Chronic kidney disease and cardiovascular risk in six regions of the world (ISN-KDDC): a cross-sectional study

Bogdan Ene-Iordache, Norberto Perico, Boris Bikbov*, Sergio Carminati, Andrea Remuzzi, Annalisa Perna, Nazmul Islam, Rodolfo Flores Bravo, Mirna Aleckovic-Halilovic, Hequn Zou, Luxia Zhang, Zaghloul Gouda, Irma Tchokhonelidze, Georgi Abraham, Mitra Mahdavi-Mazdeh, Maurizio Gallieni, Igor Codreanu, Ariunaa Togtokh, Sanjib Kumar Sharma, Puru Koirala, Samyog Uprety, Ifeoma Ulasi, Giuseppe Remuzzi*

Summary

Background Chronic kidney disease is an important cause of global mortality and morbidity. Data for epidemiological features of chronic kidney disease and its risk factors are limited for low-income and middle-income countries. The International Society of Nephrology's Kidney Disease Data Center (ISN-KDDC) aimed to assess the prevalence and awareness of chronic kidney disease and its risk factors, and to investigate the risk of cardiovascular disease, in countries of low and middle income.

Methods We did a cross-sectional study in 12 countries from six world regions: Bangladesh, Bolivia, Bosnia and Herzegovina, China, Egypt, Georgia, India, Iran, Moldova, Mongolia, Nepal, and Nigeria. We analysed data from screening programmes in these countries, matching eight general and four high-risk population cohorts collected in the ISN-KDDC database. High-risk cohorts were individuals at risk of or with a diagnosis of either chronic kidney disease, hypertension, diabetes, or cardiovascular disease. Participants completed a self-report questionnaire, had their blood pressure measured, and blood and urine samples taken. We defined chronic kidney disease according to modified KDIGO (Kidney Disease: Improving Global Outcomes) criteria; risk of cardiovascular disease development was estimated with the Framingham risk score.

Findings 75 058 individuals were included in the study. The prevalence of chronic kidney disease was 14·3% (95% CI 14·0–14·5) in general populations and 36·1% (34·7–37·6) in high-risk populations. Overall awareness of chronic kidney disease was low, with 409 (6%) of 6631 individuals in general populations and 150 (10%) of 1524 participants from high-risk populations aware they had chronic kidney disease. Moreover, in the general population, 5600 (44%) of 12 751 individuals with hypertension did not know they had the disorder, and 973 (31%) of 3130 people with diabetes were unaware they had that disease. The number of participants at high risk of cardiovascular disease, according to the Framingham risk score, was underestimated compared with KDIGO guidelines. For example, all individuals with chronic kidney disease should be considered at high risk of cardiovascular disease, but the Framingham risk score detects only 23% in the general population, and only 38% in high-risk cohorts.

Interpretation Prevalence of chronic kidney disease was high in general and high-risk populations from countries of low and middle income. Moreover, awareness of chronic kidney disease and other non-communicable diseases was low, and a substantial number of individuals who knew they were ill did not receive treatment. Prospective programmes with repeat testing are needed to confirm the diagnosis of chronic kidney disease and its risk factors. Furthermore, in general, health-care workforces in countries of low and middle income need strengthening.

Funding International Society of Nephrology.

Introduction

Chronic kidney disease is an important cause of global morbidity and mortality.[1,2] In the 2013 Global Burden of Disease study, 956 200 people were estimated to have died from chronic kidney disease, a 134% increase from 1990, one of the largest rises among the top causes of death.[1] Furthermore, even in the early stages of chronic kidney disease, the risk of fatal and non-fatal cardiovascular events attributable directly to renal disease rises substantially.[3] Thus, kidney disease should be a global public health priority, particularly because, worldwide, more than 1·4 million individuals with end-stage renal disease are estimated to receive renal replacement therapy with dialysis or transplantation, with 8% annual growth.[4] A steep increase in cases of hypertension, diabetes, and other diseases that are risk factors for chronic kidney disease is also driving growth in prevalence of chronic kidney disease, putting enormous pressure on health-care resources.[5]

High-quality screening programmes in high-income countries, including the USA,[6] Norway,[7] the Netherlands,[8] and Australia,[9] have shown the prevalence of chronic kidney disease in the general adult population is 10–13%. However, for many low-income and middle-income countries and regions, data for epidemiological features

