n (%)	eGFR	eGFR<60	n (%)	eGFR	eGFR<60
		estimate (95% CI) ^a	OR (95% CI) ^a		estimate (95% CI) ^a	OR (95% CI) ^a
Age (years) ^b						
<39	2335 (43)	0.00 (ref)	1.00 (ref)	3786 (54)	0.00 (ref)	1.00 (ref)
40-49	1568 (29)	-9 (-9.97, -8.03)	2.36 (1.2, 4.62)	1908 (27)	-12.52 (-13.29, -11.76)	4.5 (1.95, 10.36)
50-59	843 (16)	-16.84 (-18.03, -15.65)	3.82 (1.91, 7.66)	863 (12)	-21.51 (-22.53, -20.48)	11.78 (5.2, 26.68)
60-69	479 (9)	-25.35 (-26.83, -23.86)	13.07 (6.97, 24.49)	414 (6)	-30.05 (-31.46, -28.64)	32.95 (14.87, 73.02)
>=70	209 (4)	-34.26 (-36.4, -32.12)	31.08 (16.33, 59.17)	95 (1)	-34.78 (-37.6, -31.96)	43.43 (15.93, 118.37)
Education (number of completed years)						
0	823 (15)	0.00 (ref)	1.00 (ref)	1997 (28)	0.00 (ref)	1.00 (ref)
≤5	703 (13)	3.28 (1.82, 4.74)	0.24 (0.13, 0.46)	1006 (14)	0.73 (-0.27, 1.73)	0.81 (0.42, 1.56)
6-≤10	2363 (43)	1.68 (0.51, 2.84)	0.31 (0.20, 0.48)	2454 (35)	0.67 (-0.13, 1.48)	0.43 (0.21, 0.86)
> 10	1545 (28)	-1.35 (-2.6, -0.1)	0.27 (0.15, 0.47)	1609 (23)	-2.39 (-3.27, -1.5)	0.76 (0.40, 1.46)
Area ^c	3583 (66)					
Urban	1851 (34)	0.00 (ref)	1.00 (ref)	4911 (70)	0.00 (ref)	1.00 (ref)
Rural		-4.02 (-4.85, -3.19)	2.72 (1.84, 4.01)	2155 (30)	-3.69 (-4.36, -3.02)	1.99 (1.26, 3.14)
Latitude ^d						
North	2861 (53)	0.00 (ref)	1.00 (ref)	3402 (48)	0.00 (ref)	1.00 (ref)
South	2573 (47)	-1.52 (-2.3, -0.74)	1.76 (1.21, 2.56)	3664 (52)	2.58 (1.96, 3.19)	1.30 (0.83, 2.05)
Current tobacco consumption						
No	2804 (52)	0.00 (ref)	1.00 (ref)	6553 (93)	0.00 (ref)	1.00 (ref)
Yes	2630 (48)	1.15 (0.36, 1.93)	1.32 (0.91, 1.92)	513 (7)	-1.93 (-3.14, -0.73)	1.54 (0.87, 2.73)
Alcohol consumption ever						
No	3035 (56)	0.00 (ref)	1.00 (ref)	7059 (100)	0.00 (ref)	1.00 (ref)

4	Yes	2399 (44)	-0.71 (-1.49, 0.06)	1.57 (1.08, 2.27)	7 (0)	-9.29 (-18.97, 0.4)	1.00 (1.00, 1.00)
5	Vegetarian						
6	No	3576 (66)	0.00 (ref)	1.00 (ref)	4396 (62)	0.00 (ref)	1.00 (ref)
7	Yes	1858 (34)	0.65 (-0.18, 1.48)	0.61 (0.41, 0.90)	2670 (38)	-2.11 (-2.75, -1.47)	0.70 (0.44, 1.11)
8	Body mass index (kg/m ²)						
9	Underweight (≤ 18.5)	2888 (56)	0.00 (ref)	1.00 (ref)	2991 (44)	0.00 (ref)	1.00 (ref)
10	Normal ($>18.5 - \leq 25$)	812 (16)	4.05 (2.92, 5.18)	0.69 (0.42, 1.14)	764 (11)	1.61 (0.57, 2.65)	1.07 (0.57, 2.03)
11	Overweight ($>25 - \leq 30$)	1209 (23)	-1.7 (-2.68, -0.73)	0.71 (0.42, 1.21)	2104 (31)	-0.11 (-0.84, 0.62)	0.67 (0.38, 1.20)
12	Obese (>30)	243 (5)	-0.71 (-2.61, 1.18)	0.36 (0.09, 1.50)	907 (13)	-0.64 (-1.61, 0.33)	0.55 (0.23, 1.31)
13	Fat free mass (kg)						
14	1st tertile (≤ 37)	361 (8)	0.00 (ref)	1.00 (ref)	3833 (58)	0.00 (ref)	1.00 (ref)
15	2nd tertile ($>37 - <45$)	1351 (28)	-0.42 (-2.10, 1.25)	0.78 (0.44, 1.38)	2535 (39)	-1.39 (-2.04, -0.74)	0.67 (0.38, 1.17)
16	3rd tertile (≥ 45)	3093 (64)	-3.75 (-5.35, -2.16)	0.50 (0.28, 0.90)	208 (3)	-1.36 (-3.17, 0.45)	0.58 (0.08, 4.25)

18 ^a Adjusted for age; ^b Not adjusted for age; ^c Urban areas include Delhi, Chennai and Sonipat district. Rural areas include Sonipat, Vishakhapatnam and Faridabad districts; ^d

19 North areas include Delhi, Sonipat and Faridabad district. South areas include Chennai and Vishakhapatnam districts.

Table S3. Multiple regression analysis of sociodemographic characteristics associated with eGFR and eGFR<60 including study participants with proteinuria (but without diabetes or hypertension), n=12533

Variable	eGFR	eGFR<60
	Coefficient (95% CI) ^a	OR (95% CI) ^a
Area ^b		
Urban	0.00 (ref)	1.00 (ref)
Rural	-4.59 (-5.14, -4.03)	1.93 (1.40, 2.66)
Latitude ^c		
North	0.00 (ref)	1.00 (ref)
South	0.29 (-0.21, 0.78)	1.33 (0.98, 1.80)
Education (number of years)		
0	0.00 (ref)	1.00 (ref)
5	0.83 (0, 1.66)	0.55 (0.35, 0.87)
10	0.04 (-0.64, 0.72)	0.51 (0.35, 0.76)
> 10	-3.81 (-4.58, -3.04)	0.66 (0.40, 1.07)
Alcohol consumption ever		
No	0.00 (ref)	1.00 (ref)
Yes	-0.78 (-1.52, -0.05)	1.23 (0.85, 1.79)
Sex		
Female	0.00 (ref)	1.00 (ref)
Male	-2.86 (-3.46, -2.26)	1.38 (0.96, 1.98)
Age (per 10 years)	-9.12 (-9.34, -8.91)	2.23 (2.00, 2.49)

^a Variables mutually adjusted, ^b Urban areas include Delhi, Chennai and Sonipat district. Rural areas include Sonipat, Vishakhapatnam and Faridabad districts; ^c North areas include Delhi, Sonipat and Faridabad district. South areas include Chennai and Vishakhapatnam districts.

Table S4. Multiple regression analysis of sociodemographic characteristics associated with eGFR and eGFR<60 including plasma fasting glucose, HbA1c and systolic blood pressure

Variable	eGFR	eGFR<60
	Coefficient (95% CI) ^a	OR (95% CI) ^a
Area ^b		
Urban	0.00 (ref)	1.00 (ref)
Rural	-4.94 (-5.51, -4.38)	2.29 (1.64, 3.20)
Latitude ^c		
North	0.00 (ref)	1.00 (ref)
South	0.23 (-0.26, 0.72)	1.30 (0.95, 1.77)
Education (number of years)		
0	0.00 (ref)	1.00 (ref)
5	1.03 (0.20, 1.86)	0.49 (0.31, 0.79)
10	0.19 (-0.49, 0.87)	0.47 (0.32, 0.71)
> 10	-3.53 (-4.30, -2.76)	0.62 (0.38, 1.02)
Alcohol consumption ever		
No	0.00 (ref)	1.00 (ref)
Yes	-0.72 (-1.46, -0.01)	1.32 (0.90, 1.93)
Sex		
Female	0.00 (ref)	1.00 (ref)
Male	-2.69 (-3.29, -2.09)	1.47 (1.01, 2.12)
Age (per 10 years)	-8.93 (-9.16, -8.70)	2.11 (1.89, 2.38)
Fasting plasma glucose (mg/dl)	-0.06 (-0.08, -0.04)	1.01 (1.00, 1.02)
Hb1Ac (%)	0.03 (-0.56, 0.62)	1.95 (1.34, 2.85)
Systolic blood pressure (mm Hg)	-0.06 (-0.84, -0.04)	1.0 (0.99, 1.02)

^a Variables mutually adjusted, ^b Urban areas include Delhi, Chennai and Sonipat district. Rural areas include Sonipat, Vishakhapatnam and Faridabad districts; ^c North areas include Delhi, Sonipat and Faridabad district. South areas include Chennai and Vishakhapatnam districts.

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

	Item No	Recommendation	Page/line where the checklist items are located in the paper
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	Title and abstract (page 2, lines 29-30)
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 2, lines 27-45
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 4, lines 68-90
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 4-5, lines 91-95
Methods			
Study design	4	Present key elements of study design early in the paper	Page 5, lines 103-111, table 1
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Table 1 and page 6, line 123
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants	Page 5, lines 112-121
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Page 6, lines 149-171
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	Page 6, lines 123-147
Bias	9	Describe any efforts to address potential sources of bias	Page 6, lines 123-127, 134-138, 145-147
Study size	10	Explain how the study size was arrived at	Figure 1
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Page 6, lines 123-147
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	Page 6, 154-160
		(b) Describe any methods used to examine subgroups and interactions	Page 6, line 156; page 6, lines 162-171
		(c) Explain how missing data were addressed	Page 6, lines 160-162
		(d) If applicable, describe analytical methods taking account of sampling strategy	-
		(e) Describe any sensitivity analyses	Page 10, lines 233-235, 139-242
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for	Figure 1

		eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	
		(b) Give reasons for non-participation at each stage	Figure 1
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 2.; page 7-8, lines 177-185
		(b) Indicate number of participants with missing data for each variable of interest	Page 6, lines 160-162
Outcome data	15*	Report numbers of outcome events or summary measures	Page 8, line 187-201
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	Page 8, lines 203-220; table 3 and table 4
		(b) Report category boundaries when continuous variables were categorized	Table 3 and Table 4
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Page 9, lines 221-231; page 10, lines 233-250
Discussion			
Key results	18	Summarise key results with reference to study objectives	Page 10, lines 252-263
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	Pages 12-13, lines 310-322
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Pages 11-12, lines 264-309
Generalisability	21	Discuss the generalisability (external validity) of the study results	Pages 13, lines 323-325
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	Page 3, lines 59-66

*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

Prevalence of and risk factors for chronic kidney disease of unknown aetiology in India: secondary data analysis of three population-based cross-sectional studies

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3 1 **TITLE PAGE**
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6 2 **Title:** Prevalence of and risk factors for chronic kidney disease of unknown aetiology in India: secondary data analysis
7
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25 ABSTRACT

26 **Objectives:** To assess whether chronic kidney disease of unknown aetiology (CKDu) is present in India and to
27 identify risk factors for it using population-based data and standardised methods.