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*Contributed equally

IRCCS—Istituto di Ricerche Farmacologiche "Mario Negri", Clinical Research Center for Rare Diseases "Aldo e Cele Daccò", Ranica, Italy (B Ene-Iordache PhD, N Perico MD, S Carminati IT, A Remuzzi EngD, A Perna MSc, Prof G Remuzzi MD); **Department of Nephrology, A I Evdokimov Moscow State University of Medicine and Dentistry, Moscow, Russia** (B Bikbov MD); **Department of Nephrology Issues of Transplanted Kidney, Academician V I Shumakov Federal Research Center of Transplantology and Artificial Organs, Moscow, Russia** (B Bikbov); **Department of Management, Information and Production and Engineering, University of Bergamo, Dalmine, Italy** (A Remuzzi); **Department of Nephrology, North East Medical College Hospital, Sylhet, Bangladesh** (N Islam MD); **Department of Medicine, Hospital Juan XXIII, La Paz, Bolivia** (R Flores Bravo MD); **Department of Nephrology, Dialysis and Kidney Transplantation, University Clinical Center Tuzla, Tuzla, Bosnia and Herzegovina** (Prof M Aleckovic-Halilovic MD); **Department of Nephrology, Institute of Nephrology and Urology, The Third Affiliated Hospital of Southern Medical University, Guangzhou, China** (Prof H Zou MD); **Renal Division, Department of Medicine, Peking University First Hospital, Peking University Institute of Nephrology, Beijing, China** (Prof L Zhang MD); **Department of Nephrology, Damanhour Medical National Institute, General Organization of Teaching Hospitals and Institutes, Damanhour, Egypt**

(Z Gouda MD); **Nephrology Development Clinical Center, Tbilisi State Medical University, Tbilisi, Georgia** (Prof I Tchokhonelidze MD); **Tamilnad Kidney Research Foundation, Chennai, India** (Prof G Abraham MD); **Department of Nephrology, Tehran University of Medical Sciences, Research Center of Iranian Tissue Bank, Tehran, Iran** (Prof M Mahdavi-Mazdeh MD); **Nephrology and Dialysis Unit, San Carlo Borromeo Hospital, University of Milan, Milan, Italy** (Prof M Gallieni MD); **Transplant Agency of Moldova, Chisinau, Moldova** (I Codreanu MD); **Department of Nephrology, University of Mongolia, Ulaan Bataar, Mongolia** (A Togtokh MD); **Department of Internal Medicine, BP Koirala Institute of Health Sciences, Dharan, Nepal** (Prof S Kumar Sharma MD, P Koirala MD); **School of Public Health and Department of Community Medicine, BP Koirala Institute of Health Sciences, Dharan, Nepal** (S Uprety MD); **Renal Unit, Department of Medicine, College of Medicine, University of Nigeria Teaching Hospital, Enugu, Nigeria** (Prof I Ulasi MBBS); **Department of Medicine, Unit of Nephrology and Dialysis, Azienda Ospedaliera Papa Giovanni XXIII, Bergamo, Italy** (Prof G Remuzzi); **and Department of Biomedical and Clinical Sciences, University of Milan, Milan, Italy** (Prof G Remuzzi)

Correspondence to:
Dr Bogdan Ene-Iordache, Clinical Research Centre for Rare Diseases "Aldo e Cele Daccò", IRCCS – Istituto di Ricerche Farmacologiche "Mario Negri", 24020 Ranica, Italy
bogdan.ene-iordache@marionegri.it

Research in context

Evidence before this study

Several systematic reviews have been done to assess prevalence of chronic kidney disease, and in the 2013 Global Burden of Disease Study, mortality and morbidity from chronic kidney disease was estimated. To retrieve the most representative examples of screening programmes done in randomly selected populations or community settings, particularly low-income and middle-income countries, we did a non-systematic search of PubMed with the keywords "chronic kidney disease (community OR random) screening" and "chronic kidney disease awareness", and we searched manually through the recent content of relevant journals, up to July, 2015. In 2013, 956 200 deaths globally were attributed directly to chronic kidney disease, one of the highest increases in the past two decades. In several (mainly developed) countries, screening programmes detected a high prevalence of chronic kidney disease and low awareness. Criteria for chronic kidney disease and its components varied substantially between some of these screening programmes, and most were done with different methods, developed by local researchers. The latest KDIGO (Kidney Disease: Improving Global Outcomes) guidelines standardised the classification and prognosis of chronic kidney disease based on glomerular filtration rate (GFR) and albuminuria categories.

Added value of this study

Our cross-sectional data were obtained from screening programmes done on behalf of the International Society of Nephrology (ISN), across different populations from low-income and middle-income countries, but using a uniform process and definition of chronic kidney disease. Decreased estimated GFR (eGFR) and increased albuminuria, and the resulting positive screening for prevalence of chronic kidney disease, are common in the general population of countries of low and middle income. Our applied screening method allowed estimation of low awareness, not only of chronic kidney disease but also of hypertension and diabetes. Moreover, a substantial proportion of individuals with known diseases did not take drugs, indicating poor access to basic treatment. Our data confirmed an association between a positive screening test for chronic kidney disease and hypertension, diabetes, obesity, and high amounts in serum of cholesterol. We noted an incremental increase and cumulative effect of reduced eGFR and increased albuminuria on the Framingham risk score of developing cardiovascular disease within the next 10 years, but this risk was substantially underestimated in almost all patients with chronic kidney disease.

Implications of all the available evidence

Current recommendations in developed countries do not encourage screening for chronic kidney disease in the general population. However, in countries of low and middle income, we advocate screening programmes with confirmatory testing as a unique method for detecting chronic kidney disease and other non-communicable diseases, with subsequent prevention, follow-up, and treatment. Further cost-effectiveness analyses should quantify the benefit of such programmes for limitation of morbidity and mortality related to renal and cardiovascular complications. The epidemiology of chronic kidney disease has to be studied worldwide, and the ready-to-use method developed by ISN could help to achieve this important goal.

of chronic kidney disease are scarce or even missing[10] because of an absence of resources, inadequate data collection methods, and low awareness of the disorder. Moreover, in these different settings, the primary causes of chronic kidney disease vary, and kidney disease might not be contained entirely within the envelope of diabetes and hypertension. Indeed, in developing countries, up to 40% of individuals whose chronic kidney disease is identified in screening programmes do not have diabetes or cardiovascular disease; other risk factors such as HIV,[11] tuberculosis, and exposure to toxins[12] can cause chronic kidney disease, or the cause could remain unknown.[13] Therefore, careful assessment of epidemiological features of chronic kidney disease is needed, particularly for people living in countries of low and middle income who cannot afford the high costs of renal replacement therapy.[5]

In 2005, the International Society of Nephrology (ISN) established programmes to build global capacity to screen populations to detect chronic kidney disease and its risk factors early, and for patients' management and follow-up.[14] To support data collection and analysis, ISN also funded the establishment of a global database, the Kidney Disease Data Center (KDDC), which provided the unique opportunity to gather information using a simple and uniform template. In the ISN-KDDC cross-sectional study, we aimed to estimate the prevalence of chronic kidney disease according to the latest KDIGO (Kidney Disease: Improving Global Outcomes) guidelines,[3] to investigate awareness of chronic kidney disease and its major risk factors, to assess risk factors associated with chronic kidney disease, and to calculate cardiovascular risk for screened populations.

Methods

Study population

We identified adult cohorts in the KDDC database from 12 low-income and middle-income countries: Bangladesh, Bolivia, Bosnia and Herzegovina, China, Egypt, Georgia, India, Iran, Moldova, Mongolia, Nepal, and Nigeria. Almost all cohorts, with the exception of the Iranian cohort, included participants from the ISN programme on Detection and Management of Chronic Kidney Disease, Hypertension, Diabetes and Cardiovascular Disease in Developing Countries (KHDC).[14] KHDC guidelines provide a template for setting up early detection and intervention programmes

in developing countries based on specific needs, organisation facilities, and economic imperatives of each country. Volunteer bias was not handled in the KHDC-based screenings.

General population cohorts in the KDDC database (from KHDC-based programmes) were from eastern Asia (China,[15] Mongolia[15]), southern Asia (India,[16] Nepal[15]), Africa (Nigeria), eastern Europe (Moldova[17]), and Latin America (Bolivia[18]). Data from a non-KHDC screening programme were available for a large-scale, general population, cross-sectional survey in Tehran, Iran.[19] High-risk population cohorts, defined as individuals at risk of or with a diagnosis of chronic kidney disease, hypertension, diabetes, or cardiovascular disease, were from southern Asia (Bangladesh[18]), the Middle East (the EGIPT-CKD programme in Damanhour, Egypt[20]), and eastern Europe (Bosnia and Herzegovina, Georgia[18]). In Bangladesh, high-risk individuals were identified at the first screening interview; in Egypt, those at high risk were first-degree relatives of patients treated for chronic kidney disease with known microalbuminuria; in Bosnia and Herzegovina, high-risk individuals were inhabitants of Balkan endemic nephropathy areas, refugee camps, or gypsy communities; and in Georgia, those at high risk were people at risk of non-communicable diseases diagnosed in university hospitals.