28 **Design:** Secondary data analysis of three population-based cross-sectional studies conducted between 2010-2014.

29 **Setting:** Urban and rural areas of Northern India (states of Delhi and Haryana) and Southern India (states of Tamil
30 Nadu and Andhra Pradesh)

31 **Participants:** 12,500 individuals without diabetes, hypertension or heavy proteinuria

32 **Outcome measures:** Mean estimated the glomerular filtration rate (eGFR) and prevalence of eGFR below 60ml/min
33 per 1.73m² (eGFR<60) in individuals without diabetes, hypertension or heavy proteinuria (proxy definition of
34 CKDu).

35 **Results:** The mean eGFR was 105.0±17.8 ml/min per 1.73m². The prevalence of eGFR<60 was 1.6% (95%CI=1.4,
36 1.7), but this figure varied markedly between areas, being highest in rural areas of Southern Indian [4.8% (3.8, 5.8)].
37 In Northern India, older age was the only risk factor associated with lower mean eGFR and eGFR<60 [regression
38 coefficient (95%CI)= -0.94 (0.97, 0.91); OR (95%CI)=1.10 (1.08, 1.11)]. In Southern India, risk factors for lower
39 mean eGFR and eGFR<60 respectively were residence in a rural area [-7.78 (-8.69, -6.86); 4.95 (2.61, 9.39)], older
40 age [-0.90 (-0.93, -0.86); 1.06 (1.04, 1.08)] and less education [-0.94 (-1.32, -0.56); 0.67 (0.50, 0.90) for each five
41 years at school].

42 **Conclusions:** CKDu is present in India and is not confined to Central America and Sri Lanka. Identified risk factors
43 are consistent with risk factors previously reported for CKDu in Central America and Sri Lanka.

44 KEYWORDS

45 Epidemiology; Chronic kidney disease; Chronic kidney disease of unknown aetiology; India; Rural population

46 ARTICLE SUMMARY

47 Strengths and limitations of this study

- 48 • The use of a random selection of population-based participants allows the estimation of CKDu prevalence in
49 the general population.

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3 50 • A large sample size including participants from different areas of India (urban and rural, and Northern and
4
5 51 Southern India) increases the representativeness of the results.
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7 52 • The use of standardized definitions of CKDu facilitates international comparisons of CKDu prevalence and
8
9 53 risk factors.
10
11 54 • The prevalence of eGFR<60 observed in this study is likely to be underestimated; however, this is unlikely
12
13 55 to have biased the internal comparisons conducted in this study.
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65 INTRODUCTION

66 High prevalence of CKDu has mainly been reported in the last decades amongst the working age populations of
67 agricultural communities of tropical/subtropical regions, specifically in Central America and Sri Lanka [1–3]. In
68 Nicaragua and El Salvador, the estimated prevalence of estimated glomerular filtration rate (eGFR; the clinical measure
69 of kidney function) below 60ml/min per 1.73m² (eGFR<60), in the absence of diabetes and hypertension, was 10-20%
70 [4–6]. It has been suggested that CKDu may also be highly prevalent in other low and middle income countries
71 (LMICs), including India [7–11]. However, it is not clear in which other regions of the world CKDu occurs, whether
72 the underlying aetiology is the same in different regions and what the risk factors are. Currently, there is no consensus
73 but factors such as heat stress, strenuous work, climatic conditions, agrochemical use, heavy metal exposure and
74 infections have been suggested as risk factors [1,12–15].

75 Data on CKDu from India are scarce. The recent report of verbal autopsy data from India suggests CKD of all causes
76 is a growing problem. However, it does not provide accurate population-based data on CKDu [16,17]. Existing reports
77 indicate that CKDu may be common but it is difficult to be definite about this because of the absence of population-
78 based studies using standardised and comparable methods. Data from the Indian CKD Registry, a hospital based
79 registry of incident cases of CKD between 2006-2010, found that CKDu was the second commonest form of CKD
80 after diabetic nephropathy [10]. However, this is restricted to referred cases and therefore may not be representative of
81 the general population. There are also sporadic reports of high numbers of CKDu cases among agricultural
82 communities of the South Eastern Indian states of Andhra Pradesh and Odisha (reviewed by Chatterjee [18] and
83 Ganguli [19]). However, population-based data have not been reported for India.

84 We conducted a secondary analysis of representative sample surveys conducted in India between 2010-2014. Given
85 the absence of a clear case definition for CKDu it is necessary to make a presumptive diagnosis based on
86 measures/estimates of GFR in the absence of known risk factors for kidney disease. The overall aim of the current
87 study was to use a methodology which is comparable to previous studies elsewhere in the world (particularly in Central
88 America) to assess the extent to which reduced kidney function is a problem in India, and which areas and
89 subpopulations are most affected. We therefore: (i) assessed the distribution eGFR and prevalence of eGFR below
90 60ml/min per 1.73m² (eGFR<60) in Indian populations restricted to those without known risk factors for CKD, i.e.

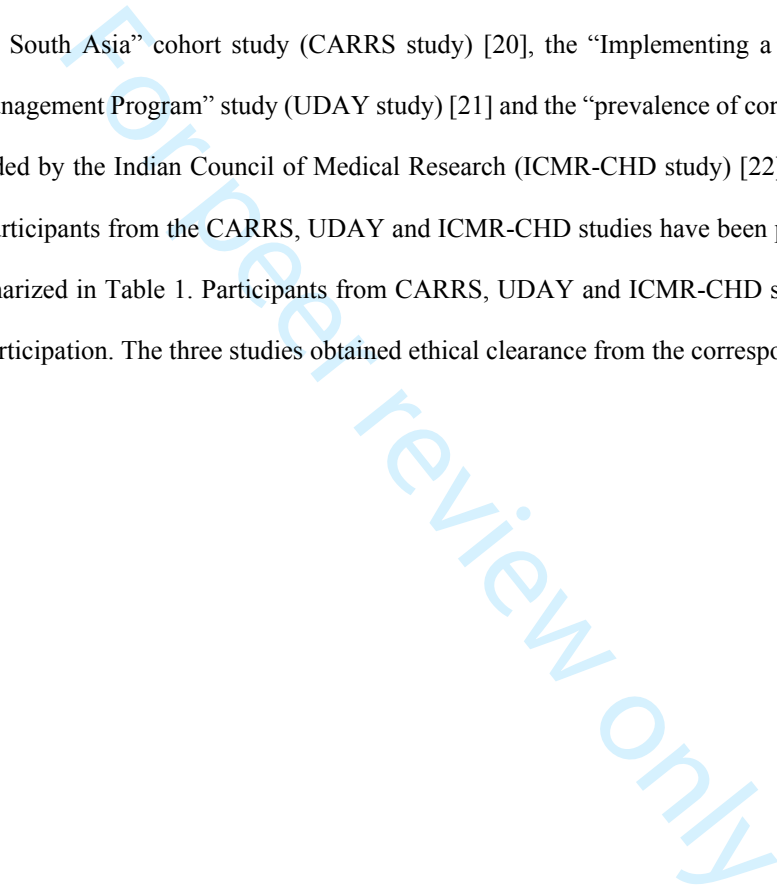
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91 diabetes, hypertension or heavy proteinuria; ii) compared these outcomes in North and South India and in urban and
92 rural populations; and (iii) identified the risk factors associated with these outcomes.

93 **METHODS**

94 **Study population**

95 We used cross-sectional data from three population-based studies conducted in India: the “Centre for Cardiometabolic
96 Risk Reduction in South Asia” cohort study (CARRS study) [20], the “Implementing a Comprehensive Diabetes
97 Prevention and Management Program” study (UDAY study) [21] and the “prevalence of coronary heart disease repeat
98 survey” study funded by the Indian Council of Medical Research (ICMR-CHD study) [22]. Details on study design
99 and selection of participants from the CARRS, UDAY and ICMR-CHD studies have been previously described [20–
100 22] and are summarized in Table 1. Participants from CARRS, UDAY and ICMR-CHD studies provided informed
101 consent prior to participation. The three studies obtained ethical clearance from the corresponding institutions.



102 **Table 1.** Design and methods of the three studies included in the current analysis

	CARRS		UDAY				ICMR-CHD	
Latitude (North/South)	North	South	North		South		North	
Residence (Urban/Rural)	Urban		Urban	Rural	Urban	Rural	Urban	Rural
District (and State)	Delhi (state of Delhi)	Chennai (state of Tamil Nadu)	Sonapat (state of Haryana)		Vishakhapatnam (state of Andhra Pradesh)		National Capital Territory of Delhi (state of Delhi)	Faridabad (state of Haryana)
Household sampling	Multistage cluster random (wards - census enumeration blocks - households)		Multistage cluster random (Census Enumeration blocks (urban) or villages (rural) - households)			Multistage cluster random (wards - census enumeration blocks - households)		Simple cluster random (based on Health and Demographic Surveillance System)
Individual sampling	1 man and 1 woman from each household (selected by Kish method, [23].) ^b		1 man and 1 woman from each household (selected by Kish method, [23].) ^b			All adults		
Age groups included	≥ 20		≥ 30				≥ 30	
Exclusion criteria	Pregnant, bedridden and participants who were unable to comprehend the questionnaires due cognitive deficiencies were excluded							
Study period	October 2010 - November 2011		July 2014 - December 2014			August 2010 - January 2012		
Laboratory^a	PHFI ^c	MDRF ^d	PHFI ^c			PHFI ^c		

103 ^a Study laboratories participated in Randox International Quality Assurance Scheme (RIQAS) for clinical chemistry
 104 and HbA1c during the entire study periods. ^b In households where only eligible men or only eligible women were
 105 present, we selected just one adult. ^c Public Health Foundation of India; ^d Madras Diabetes Research Foundation

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3 106 For the current analyses, we excluded participants with missing information on serum creatinine, as this variable was
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5 107 necessary to estimate eGFR. As the focus of our study was CKDu, we excluded participants with known risk factors
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7 108 for CKD (i.e. diabetes and hypertension) or evidence of primary glomerular disease (as assessed by heavy proteinuria)
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9 109 or with missing information for these risk factors. We also excluded participants with missing information on basic
10
11 110 co-variables (education) for all the analyses conducted. A study flowchart is presented in Figure 1. We classified
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13 111 participants as having: diabetes, if plasma fasting glucose was ≥ 126 mg/dl, or glycated haemoglobin A1c (HbA1c)
14
15 112 was $\geq 6.5\%$, or self-reported diabetes; hypertension, if systolic blood pressure was ≥ 140 mm Hg, or diastolic blood
16
17 113 pressure was ≥ 90 mm Hg, or self-reported hypertension; and heavy proteinuria, if the albumin/creatinine ratio (ACR)
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19 114 in urine was ≥ 300 mg/g. We used the CKD-EPI equation to estimate GFR (eGFR) [24].

21 115 **Data collection and laboratory analyses**

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23
24 116 Data collection was conducted between October 2010 and December 2014. All three studies used a standardized
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26 117 questionnaire to collect data on age, sex, completed years of education (0, ≤ 5 , $> 5 - \leq 10$, > 10), alcohol intake (ever,
27
28 118 never) and dietary habits (vegetarian yes, no). Weight, height and body composition were measured using stadiometers
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30 119 (SECA 214 in the three studies) and electronic bioimpedance measuring instruments (Tanita BC 418 in CARRS and
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32 120 ICMR-CHD studies, and Tanita BC 601 in UDAY study). Body mass index (BMI, kg/m^2) was calculated and
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34 121 categorized (≤ 18.5 : underweight; $> 18.5 - \leq 25$: normal weight; $> 25 - \leq 30$: overweight; > 30 : obese) and fat free mass
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36 122 was derived from bioelectric impedance analysis (BIA). In CARRS and ICMR-CHD studies, fat free mass (Kg) was
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38 123 directly measured as previously described [25], whereas in UDAY study, fat free mass was estimated from the
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40 124 percentage of total body fat. To estimate total fat free mass from the percentage of body fat, we calculated the amount
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42 125 of total body fat by multiplying the percentage of body fat by the weight of the participant, and from that value we
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44 126 estimated the amount of fat free mass by subtracting the weight of total body fat from the total weight of the participant.
45
46 127 Blood pressure was measured using electronic sphygmomanometers (OMRON (HEM-7080) in CARRS and ICMR-
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48 128 CHD studies, and OMRON (HEM 7200) in UDAY study), as previously reported [20,26]. Stadiometers, electronic
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50 129 bioimpedance measuring instruments, and electronic sphygmomanometers were calibrated before each study, and no
51
52 130 re-calibration was needed during the duration of different studies. A fasting venous blood sample was used to measure
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54 131 glucose levels, HbA1c and serum creatinine levels and urine sample to measure albuminuria and creatinuria [20].
55
56 132 Glucose levels were measured using hexokinase/kinetic methods, HbA1c using high-performance liquid

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3 133 chromatography, serum creatinine using the rate-blanked and compensated kinetic Jaffe method, traceable to isotope
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5 134 dilution mass spectrometry, and albuminuria using immune turbidimetric method [20]. Samples from UDAY, ICMR-
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7 135 CHD, and samples from CARRS from Delhi were analysed at Public Health Foundation of India (PHFI) laboratory
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9 136 and samples from CARRS from Chennai were analysed at Madras Diabetes Research Foundation (MDRF) laboratory.
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11 137 Both PHFI and MDRF laboratories used the same methodologies and protocols to analyse the samples and participated
12
13 138 in Randox International Quality Assurance Scheme (RIQAS) for clinical chemistry and HbA1c during the entire study
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15 139 periods. Data from the three studies were homogenized and merged in a single data set.

16 17 140 **Statistical analyses**

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20 141 We reported mean eGFR and prevalence of eGFR<60 according to different characteristics of the study populations.
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22 142 UDAY and CARRS studies did not involve fully random population samples (since sampling was based on
23
24 143 households, with one participant per household) and the proportions of study participants with particular outcomes
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26 144 (e.g. eGFR<60), will not be exactly the same (but very similar) to what would have been obtained with genuine random
27
28 145 population samples; thus in this paper we refer to the prevalence in the study participants, not overall population
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30 146 prevalence estimates. We used linear regression models to estimate the associations between potential risk factors and
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32 147 eGFR and logistic regression models to estimate the associations between potential risk factors and eGFR<60. We also
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34 148 repeated the analyses separately for males and females. Variables associated with eGFR in the basic analyses (adjusted
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36 149 for age and sex) were considered for the multiple regression analysis. In the final multiple regression model, we
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38 150 included all variables that were of a priori interest and/or had shown independent associations with eGFR. We then
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40 151 checked for multicollinearity for each variable in the multiple regression analyses in comparison with the basic
41
42 152 analyses [27]. 6% of participants had missing values for basic co-variables (i.e. education) and were excluded from
43
44 153 the analysis. 5% and 9% of participants had missing values for BMI and for fat free mass respectively. These
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46 154 participants were included in the main analysis, but we excluded them to compare models non-adjusted and adjusted
47
48 155 for these variables. We calculated prevalence ratios of eGFR<60 for rural versus urban areas in different age groups.
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50 156 Urban areas were defined as “all places with a municipality, corporation, cantonment board or notified town area
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52 157 committee, etc., and all other places which satisfied the following criteria: a minimum population of 5,000; at least 75
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54 158 per cent of the male main working population engaged in non-agricultural pursuits; and a density of population of at
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56 159 least 400 persons per km²”, according to the 2011 Census of India definition [28]. Finally, we estimated potential

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3 160 interactions between urban (versus rural) residence and latitude (Northern India (i.e. states of Delhi and Haryana)
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5 161 versus Southern India (states of Tamil Nadu and Andhra Pradesh). Classification of latitude was done in concordance
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7 162 with the classification of major geographical areas on India defined by the Indian Council of Medical Research [29],
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9 163 Figure 1. We conducted all analyses using Stata version 14 (StataCorp, College Station, TX, USA).

12 164 **Patient and Public Involvement**

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14
15 165 Patients were not involved in the design of this analysis.

18 166 **RESULTS**

21 167 **Characteristics of study participants**

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24 168 12,500 people were eligible for the current analyses (Figure 2). Table 2 summarizes the socio-demographic and
25
26 169 anthropometric characteristics of the 12,500 study participants included in this analysis (the same information
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28 170 including participants with known risk factors for CKD (n=24,774) in supplementary material Table S1). The mean
29
30 171 (standard deviation (\pm SD)) age of participants was 41.5 \pm 11.6 years. 88% (4,805/5,434) of the male population was
31
32 172 formally employed; 76% (5,346/7,066) of women worked on house duties (i.e. housewives). The mean BMI was
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34 173 24 \pm 5.0 kg/m² and mean fat free mass was 42 \pm 15 kg/m². The mean fasting plasma glucose was 91.9 \pm 12.3 mg/dl and
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36 174 the mean HbA1c was 5.5 \pm 0.4 %. The mean systolic and diastolic blood pressures were 114 \pm 12 mm Hg and 74 \pm 9 mm
37
38 175 Hg, respectively. The median (inter quartile range, IQR) albumin/creatinine ratio (ACR) was 2.4 (4.3) mg/g (after
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40 176 exclusion of those with ACR>300mg/g, n=1,208).

43 177 **Mean eGFR and prevalence of eGFR<60**

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45
46 178 The mean eGFR was 105.0 \pm 17.8 ml/min per 1.73m². The mean eGFR was lower at increasing ages, in males, in
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48 179 inhabitants from rural areas and in those from Northern India, in participants with no formal education, and in
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50 180 participants who reported tobacco consumption, alcohol intake and being vegetarian (Table 2). We observed
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52 181 differences in mean eGFR depending on the area, being 104.5 \pm 17.6 in urban areas of Northern India, 100.3 \pm 16.2 in
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54 182 rural areas of Northern India, 110.9 \pm 15.7 in urban areas of Southern India and 97.4 \pm 19.8 in the rural area of Southern
55
56 183 India.

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3 184 The prevalence of eGFR<60 among the study population was 1.6% (95% confidence interval (95% CI)=1.4, 1.9).
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5 185 Seventeen per cent (95% CI=16, 17) of study participants had eGFR \geq 60 - <90 ml/min per 1.73m² and 82% [95%
6
7 186 confidence interval (95% CI)=81, 82] had eGFR \geq 90 ml/min per 1.73m². The prevalences of different categories of
8
9 187 eGFR differed by formal education, tobacco consumption, alcohol intake and vegetarianism (Table 2). Also, we
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11 188 observed marked differences in the prevalence of eGFR<60 depending on the area, being 1.4 % (95% CI=1.1, 1.8) in
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13 189 urban areas of Northern India, 1.9 (95% CI=1.4, 2.6) in rural areas of Northern India, 0.43% (95% CI=0.03, 0.07) in
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15 190 urban areas of Southern India and 4.8 % (95% CI=3.9, 5.9) in the rural area of Southern India. The prevalence ratio of
16
17 191 eGFR<60 for rural versus urban residence was higher in participants younger than 50 years (prevalence ratio in age
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19 192 group \leq 39=5.5, and prevalence ratio in age group 40 - 49=5.8) than in older participants (Figure 3).
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193 **Table 2.** Sociodemographic and anthropometric characteristics of study participants (population without diabetes,
194 hypertension or heavy proteinuria)

Variable	n (%) ^a n=12,500	eGFR mean (SD)	eGFR categories, n(%) ^b		
			≥90	90 - 60	<60
Socio-demographic					
Age (years)					
<39	6121 (49)	113.8 (14.6)	5656 (92)	443 (7)	22 (0)
40 - 49	3476 (28)	102.5 (14.2)	2864 (82)	572 (16)	40 (1)
50 - 59	1706 (14)	93.9 (14.3)	1163 (68)	503 (29)	40 (2)
60 - 69	893 (7)	85.3 (16.2)	463 (52)	368 (41)	62 (7)
≥70	304 (2)	77.5 (15.1)	62 (20)	201 (66)	41 (13)
Sex					
Female	7066 (57)	107.9 (17.1)	6039 (85)	945 (13)	82 (1)
Male	5434 (43)	101.3 (17.9)	4169 (77)	1142 (21)	123 (2)
Education (number completed years)					
0	2820 (23)	100.7 (19.0)	2165 (77)	551 (20)	104 (4)
≤5	1709 (14)	105.9 (17.3)	1412 (83)	273 (16)	24 (1)
6 - ≤10	4817 (39)	107.2 (16.8)	4095 (85)	675 (14)	47 (1)
>10	3154 (25)	105.0 (17.5)	2536 (80)	588 (19)	30 (1)
Area ^c					
Urban	8494 (68)	107.8 (16.1)	7247 (85)	1171 (14)	76 (1)
Rural	4006 (32)	99.0 (18.0)	2961 (74)	916 (23)	129 (3)
Latitude ^d					
North	6263 (50)	103.0 (17.2)	4967 (79)	1197 (19)	99 (2)
South	6237 (50)	107.0 (18.1)	5241 (84)	890 (14)	106 (2)
Life-style factors					
Current tobacco consumption					
No	9357 (75)	106.8 (17.3)	7836 (84)	1406 (15)	115 (1)
Yes	3143 (25)	99.8 (18.1)	2372 (75)	681 (22)	90 (3)
Alcohol consumption ever					