We judged participants eligible for our study if they were aged 18 years or older and had complete data for calculation of estimated glomerular filtration rate (eGFR) and for assessment of albuminuria. All KHDC-based programmes included in this study, and the one from Iran, have been approved by the ethics committees of local hospitals (or equivalent when available), and written or oral consent was obtained from participants.

Procedures

Questionnaires based on the KHDC template comprise self-reported information on sociodemographic factors (date of birth, sex, marital status, ethnic origin, level of education, and work), lifestyle (smoking, alcohol consumption, physical activity, and fruit and vegetable consumption), and medical history (chronic kidney disease, hypertension, diabetes, and cardiovascular disease), and we included these data when available. We coded data from the non-KHDC programme[19] in the same format as the KHDC template then imported it into the ISN-KDDC study database. We categorised ethnic origin as eastern or southern Asian, black African, white, and other—a group that included Hispanic and indigenous together.

For more than 85% of participants, measurement of serum creatinine was possible, in addition to dipstick testing for albuminuria or proteinuria; furthermore, for a smaller subset (26%), the albumin-to-creatinine ratio (ACR) or protein-to-creatinine ratio was also available. We calculated eGFR (in mL/min per 1·73 m²) with the CKD-EPI equation,[21] based on serum creatinine, age, sex, and a two-level racial variable (black *vs* other). We defined eGFR categories as: G1, normal or high (≥90 mL/min per 1·73 m²); G2, mildly decreased (60–89 mL/min per 1·73 m²); G3a, mildly to moderately decreased (45–59 mL/min per 1·73 m²); G3b, moderately to severely decreased (30–44 mL/min per 1·73 m²); G4, severely decreased (15–29 mL/min per 1·73 m²) and G5, kidney failure (<15 mL/min per 1·73 m²).[3] We assessed albuminuria as ACR approximate equivalent,[3,22] using an algorithm that relies on ACR, protein-to-creatinine ratio, and protein dipstick, strictly in this order. We defined albuminuria categories as: A1 (normal to mildly increased) for ACR less than 30 mg/g, protein-to-