195	No	10094 (81)	105.9 (17.4)	8362 (83)	1589 (16)	143 (1)	
	Yes	2406 (19)	101.1 (18.5)	1846 (77)	498 (21)	62 (3)	a
	Vegetarian						
	No	7972 (64)	107.0 (18.0)	6690 (84)	1154 (14)	128 (2)	
	Yes	4528 (36)	101.6 (16.6)	3518 (78)	933 (21)	77 (2)	
	Biological factors						
	Body mass index (kg/m ²)						
	Underweight (≤ 18.5)	5879 (47)	104.2 (17.9)	4734 (81)	1029 (18)	116 (2)	
	Normal ($> 18.5 - \leq 25$)	1576 (13)	104.7 (19.3)	1283 (81)	257 (16)	36 (2)	
	Overweight ($> 25 - \leq 30$)	3313 (27)	105.0 (16.9)	2710 (82)	568 (17)	35 (1)	
	Obese (> 30)	1150 (9)	105.5 (16.4)	948 (82)	194 (17)	8 (1)	
	Missing data	582 (5)		533 (92)	39 (7)	10 (2)	
	Fat free mass (kg)						
	1 st tertile (≤ 37)	3746 (30)	106.6 (18.1)	3146 (84)	532 (14)	68 (2)	
	2 nd tertile ($> 37 - < 45$)	3801 (30)	105.9 (17.2)	3145 (83)	601 (16)	55 (1)	
	3 rd tertile (≥ 45)	3834 (31)	102.1 (17.0)	2981 (78)	801 (21)	52 (1)	
	Missing data	1119 (9)		936 (84)	153 (14)	30 (3)	

196 Percentages in columns;^b percentages in rows; ^c Urban areas include Delhi, Chennai and Sonipat district. Rural areas
 197 include Sonipat, Vishakhapatnam and Faridabad districts; ^d North areas include Delhi, Sonipat and Faridabad district.
 198 South areas include Chennai and Vishakhapatnam districts.

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3 **199 Risk factors for lower eGFR and eGFR<60**
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6 200 As expected, age was an important risk factor for reduced eGFR: eGFR was 9.30 ml/min per 1.73 m² (95%CI= -9.51,
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8 201 -9.09, model adjusted for sex) lower for each additional 10 years of age. Additionally, being male, living in a rural
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10 202 setting, and consuming alcohol were associated with decreased mean eGFR (Table 3). Similarly, the odds of eGFR<60
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12 203 also increased with age [OR per 10 years, adjusted for sex (95%CI)=2.34 (2.12, 2.59)] and being male, living in a rural
13
14 204 setting, living in Southern India and consuming alcohol were also associated with eGFR<60 (Table 3). In general, risk
15
16 205 factors for decreased mean eGFR and for eGFR<60 were similar for men and women (supplementary material, Table
17
18 206 S2), but few differences were observed. Regarding mean eGFR, living in Southern India was associated with decreased
19
20 207 mean eGFR in men and with increased mean eGFR in women; tobacco consumption was associated with increased
21
22 208 mean eGFR in men and with decreased mean eGFR in women; vegetarianism was associated with decreased mean
23
24 209 eGFR in women but not in men; and being overweight was associated with decreased mean eGFR but in men but not
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26 210 in women. Regarding risk of eGFR<60, living in Southern India was associated with increased risk of eGFR<60 in
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28 211 men but not in women.
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212 **Table 3.** Associations between sociodemographic and anthropometric characteristics and eGFR and eGFR<60

Variable	eGFR Coefficient (95 CI) ^a	eGFR<60 OR (95 CI) ^a
Age (years) ^b		
<39	0.00 (ref)	1.00 (ref)
40 - 49	-11.08 (-11.68, -10.47)	3.15 (1.87, 5.32)
50 - 59	-19.43 (-20.20, -18.65)	6.41 (3.80, 10.83)
60 - 69	-27.84 (-28.86, -26.82)	19.68 (12.01, 32.26)
≥70	-35.04 (-36.71, -33.37)	39.23 (22.87, 67.23)
Sex ^c		
Female	0.00 (ref)	1.00 (ref)
Male	-3.55 (-4.05, -3.06)	1.33 (0.99, 1.78)
Education (number of completed years)		
0	0.00 (ref)	1.00 (ref)
≤5	1.92 (1.09, 2.76)	0.41 (0.26, 0.65)
6 - ≤10	1.27 (0.61, 1.93)	0.36 (0.25, 0.53)
> 10	-1.86 (-2.59, -1.14)	0.40 (0.26, 0.62)
Area ^d		
Urban	0.00 (ref)	1.00 (ref)
Rural	-3.84 (-4.37, -3.32)	2.39 (1.78, 3.22)
Latitude ^e		
North	0.00 (ref)	1.00 (ref)
South	0.86 (0.37, 1.35)	1.55 (1.16, 2.07)
Current tobacco consumption		
No	0.00 (ref)	1.00 (ref)
Yes	0.38 (-0.26, 1.02)	1.39 (1.01, 1.91)
Alcohol consumption ever		

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2			
3	No	0.00 (ref)	1.00 (ref)
4			
5	Yes	-0.81 (-1.55, -0.08)	1.57 (1.09, 2.27)
6			
7	Vegetarian		
8			
9	No	0.00 (ref)	1.00 (ref)
10			
11	Yes	-0.99 (-1.50, -0.47)	0.65 (0.48, 0.88)
12			
13	Body mass index (kg/m ²)		
14			
15	Underweight (≤ 18.5)	2.96 (2.20, 3.73)	0.81 (0.55, 1.20)
16			
17	Normal ($>18.5 - \leq 25$)	0.00 (ref)	1.00 (ref)
18			
19	Overweight ($>25 - \leq 30$)	-0.75 (-1.34, -0.16)	0.68 (0.46, 1.01)
20			
21	Obese (>30)	-0.71 (-1.59, 0.17)	0.47 (0.23, 0.98)
22			
23	Fat free mass (kg)		
24			
25	1st tertile (≤ 37)	0.00 (ref)	1.00 (ref)
26			
27	2nd tertile ($>37 - <45$)	-0.91 (-1.54, -0.28)	0.69 (0.47, 1.03)
28			
29	3rd tertile (≥ 45)	-3.90 (-4.77, -3.04)	0.49 (0.31, 0.80)

- 213 ^a Adjusted for age and sex; ^b Adjusted just for sex; ^c Adjusted just for age; ^d Urban areas include Delhi, Chennai and
 214 Sonipat district. Rural areas include Sonipat, Vishakhapatnam and Faridabad districts; ^e North areas include Delhi,
 215 Sonipat and Faridabad district. South areas include Chennai and Vishakhapatnam districts.

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3 216 In the multiple regression analyses, decreased mean eGFR remained associated with older age, being male, living in a
4
5 217 rural setting, and alcohol consumption (Table 4). Risk of eGFR<60 remained associated with older age, being male
6
7 218 and living in a rural setting, and having no formal education (Table 4). We adjusted all the multiple regression models
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9 219 for fat free mass and vegetarianism to assess the possibility that differences observed between urban and rural
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11 220 participants were due to differences in diet and/or body composition. These adjustments had little effect on the results
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13 221 (Table 4).
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222 **Table 4.** Multiple regression analyses of sociodemographic characteristics associated with eGFR and eGFR<6).

Variable	eGFR Coefficient (95% CI)			eGFR<60 OR (95% CI)		
	Model 1 ^a	Model 2 ^b	Model 3 ^c	Model 1 ^a	Model 2 ^b	Model 3 ^c
Area ^d						
Urban	0.00 (ref)	0.00 (ref)	0.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Rural	-4.57 (-5.13, -4.02)	-3.94 (-4.53, -3.36)	-4.10 (-4.70, -3.51)	1.99 (1.43, 2.76)	1.61 (1.12, 2.30)	1.65 (1.14, 2.37)
Latitude ^e						
North	0.00 (ref)	0.00 (ref)	0.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
South	0.31 (-0.18, 0.80)	-0.10 (-0.61, 0.41)	0.26 (-0.37, 0.89)	1.33 (0.98, 1.81)	1.60 (1.14, 2.32)	1.33 (0.86, 2.04)
Education (number of completed years)						
0	0.00 (ref)	0.00 (ref)	0.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
≤5	0.94 (0.01, 1.77)	1.16 (0.30, 2.02)	1.18 (0.32, 2.04)	0.50 (0.31, 0.80)	0.44 (0.26, 0.74)	0.45 (0.26, 0.75)
6 - ≤10	0.04 (-0.64, 0.72)	0.21 (-0.49, 0.91)	0.21 (-0.50, 0.92)	0.50 (0.34, 0.75)	0.38 (0.24, 0.60)	0.39 (0.25, 0.62)
>10	-3.81 (-4.6, -3.0)	-3.81 (-4.60, -3.02)	-3.78 (-4.59, -2.97)	0.68 (0.42, 1.11)	0.61 (0.36, 1.03)	0.65 (0.38, 1.11)
Alcohol consumption ever						
No	0.00 (ref)	0.00 (ref)	0.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Yes	-0.85 (-1.58, -0.12)	-0.69 (-1.47, 0.08)	-0.63 (-1.41, 0.15)	1.28 (0.88, 1.87)	1.18 (0.78, 1.79)	1.15 (0.76, 1.74)

Sex						
Female	0.00 (ref)	0.00 (ref)	0.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Male	-2.85 (-3.44, -2.25)	-3.00 (-3.62, -2.38)	-2.52 (-3.18, -1.86)	1.39 (0.96, 2.01)	1.49 (1.00, 2.21)	1.50 (0.97, 2.31)
Age (per 10 years)	-9.10 (-9.32, -8.88)	-9.09 (-9.32, -8.86)	-9.15 (-9.38, -8.91)	2.21 (1.98, 2.47)	2.25 (2.00, 2.55)	2.27 (2.00, 2.57)
Fat free mass (kg)			-0.04 (-0.06, -0.02)			1.0 (0.98, 1.02)
Vegetarian						
No			0.00 (ref)			1.00 (ref)
Yes			0.66 (-0.03, 1.35)			0.74 (0.47, 1.18)

^a Model 1 included the following variables: area, latitude, education, alcohol consumption, sex and age; n=12,500; ^b Model 2 included the same variables than model 1. Participants with missing information on fat free mass were excluded from the analysis, n=11,381; ^c Model 3 included the same variables than model 1 plus fat free mass and vegetarianism, n=11,381. ^d Urban areas include Delhi, Chennai and Sonipat district. Rural areas include Sonipat, Vishakhapatnam and Faridabad districts; ^e North areas include Delhi, Sonipat and Faridabad district. South areas include Chennai and Vishakhapatnam districts.

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3 227 We observed an interaction between the effects of latitude (North/South) and urban/rural residence in
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5 228 association with reduced eGFR (p-value for interaction<0.001). The mean eGFR was lower in rural settings in
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7 229 both Northern and Southern India (controlling for age, sex, education and alcohol intake). However, this
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9 230 decrease was much more marked in Southern India. In Northern India, rural residence, formal education (and
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11 231 duration) and age were the only other risk factor associated with reduced eGFR. In Southern India, being male
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13 232 was also a risk factor for reduced eGFR, whereas formal education was only a risk factor for reduced eGFR
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15 233 among those with more than 10 years of schooling (Table 5). We also observed an interaction between the
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17 234 effects of latitude (North/South) and urban/rural residence in association with eGFR<60 (p-value likelihood-
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19 235 ratio test for interaction<0.001). In Northern India, eGFR<60 was not associated with urban/rural residence,
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21 236 and older age was the only factor associated with eGFR<60. In Southern India, rural residence was the strongest
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23 237 risk factor for eGFR<60 but older age and lower years of formal education also increased the risk of eGFR<60
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25 238 (Table 5).
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239 **Table 5.** Multivariate analysis of sociodemographic characteristics associated with eGFR and with eGFR<60
 240 according to latitude ^a

Variables	eGFR (n=12,500)		eGFR<60(n=12,500)	
	North (n=6263) ^a	South (n=6237) ^b	North (n=6263) ^a	South (n=6237) ^b
	Coefficient (95% CI)	Coefficient (95% CI)	OR (95% CI)	OR (95% CI)
Area ^c				
Urban	0.00 (ref)	0.00 (ref)	1.00 (ref)	1.00 (ref)
Rural	-1.42 (-2.15, -0.70)	-7.90 (-8.81, -7.00)	0.88 (0.57, 1.37)	4.68 (2.50, 8.77)
Education (number of completed years)				
0	0.00 (ref)	0.00 (ref)	1.00 (ref)	1.00 (ref) **
≤5	-1.32 (-2.58, -0.05)	1.05 (-0.06, 2.16)	1.16 (0.57, 2.35)	0.40 (0.20, 0.80)
6-≤10	-3.50 (-4.48, -2.52)	0.28 (-0.74, 1.30)	1.34 (0.74, 2.41)	0.35 (0.16, 0.74)
> 10	-6.93 (-7.97, -5.89)	-2.85 (-4.03, -1.67)	1.34 (0.69, 2.58)	0.61 (0.24, 1.57)
Alcohol consumption				
ever				
No	0.00 (ref)	0.00 (ref)	1.00 (ref)	1.00 (ref)
Yes	-0.54 (-1.55, 0.47)	-0.06 (-1.11, 0.99)	1.09 (0.62, 1.92)	1.36 (0.74, 2.17)
Sex				
Female	0.00 (ref)	0.00 (ref)	1.00 (ref)	1.00 (ref)
Male	-0.17 (-0.96, 0.63)	-5.40 (-6.29, -4.51)	0.97 (0.59, 1.59)	1.58 (0.91, 2.75)
Age (per 10 years)	-9.26 (-9.55, -8.97)	-8.96 (-9.28, -8.64)	2.51 (2.15, 2.93)	2.10 (1.77, 2.50)

241 ** Likelihood ratio test for linear trend <0.05, OR (95% CI)=0.68 (0.51, 0.91). ^aNorth areas include Delhi,
 242 Sonipat and Faridabad district. ^b South areas include Chennai and Vishakhapatnam districts. ^c Urban areas
 243 include Delhi, Chennai and Sonipat district. Rural areas include Sonipat, Vishakhapatnam and Faridabad
 244 districts

245 Sensitivity analyses

246 We performed a sensitivity analysis including those with ACR>300 (but without hypertension or diabetes,
247 n=33) as we were concerned that those with CKDu might develop proteinuria at more advanced CKD stages.
248 However, this did not alter the mean eGFR (mean eGFR among the overall study population=105.0±17.8, mean
249 eGFR in this sensitivity analysis=105.0±17.8), nor the estimated prevalence of eGFR<60 (prevalence among
250 the overall study population=1.6%; prevalence in this sensitivity analysis =1.7%). The findings on risk factors
251 were also similar to the findings from the primary analyses (supplementary material, Table S3).

252 Given concerns about potentially different thresholds to define diabetes and high blood pressure in different
253 ethnic groups [30,31], we performed a further sensitivity analysis including fasting plasma glucose, HbA1c and
254 systolic blood pressure in the multivariate model (even though there is evidence for both causation and reverse
255 causation between these factors and CKD [32]). Systolic blood pressure and fasting plasma glucose were
256 associated with reduced eGFR in this non diabetic population, but inclusion of these variables did not alter the
257 coefficients for the associations with other risk factors observed in the primary analysis (supplementary
258 material, Table S4). HbA1c was associated with eGFR<60 in this non diabetic population but inclusion of this
259 variable did not alter the OR for other risk factors observed in the primary analysis (supplementary material,
260 Table S4). Therefore, although the relationship between sub-clinical diabetes and impaired kidney function
261 requires further prospective investigation, there is no evidence that the excess risk of low eGFR (i.e. lower mean
262 eGFR and higher prevalence of eGFR<60) in rural Southern India is associated with either impaired fasting
263 glucose or higher blood pressure.

264 DISCUSSION

265 We report the distribution of eGFR in people without diabetes, hypertension or heavy proteinuria and estimate
266 the prevalence of CKDu in our study population, including participants from urban and rural settings. This is
267 the first population-based evidence, using standardised methods, which indicates that CKDu is present in India
268 and is not confined to Central America and Sri Lanka. We found that the rural population from Southern India
269 (Vishakhapatnam district) had the highest risk of decreased eGFR (lower mean eGFR and higher prevalence of
270 eGFR<60). Risk factors of decreased eGFR were different between Southern and Northern India. In Southern

271 India, rural residence, older age and being male were risk factors for both lower mean eGFR and eGFR<60;
272 education was associated with decreased risk for eGFR<60 but not with lower mean eGFR. In Northern India,
273 older age was the only risk factor for both lower mean eGFR and eGFR<60; rural residence and years of formal
274 education were associated with lower mean eGFR but not with eGFR<60. In summary, in Southern India, older
275 age, being male and rural residence were the main risk factors for decreased eGFR, whereas in Northern India
276 older age was the main risk factors for decreased eGFR.

277 As in Central America, the risk of low eGFR was higher in rural settings than in urban settings. This is in
278 concordance with a previous study from Hyderabad (India), that has provided evidence of a higher risk of low
279 eGFR in a rural population compared to urban-migrant and to urban population [33], and with various studies
280 from other LMICs that have provided evidence of clusters of CKDu among the rural population [2,3]. Exposure
281 to some of the suggested potential risk factors for CKDu such as agricultural work and agrochemical exposure,
282 amongst others [34], may be greater in rural settings. Such exposures may also differ between Southern and
283 Northern India, and potentially explain the differences observed between these areas. The associations between
284 urban/rural residence and lower mean eGFR was much more marked in Southern India than in Northern India,
285 and the associations between urban/rural residence and eGFR<60 was only observed in Southern India. The
286 higher prevalence ratio (for eGFR<60) in the working age population compared to older age groups is consistent
287 with the hypothesis that decreased eGFR could be potentially explained by occupational exposures. The
288 suggestive sex differences may also support this hypothesis. However, we did not have detailed data on
289 occupation that allowed us to explore these associations in greater detail.

290 The higher risk of low eGFR in Southern India (Chennai and Vishakhapatnam districts) observed in our study
291 is consistent with the clusters of CKDu cases previously reported in the Southern Indian states of Andhra
292 Pradesh and Odisha [11,18,19]. Visakhapatnam district (state of Andhra Pradesh) and Chennai district (state of
293 Tamil Nadu) have a similar climate than these areas where CKDu clusters have previously reported [35]. In
294 these districts, mean temperatures range from 18 °C to 37 °C and rainfall occurs mainly between June and
295 December [36]. On the other hand, sites from Northern India included in the study (Delhi (state of Delhi),
296 Sonapat and Faridabad (Haryana state)), have a different climate. In these districts mean temperature ranges

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3 297 from 8 °C to 39 °C and precipitation occurs mainly between July and August [36]. A previous study conducted
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5 298 in Costa Rica found a spatial correlation between rates of CKD mortality and temperature and rainfall [13].
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8 299 About 5% of the rural population of Vishakhapatnam (Andra Pradesh, Southern India) without diabetes,
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10 300 hypertension or proteinuria had eGFR<60. This figure is almost as high as the prevalence observed in the USA
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12 301 (i.e. 6.7%) including people with diabetes, hypertension or proteinuria [37]. Moreover, the estimates of GFR in
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14 302 our study are likely to be underestimated. The CKD-EPI equation has been standardised for the white and Afro-
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16 303 American population [24], but its validity for other ethnic groups has been questioned [38,39]. Previous studies
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18 304 using CKD-EPI equation to estimate GFR in Indian populations reported mean eGFR values similar to the mean
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20 305 eGFR reported in our study (i.e. 104.9 ± 25.52 ml/min/1.73 m²) [40]. However, two studies conducted among
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22 306 healthy kidney donors in India (population similar to those included in this analysis) have reported mean
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24 307 (measured) GFR between 81.4 and 95.5 ml/min per 1.73 m² [41,42], suggesting that the CKD-EPI equation
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26 308 substantially overestimates eGFR in the Indian population. Therefore, the prevalence of eGFR<60 observed in
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28 309 this study is likely to be substantially underestimated (although this is unlikely to have biased the internal
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30 310 comparisons, e.g. between urban and rural settings). The use of a conservative definition of the population
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32 311 susceptible to CKDu, may have also underestimated the prevalence of eGFR<60 in our study, as the population
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34 312 with diabetes, hypertension or glomerular disease may also have reduced eGFR due to other ('unknown')
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36 313 causes. To estimate the actual prevalence of reduced eGFR, future studies should include validated methods to
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38 314 estimate GFR in the Indian population. We were concerned that the validity of CKD-EPI among the Indian
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40 315 population may be also compromised by differences in muscular mass and meat consumption between
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42 316 population groups within India. We adjusted the analyses for fat free mass and vegetarianism, but this did not
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44 317 alter the results, suggesting no confounding effect by these variables.
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46 318 Our study has at least three potential limitations. First, we only had one measure of eGFR, and therefore we
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48 319 could not differentiate acute kidney injury (AKI) from CKD. This is a common limitation in epidemiological
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50 320 studies, as it is challenging to obtain more than one measure of eGFR at least 3 months apart in large population-
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52 321 based investigations. Therefore, we may have misclassified some cases of AKI as reduced eGFR, and therefore
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54 322 overestimate the prevalence of this condition. Nevertheless, there is no a priori reason to think that potential
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56 323 misclassification was different according to the evaluated risks factors. Second, the three population-based

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3 324 studies included in this analysis used different sampling strategies. CARRS and UDAY studies included only
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5 325 one man and one woman from all the eligible participants of selected households, whereas ICMR-CHD included
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7 326 all eligible adults from each selected household. This could have slightly biased our results (including our
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9 327 prevalence estimates) if risk factors potentially associated with CKDu were different between households
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11 328 inhabited only by a man and a women or by extended families. Third, information on other potential risk factors
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13 329 for CKDu, such as infections by leptospora or hantavirus infection, or use of nonsteroidal anti-inflammatory
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15 330 drugs (NSAIDs) was not available.

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17 331 The main strengths of the study are the use of a random selection of population-based participants and a large
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19 332 sample size including participants from different areas of India (urban and rural, and Northern and Southern
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21 333 India). Moreover, we used the definitions proposed in DRGREE study [43], that aims to allow international
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23 334 comparisons of CKDu prevalence and help in the description of risk factors and in identifying the causes and
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25 335 mechanisms leading to CKDu.

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28 336 In conclusion, our findings indicate that reduced eGFR, consistent with the definition of CKDu, is common in
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30 337 rural settings of Southern India (Vishakhapatnam district). This results support the hypothesis that the epidemic
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32 338 of CKDu, initially described in agricultural communities of Central America and Sri Lanka, may be common
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34 339 in other rural communities of tropical/subtropical countries. This has important implications for global health,
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36 340 since it indicates that CKDu may have a substantial public health burden globally that has been previously
37
38 341 unrecognised. Population-based studies in other tropical/subtropical countries are required to assess the global
39
40 342 patterns of burden of disease from CKDu [43].

41 42 43 **AUTHOR CONTRIBUTIONS AND ACKNOWLEDGEMENTS**

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46 344 CO-G, BC, NP and DP designed the work; RS, SA, SG, RG, AK, SM, VM, PPA, NT, and KMN collected the
47
48 345 data; CO-G and DK conducted the analysis of the data; CO-G, RS, SA, JG, KJ, DN, SM, KMN, NP, BC, and
49
50 346 DP interpreted the data of the work. CO-G, RS, BC, and NP drafted the manuscript; RS, SA, SG, JG, RG, KJ,
51
52 347 DK, AK, SM, VM, DN, PPA, NT, KMN, and DP revised the manuscript for important intellectual content,
53
54 348 provided comments and suggested revisions. All authors approved the final version for publication.

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4
5 350 for preparing Figure 1.
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8 351 **CONFLICTS OF INTERESTS**
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11 352 The authors declare that they have no competing interests
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14 353 **DATA SHARING STATEMENT**
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17 354 The datasets used and/or analysed during the current study are available from Public Health Foundation of India
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19 355 (PHFI) on reasonable request. Interested investigators should contact PHFI. Computing code can be obtained
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21 356 from the corresponding author.
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357 REFERENCES

- 358 1 Wesseling C, Crowe J, Hogstedt C, *et al*. Mesoamerican Nephropathy: Report from the First
359 International Research Workshop on MeN. Heredia, Costa Rica: 2013.
- 360 2 Correa-Rotter R, Wesseling C, Johnson RJ. CKD of unknown origin in Central America: the case for
361 a Mesoamerican nephropathy. *Am J Kidney Dis* 2014;**63**:506–20. doi:10.1053/j.ajkd.2013.10.062
- 362 3 Jayatilake N, Mendis S, Maheepala P, *et al*. Chronic kidney disease of uncertain aetiology: Prevalence
363 and causative factors in a developing country. *BMC Nephrol* 2013;**14**:1. doi:10.1186/1471-2369-14-
364 180
- 365 4 Lebov JF, Valladares E, Pena R, *et al*. A population-based study of prevalence and risk factors of
366 chronic kidney disease in Leon, Nicaragua. *Can J kidney Heal Dis* 2015;**2**:6. doi:10.1186/s40697-
367 015-0041-1
- 368 5 Peraza S, Wesseling C, Aragon A, *et al*. Decreased kidney function among agricultural workers in El
369 Salvador. *Am J Kidney Dis* 2012;**59**:531–40. doi:10.1053/j.ajkd.2011.11.039
- 370 6 Torres C, Aragón A, González M, *et al*. Decreased kidney function of unknown cause in Nicaragua: a
371 community-based survey. *Am J Kidney Dis* 2010;**55**:485–96. doi:10.1053/j.ajkd.2009.12.012
- 372 7 Seck SM, Doupa D, Gueye L, *et al*. Prevalence of chronic kidney disease and associated factors in
373 senegalese populations: a community-based study in saint-louis. *Nephrourol Mon* 2014;**6**:e19085.
374 doi:10.5812/numonthly.19085
- 375 8 Barsoum RS. Burden of chronic kidney disease: North Africa. *Kidney Int Suppl* 2013;**3**:164–6.
376 doi:10.1038/kisup.2013.5
- 377 9 El Minshawy O, Ghabrah T, El Bassuoni E. End-stage renal disease in Tabuk Area, Saudi Arabia: an
378 epidemiological study. *Saudi J Kidney Dis Transpl* 2014;**25**:192–5.
- 379 10 Rajapurkar MM, John GT, Kirpalani AL, *et al*. What do we know about chronic kidney disease in
380 India: First report of the Indian CKD registry. *BMC Nephrol* 2012;**13**. doi:10.1186/1471-2369-13-10
- 381 11 Reddy D V., Gunasekar A. Chronic kidney disease in two coastal districts of Andhra Pradesh, India:
382 Role of drinking water. *Environ Geochem Health* 2013;**35**:439–54. doi:10.1007/s10653-012-9506-7
- 383 12 Jayasumana C, Paranagama P, Agampodi S, *et al*. Drinking well water and occupational exposure to
384 Herbicides is associated with chronic kidney disease, in Padavi-Sripura, Sri Lanka -No section-
385 *Environ Heal A Glob Access Sci Source* 2015;**14**. doi:10.1186/1476-069X-14-6
- 386 13 Wesseling C, Van Wendel De Joode B, Crowe J, *et al*. Mesoamerican nephropathy: Geographical
387 distribution and time trends of chronic kidney disease mortality between 1970 and 2012 in Costa
388 Rica. *Occup Environ Med* 2015;**72**:714–21. doi:10.1136/oemed-2014-102799
- 389 14 Garcia-Garcia G, Jha V, World Kidney Day Steering Committee. Environmental and occupational
390 factors in CKD. *Occup Environ Med* 2015;**72**:238. doi:10.1136/oemed-2015-102859
- 391 15 Robey RB. Cyclical dehydration-induced renal injury and Mesoamerican nephropathy: as sweet by
392 any other name? *Kidney Int* 2014;**86**:226–9. doi:10.1038/ki.2014.47
- 393 16 Jha V, Modi G. Uncovering the rising kidney failure deaths in India. *Lancet Glob Heal* 2017;**5**:e14–5.
394 doi:10.1016/S2214-109X(16)30299-6
- 395 17 Dare AJ, Fu SH, Patra J, *et al*. Renal failure deaths and their risk factors in India 2001–13: nationally
396 representative estimates from the Million Death Study. *Lancet Glob Heal* 2017;**5**:e89–95.
397 doi:10.1016/S2214-109X(16)30308-4
- 398 18 Chatterjee R. Occupational Hazard. *Science (80-)* 1026;**352**:24–7.
- 399 19 Ganguli A. Uddanam Nephropathy/Regional Nephropathy in India: Preliminary Findings and a Plea
400 for Further Research. *Am J Kidney Dis* 2016;**68**:344–8. doi:10.1053/j.ajkd.2016.04.012
- 401 20 Nair M, Ali MK, Ajay VS, *et al*. CARRS Surveillance study: Design and methods to assess burdens
402 from multiple perspectives. *BMC Public Health* 2012;**12**:1. doi:10.1186/1471-2458-12-701

- 1
2
3 403 21 Mohan S, Jarhyan P, Ghosh S, *et al.* UDAY: Protocol of a Comprehensive Diabetes and Hypertension
4 404 Prevention and Management Program in India. *BMJ open* 2018;**8**:e015919. doi:e015919. doi:
5 405 10.1136/bmjopen-2017-015919
- 6 406 22 Prabhakaran D, Roy A, Praveen PA, *et al.* 20-Year Trend of Cardiovascular Disease Risk Factors.
7 407 *Glob Heart* Published Online First: 2017. doi:10.1016/j.ghheart.2016.11.004
- 8 408 23 World Health Organization. STEPS Manual. 2015.
- 10 409 24 Levey AS, Stevens LA, Schmid CH, *et al.* A new equation to estimate glomerular filtration rate. *Ann*
11 410 *Intern Med* 2009;**150**:604–12.
- 12 411 25 Patel SA, Deepa M, Shivashankar R, *et al.* Comparison of multiple obesity indices for cardiovascular
13 412 disease risk classification in South Asian adults: The CARRS Study. *PLoS One* 2017;**12**:e0174251.
- 14 413 26 Anand S, Shivashankar R, Ali MK, *et al.* Prevalence of chronic kidney disease in two major Indian
15 414 cities and projections for associated cardiovascular disease. *Kidney Int* 2015;**88**:178–85.
16 415 doi:10.1038/ki.2015.58
- 18 416 27 Greenland S, Daniel R, Pearce N, *et al.* Outcome modelling strategies in epidemiology: traditional
19 417 methods and basic alternatives. *Int J Epidemiol* 2016;:1–11. doi:10.1093/ije/dyw040
- 20 418 28 Census of India. 2011.<http://censusindia.gov.in/> (accessed 1 Aug 2018).
- 22 419 29 Longvah T, Ananthan R, Bhaskarachary K, *et al.* Indian Food Composition tables. Hyderabad: 2017.
- 23 420 30 Herman WH. Do race and ethnicity impact hemoglobin A1c independent of glycemia? *J Diabetes Sci*
24 421 *Technol* 2009;**3**:656–60. doi:10.1177/193229680900300406
- 25 422 31 Modesti PA, Reboldi G, Cappuccio FP, *et al.* Panethnic Differences in Blood Pressure in Europe: A
26 423 Systematic Review and Meta-Analysis. *PLoS One* 2016;**11**:e0147601.
27 424 doi:10.1371/journal.pone.0147601
- 28 425 32 Verhave JC, Hillege HL, Burgerhof JGM, *et al.* The association between atherosclerotic risk factors
29 426 and renal function in the general population. *Kidney Int* 2005;**67**:1967–73. doi:10.1111/j.1523-
30 427 1755.2005.00296.x
- 32 428 33 Bailey PK, Tomson CRV, Kinra S, *et al.* The effect of rural-to-urban migration on renal function in
33 429 an Indian population: Cross-sectional data from the Hyderabad arm of the Indian Migration Study.
34 430 *BMC Nephrol* 2013;**14**. doi:10.1186/1471-2369-14-240
- 35 431 34 Lunyera J, Mohottige D, von Isenburg M, *et al.* CKD of uncertain etiology: A systematic review. *Clin*
36 432 *J Am Soc Nephrol* 2016;**11**:379–85. doi:10.2215/CJN.07500715
- 37 433 35 Peel MC, Finlayson BL, McMahon TA. Updated world map of the Koppen-Geiger climate
38 434 classification. *Hydrol Earth Syst Sci* 2007;**11**:1633–1644.
- 40 435 36 Norwegian Meteorological Institute and the Norwegian Broadcasting Corporation. Yr.
- 41 436 37 Levey AS, Coresh J. Chronic kidney disease. *Lancet* 2012;**379**:165–80. doi:10.1016/S0140-
42 437 6736(11)60178-5
- 44 438 38 Eastwood JB, Kerry SM, Plange-Rhule J, *et al.* Assessment of GFR by four methods in adults in
45 439 Ashanti, Ghana: the need for an eGFR equation for lean African populations. *Nephrol Dial*
46 440 *Transplant* 2010;**25**:2178–87. doi:10.1093/ndt/gfp765
- 47 441 39 Teo BW, Xu H, Wang D, *et al.* GFR estimating equations in a multiethnic Asian population. *Am J*
48 442 *Kidney Dis* 2011;**58**:56–63. doi:10.1053/j.ajkd.2011.02.393
- 49 443 40 Singh AK, Farag YMK, Mittal B V., *et al.* Epidemiology and risk factors of chronic kidney disease in
50 444 India - Results from the SEEK (Screening and Early Evaluation of Kidney Disease) study. *BMC*
51 445 *Nephrol* 2013;**14**:1. doi:10.1186/1471-2369-14-114
- 52 446 41 Barai S, Bandopadhyaya GP, Patel CD, *et al.* Do healthy potential kidney donors in India have an
53 447 average glomerular filtration rate of 81.4 ml/min? *Nephron - Physiol* 2005;**101**:21–6.
54 448 doi:10.1159/000086038
- 56 449 42 Srinivas S, Annigeri RA, Mani MK, *et al.* Estimation of glomerular filtration rate in South Asian

- 1
2
3 450 healthy adult kidney donors. *Nephrology* 2008;**13**:440–6. doi:10.1111/j.1440-1797.2008.00967.x
4 451 43 Caplin B, Jakobsson K, Glaser J, *et al.* International Collaboration for the Epidemiology of eGFR in
5 452 Low and Middle Income Populations - Rationale and core protocol for the Disadvantaged Populations
6 453 eGFR Epidemiology Study (DEGREE). *BMC Nephrol* 2017;**18**:1–8. doi:10.1186/s12882-016-0417-1
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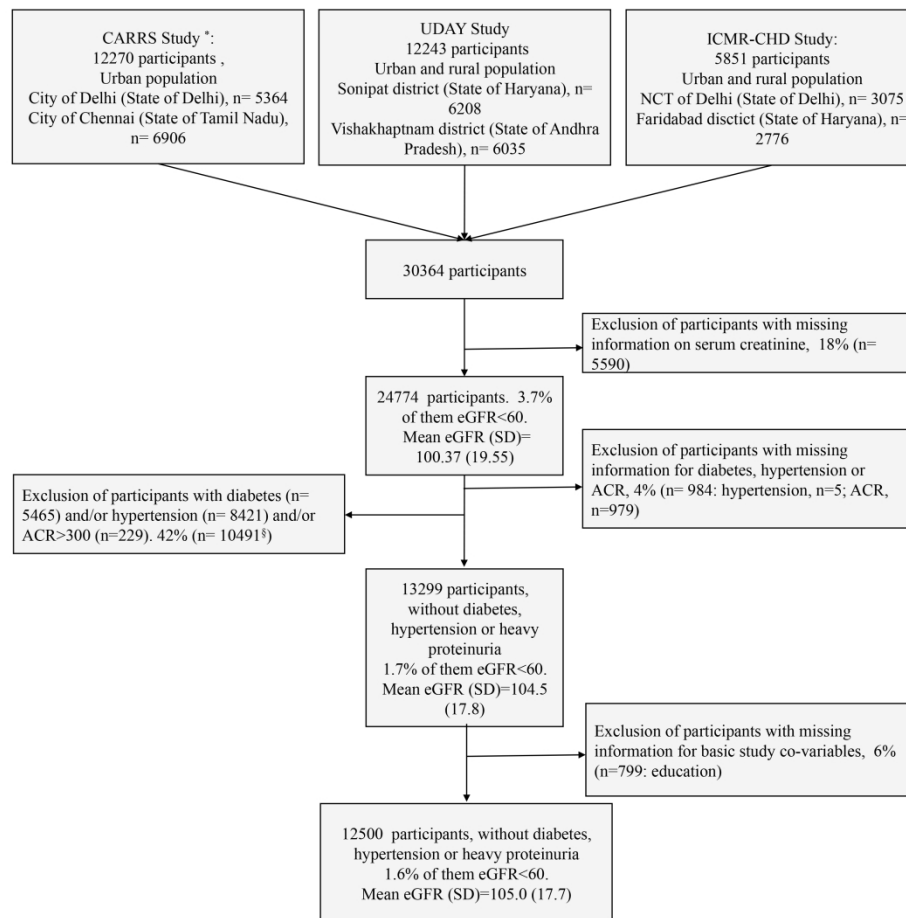
454 **FIGURES LEGENDS**

455 **Figure 1** Study areas

456 **Figure 2** Study flowchart

457 **Figure 3** Prevalence ratio of eGFR<60 for rural versus urban residence in different age groups

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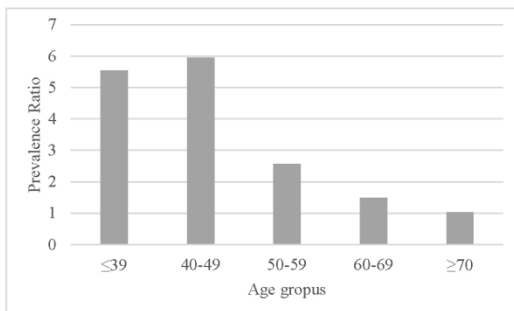


* The original sample size in the CARRS study is 12271, one transgender person was excluded for the current analysis; § 2353 participants with diabetes only; 5185 participants with hypertension only; 35 participants with ACR>30 only; 2724 participants with diabetes, and hypertension; 35 participants with diabetes and ACR>30; 47 participants with hypertension and ACR>30; 112 participants with diabetes, hypertension and ACR>30.

Study flowchart

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Prevalence ratio of eGFR<60 by age group between rural and urban areas

420x594mm (300 x 300 DPI)

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3 **1 SUPPLEMENTARY MATERIAL**

4
5 **2 Content**

- 6
7
8 **3 Table S1.** Sociodemographic and anthropometric characteristics of overall study participants (prior to
9 exclusion of population with diabetes, hypertension and proteinuria)
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13 **4 Table S2.** Associations between sociodemographic and anthropometric characteristics and estimated
14 glomerular filtration rate (eGFR) and eGFR<60 by sex
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18 **5 Table S3.** Multiple regression analysis of sociodemographic and anthropometric characteristics associated
19 with eGFR and eGFR<60 including study participants with proteinuria (but without diabetes or
20 hypertension)
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24 **6 Table S4.** Multiple regression analysis of sociodemographic and anthropometric characteristics associated
25 with eGFR and eGFR<60 including fasting plasma glucose, HbA1c and systolic blood pressure
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Table S1. Sociodemographic and anthropometric characteristics of overall study participants (prior to exclusion of population with diabetes, hypertension and proteinuria)

Variable	n (%) ^a n=24774	eGFR categories, n(%) ^b			
		mean (SD)	≥90	90 - 60	<60
Socio-demographic factors					
Age (years)					
<39	9007 (36)	112.9 (14.9)	8248 (92)	716 (8)	43 (0)
40 - 49	6924 (28)	101.9 (14.8)	5617 (81)	1215 (18)	92 (1)
50 - 59	4524 (18)	92.9 (15.2)	2997 (66)	1378 (30)	149 (3)
60 - 69	3045 (12)	82.8 (17.1)	1410 (46)	1315 (43)	320 (11)
≥70	1274 (5)	72.0 (17.3)	164 (13)	806 (63)	304 (24)
Sex					
Female	13433 (54)	102.6 (19.5)	10404 (77)	2585 (19)	444 (3)
Male	11341 (46)	97.7 (19.3)	8032 (71)	2845 (25)	464 (4)
Education (number of years)					
0	4794 (19)	97.7 (20.2)	3458 (72)	1075 (22)	261 (5)
5	3194 (13)	101.7 (19.4)	2456 (77)	625 (20)	113 (4)
10	8855 (36)	103.2 (18.9)	6995 (79)	1620 (18)	240 (3)
>10	6358 (26)	100.0 (19.2)	4638 (73)	1538 (24)	182 (3)
Missing data	1573 (6)		889 (57)	572 (36)	112 (7)
Area ^d					
Urban	17732 (72)	102 (19.5)	13577 (77)	3602 (20)	553 (3)
Rural	7042 (28)	96.3 (19.1)	4859 (69)	1828 (26)	355 (5)
Latitude ^e					
North	13570 (55)	98.1 (19.1)	9599 (71)	3439 (25)	532 (4)
South	11204 (45)	103.1 (19.7)	8837 (79)	1991 (18)	376 (3)
Life-style factors					
Current smoking					
No	18402 (74)	101.5 (19.6)	13920 (76)	3838 (21)	644 (3)
Yes	6372 (26)	97.1 (19.1)	4516 (71)	1592 (25)	264 (4)
Alcohol consumption ever					
No	19588 (79)	100.9 (19.6)	14671 (75)	4203 (21)	714 (4)
Yes	5186 (21)	98.5 (19.1)	3765 (73)	1227 (24)	194 (4)
Vegetarian					
No	15043 (61)	102.7 (19.7)	11721 (78)	2835 (19)	487 (3)
Yes	9731 (39)	96.8 (18.9)	6715 (69)	2595 (27)	421 (4)
Biological factors					
Body mass index (kg/m ²)					
Underweight (≤18.5)	10297 (42)	100.1 (19.6)	7626 (74)	2284 (22)	387 (4)
Normal (>18.5 - ≤25)	2403 (10)	101.58 (20.5)	1838 (76)	471 (20)	94 (4)
Overweight (>25 - ≤30)	7221 (29)	99.9 (18.8)	5309 (74)	1680 (23)	232 (3)
Obese (>30)	3286 (13)	99.3 (19.2)	2392 (73)	766 (23)	128 (4)
Missing data	1567 (6)		1271 (81)	229 (15)	67 (4)
Fat free mass (kg)					
1 st tertile (≤37)	7141 (29)	101.9 (20.1)	5481 (77)	1381 (19)	279 (4)
2 nd tertile (>37 - <45)	7141 (29)	101.3 (19.1)	5419 (76)	1487 (21)	235 (3)

3 rd tertile (≥ 45)	7141 (29)	98.3 (18.6)	5110 (72)	1797 (25)	234 (3)
Missing data	3351 (14)		2426 (72)	765 (23)	160 (5)

14 ^a Percentages in columns; ^b percentages in rows; ^d Urban areas include Delhi, Chennai and Sonipat district.

15 Rural areas include Sonipat, Vishakhapatnam and Faridabad districts; ^e North areas include Delhi, Sonipat

16 and Faridabad district. South areas include Chennai and Vishakhapatnam districts.

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17 **Table S2.** Associations between sociodemographic and anthropometric characteristics and estimated glomerular filtration rate (eGFR) and eGFR<60 by sex

Variable	Men, n=5 434			Women, n=4 066		
	n (%)	eGFR estimate (95% CI) ^a	eGFR<60 OR (95% CI) ^a	n (%)	eGFR estimate (95% CI) ^a	eGFR<60 OR (95% CI) ^a
Age (years) ^b						
<39	2335 (43)	0.00 (ref)	1.00 (ref)	3786 (54)	0.00 (ref)	1.00 (ref)
40-49	1568 (29)	-9 (-9.97, -8.03)	2.36 (1.2, 4.62)	1908 (27)	-12.52 (-13.29, -11.76)	4.5 (1.95, 10.36)
50-59	843 (16)	-16.84 (-18.03, -15.65)	3.82 (1.91, 7.66)	863 (12)	-21.51 (-22.53, -20.48)	11.78 (5.2, 26.68)
60-69	479 (9)	-25.35 (-26.83, -23.86)	13.07 (6.97, 24.49)	414 (6)	-30.05 (-31.46, -28.64)	32.95 (14.87, 73.02)
≥70	209 (4)	-34.26 (-36.4, -32.12)	31.08 (16.33, 59.17)	95 (1)	-34.78 (-37.6, -31.96)	43.43 (15.93, 118.37)
Education (number of completed years)						
0	823 (15)	0.00 (ref)	1.00 (ref)	1997 (28)	0.00 (ref)	1.00 (ref)
≤5	703 (13)	3.28 (1.82, 4.74)	0.24 (0.13, 0.46)	1006 (14)	0.73 (-0.27, 1.73)	0.81 (0.42, 1.56)
6-≤10	2363 (43)	1.68 (0.51, 2.84)	0.31 (0.20, 0.48)	2454 (35)	0.67 (-0.13, 1.48)	0.43 (0.21, 0.86)
>10	1545 (28)	-1.35 (-2.6, -0.1)	0.27 (0.15, 0.47)	1609 (23)	-2.39 (-3.27, -1.5)	0.76 (0.40, 1.46)
Area ^c	3583 (66)					
Urban	1851 (34)	0.00 (ref)	1.00 (ref)	4911 (70)	0.00 (ref)	1.00 (ref)
Rural		-4.02 (-4.85, -3.19)	2.72 (1.84, 4.01)	2155 (30)	-3.69 (-4.36, -3.02)	1.99 (1.26, 3.14)
Latitude ^d						
North	2861 (53)	0.00 (ref)	1.00 (ref)	3402 (48)	0.00 (ref)	1.00 (ref)
South	2573 (47)	-1.52 (-2.3, -0.74)	1.76 (1.21, 2.56)	3664 (52)	2.58 (1.96, 3.19)	1.30 (0.83, 2.05)
Current tobacco consumption						
No	2804 (52)	0.00 (ref)	1.00 (ref)	6553 (93)	0.00 (ref)	1.00 (ref)
Yes	2630 (48)	1.15 (0.36, 1.93)	1.32 (0.91, 1.92)	513 (7)	-1.93 (-3.14, -0.73)	1.54 (0.87, 2.73)
Alcohol consumption ever						
No	3035 (56)	0.00 (ref)	1.00 (ref)	7059 (100)	0.00 (ref)	1.00 (ref)

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Yes	2399 (44)	-0.71 (-1.49, 0.06)	1.57 (1.08, 2.27)	7 (0)	-9.29 (-18.97, 0.4)	1.00 (1.00, 1.00)
Vegetarian						
No	3576 (66)	0.00 (ref)	1.00 (ref)	4396 (62)	0.00 (ref)	1.00 (ref)
Yes	1858 (34)	0.65 (-0.18, 1.48)	0.61 (0.41, 0.90)	2670 (38)	-2.11 (-2.75, -1.47)	0.70 (0.44, 1.11)
Body mass index (kg/m ²)						
Underweight (≤ 18.5)	2888 (56)	0.00 (ref)	1.00 (ref)	2991 (44)	0.00 (ref)	1.00 (ref)
Normal ($>18.5 - \leq 25$)	812 (16)	4.05 (2.92, 5.18)	0.69 (0.42, 1.14)	764 (11)	1.61 (0.57, 2.65)	1.07 (0.57, 2.03)
Overweight ($>25 - \leq 30$)	1209 (23)	-1.7 (-2.68, -0.73)	0.71 (0.42, 1.21)	2104 (31)	-0.11 (-0.84, 0.62)	0.67 (0.38, 1.20)
Obese (>30)	243 (5)	-0.71 (-2.61, 1.18)	0.36 (0.09, 1.50)	907 (13)	-0.64 (-1.61, 0.33)	0.55 (0.23, 1.31)
Fat free mass (kg)						
1st tertile (≤ 37)	361 (8)	0.00 (ref)	1.00 (ref)	3833 (58)	0.00 (ref)	1.00 (ref)
2nd tertile ($>37 - <45$)	1351 (28)	-0.42 (-2.10, 1.25)	0.78 (0.44, 1.38)	2535 (39)	-1.39 (-2.04, -0.74)	0.67 (0.38, 1.17)
3rd tertile (≥ 45)	3093 (64)	-3.75 (-5.35, -2.16)	0.50 (0.28, 0.90)	208 (3)	-1.36 (-3.17, 0.45)	0.58 (0.08, 4.25)

^a Adjusted for age; ^b Not adjusted for age; ^c Urban areas include Delhi, Chennai and Sonipat district. Rural areas include Sonapat, Vishakhapatnam and Faridabad districts; ^d

North areas include Delhi, Sonipat and Faridabad district. South areas include Chennai and Vishakhapatnam districts.

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Table S3. Multiple regression analysis of sociodemographic characteristics associated with eGFR and eGFR<60 including study participants with proteinuria (but without diabetes or hypertension), n=12533

Variable	eGFR	eGFR<60
	Coefficient (95%CI) ^a	OR (95%CI) ^a
Area ^b		
Urban	0.00 (ref)	1.00 (ref)
Rural	-4.59 (-5.14, -4.03)	1.93 (1.40, 2.66)
Latitude ^c		
North	0.00 (ref)	1.00 (ref)
South	0.29 (-0.21, 0.78)	1.33 (0.98, 1.80)
Education (number of years)		
0	0.00 (ref)	1.00 (ref)
5	0.83 (0, 1.66)	0.55 (0.35, 0.87)
10	0.04 (-0.64, 0.72)	0.51 (0.35, 0.76)
>10	-3.81 (-4.58, -3.04)	0.66 (0.40, 1.07)
Alcohol consumption ever		
No	0.00 (ref)	1.00 (ref)
Yes	-0.78 (-1.52, -0.05)	1.23 (0.85, 1.79)
Sex		
Female	0.00 (ref)	1.00 (ref)
Male	-2.86 (-3.46, -2.26)	1.38 (0.96, 1.98)
Age (per 10 years)	-9.12 (-9.34, -8.91)	2.23 (2.00, 2.49)

^a Variables mutually adjusted, ^b Urban areas include Delhi, Chennai and Sonipat district. Rural areas include Sonipat, Vishakhapatnam and Faridabad districts; ^c North areas include Delhi, Sonipat and Faridabad district. South areas include Chennai and Vishakhapatnam districts.

Table S4. Multiple regression analysis of sociodemographic characteristics associated with eGFR and eGFR<60 including plasma fasting glucose, HbA1c and systolic blood pressure

Variable	eGFR	eGFR<60
	Coefficient (95%CI) ^a	OR (95%CI) ^a
Area ^b		
Urban	0.00 (ref)	1.00 (ref)
Rural	-4.94 (-5.51, -4.38)	2.29 (1.64, 3.20)
Latitude ^c		
North	0.00 (ref)	1.00 (ref)
South	0.23 (-0.26, 0.72)	1.30 (0.95, 1.77)
Education (number of years)		
0	0.00 (ref)	1.00 (ref)
5	1.03 (0.20, 1.86)	0.49 (0.31, 0.79)
10	0.19 (-0.49, 0.87)	0.47 (0.32, 0.71)
>10	-3.53 (-4.30, -2.76)	0.62 (0.38, 1.02)
Alcohol consumption ever		
No	0.00 (ref)	1.00 (ref)
Yes	-0.72 (-1.46, -0.01)	1.32 (0.90, 1.93)
Sex		
Female	0.00 (ref)	1.00 (ref)
Male	-2.69 (-3.29, -2.09)	1.47 (1.01, 2.12)
Age (per 10 years)	-8.93 (-9.16, -8.70)	2.11 (1.89, 2.38)
Fasting plasma glucose (mg/dl)	-0.06 (-0.08, -0.04)	1.01 (1.00, 1.02)
Hb1Ac (%)	0.03 (-0.56, 0.62)	1.95 (1.34, 2.85)
Systolic blood pressure (mm Hg)	-0.06 (-0.84, -0.04)	1.0 (0.99, 1.02)

^a Variables mutually adjusted, ^b Urban areas include Delhi, Chennai and Sonipat district. Rural areas include Sonipat, Vishakhapatnam and Faridabad districts; ^c North areas include Delhi, Sonipat and Faridabad district. South areas include Chennai and Vishakhapatnam districts.

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

	Item No	Recommendation	Page/line where the checklist items are located in the paper
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	Title and abstract (page 2, lines 29-30)
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 2, lines 27-45
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 4, lines 68-90
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 4-5, lines 91-95
Methods			
Study design	4	Present key elements of study design early in the paper	Page 5, lines 103-111, table 1
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Table 1 and page 6, line 123
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants	Page 5, lines 112-121
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Page 6, lines 149-171
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	Page 6, lines 123-147
Bias	9	Describe any efforts to address potential sources of bias	Page 6, lines 123-127, 134-138, 145-147
Study size	10	Explain how the study size was arrived at	Figure 1
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Page 6, lines 123-147
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	Page 6, 154-160
		(b) Describe any methods used to examine subgroups and interactions	Page 6, line 156; page 6, lines 162-171
		(c) Explain how missing data were addressed	Page 6, lines 160-162
		(d) If applicable, describe analytical methods taking account of sampling strategy	-
		(e) Describe any sensitivity analyses	Page 10, lines 233-235, 139-242
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for	Figure 1

		eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	
		(b) Give reasons for non-participation at each stage	Figure 1
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 2.; page 7-8, lines 177-185
		(b) Indicate number of participants with missing data for each variable of interest	Page 6, lines 160-162
Outcome data	15*	Report numbers of outcome events or summary measures	Page 8, line 187-201
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	Page 8, lines 203-220; table 3 and table 4
		(b) Report category boundaries when continuous variables were categorized	Table 3 and Table 4
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Page 9, lines 221-231; page 10, lines 233-250
Discussion			
Key results	18	Summarise key results with reference to study objectives	Page 10, lines 252-263
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	Pages 12-13, lines 310-322
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Pages 11-12, lines 264-309
Generalisability	21	Discuss the generalisability (external validity) of the study results	Pages 13, lines 323-325
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	Page 3, lines 59-66

*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.