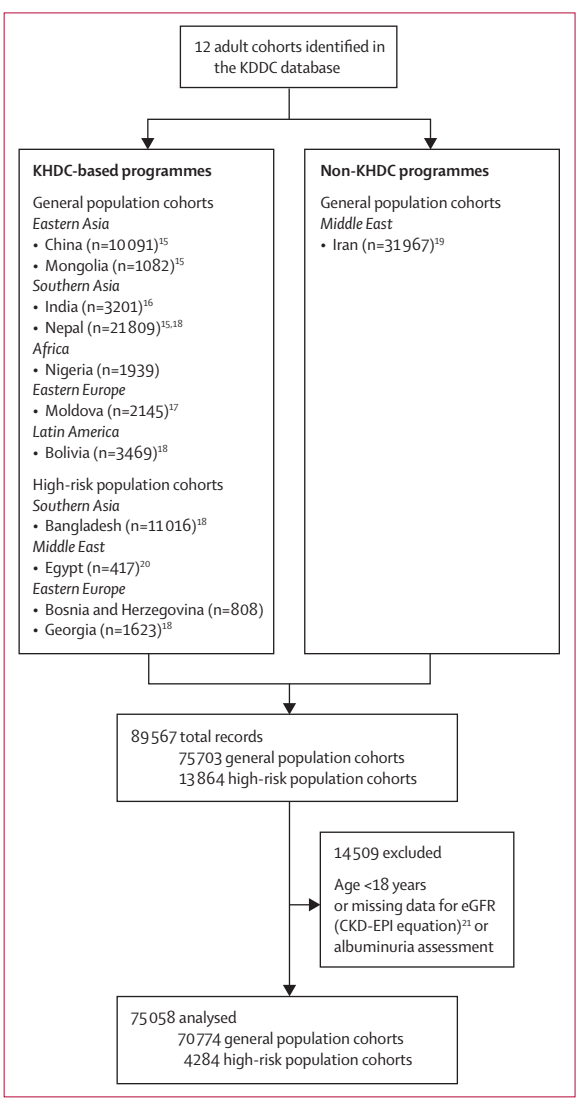

Figure 1: **Flow diagram of cohorts included in the ISN-KDDC study**
eGFR=estimated glomerular filtration rate. KDDC=Kidney Disease Data Center. KHDC=International Society of Nephrology programme on Detection and Management of Chronic Kidney Disease, Hypertension, Diabetes and Cardiovascular Disease in Developing Countries.

creatinine ratio less than 150 mg/g, or protein dipstick – to +/–; A2 (moderately increased) for ACR 30 mg/g to less than 300 mg/g, protein-to-creatinine ratio 150 mg/g to less than 500 mg/g, or protein dipstick 1+; and A3 (severely increased) for ACR 300 mg/g or higher, protein-to-creatinine ratio 500 mg/g or higher, or protein dipstick 2+ or higher. We defined chronic kidney disease according to KDIGO guidelines[3] as either decreased eGFR (<60 mL/min per 1·73 m²) or albuminuria (ACR approximate equivalent >30 mg/g).

In subsets of participants who self-reported information about chronic kidney disease, hypertension, diabetes, and related treatments, we calculated the prevalence of awareness of the disease or treatment by dividing the number of people who self-reported the disease or treatment by the number who were classified as having the disease or taking the treatment, according to objective criteria. We defined hypertension as: systolic blood pressure of 140 mm Hg or higher, diastolic blood pressure of 90 mm Hg or higher, or both;[23] use of antihypertensive drugs; or both of these. We defined diabetes as: fasting glucose of 7·0 mmol/L or higher; glycated haemoglobin of 6·5% or higher (48 mmol/mol); or use of antidiabetes drugs. We defined obesity as a body-mass index (BMI) of 27·5 kg/m² or higher for Asian populations[24] and 30 kg/m² or higher for all other populations.[25] We defined hypercholesterolaemia as total cholesterol of 6·0 mmol/L or higher in individuals without previous cardiovascular disease or 5·0 mmol/L or higher in those with previous cardiovascular disease.[22]

For individuals who did not self-report cardiovascular disease (95%), we assessed the risk of developing this disorder within the next 10 years with the Framingham risk score,[26] a model that has achieved good results nationally and internationally.[27,28] Cholesterol could be measured in a small subset of participants (53%); thus, we chose the simpler risk prediction model based on non-laboratory predictors, incorporating BMI instead of total and HDL cholesterol.[26] This model assumes sex-specific coefficients for the probability of the individual developing cardiovascular disease within the next 10 years, based on age, diabetes, and smoking status, treated or untreated

	Total (n=75 058)	General population (n=70 774)	High-risk population (n=4284)
Age (years)	44·5 (13·8)	44·2 (13·5)	49·7 (16·0)
Men	46 664 (62%)	45 041 (64%)	1623 (38%)
Women	28 394 (38%)	25 733 (36%)	2661 (62%)
Ethnic origin			
Eastern Asian	8168 (11%)	8168 (12%)	0 (0%)
Southern Asian	25 757 (34%)	24 244 (34%)	1513 (35%)
Black African	1934 (3%)	1934 (3%)	0 (0%)
White	35 793 (48%)	33 022 (47%)	2771 (65%)
Other	3406 (5%)	3406 (5%)	0 (0%)
Active worker	17 797/33 803 (53%)	15 590/30 072 (52%)	2207/3731 (59%)
Educated to high school or above	11 637/34 729 (34%)	10 724/30 972 (35%)	913/3757 (24%)
Smoker	8634/37 804 (23%)	7416/33 908 (22%)	1318/3896 (34%)
Awareness*			
Chronic kidney disease	559/8155 (7%)	409/6631 (6%)	150/1524 (10%)
Hypertension	9153/15 461 (59%)	7151/12 751 (56%)	2002/2710 (74%)
Diabetes	2745/3868 (71%)	2157/3130 (69%)	588/738 (80%)
Self-reported cardiovascular disease†	1780/37 841 (5%)	1342/33 690 (4%)	438/4151 (11%)
Body-mass index (kg/m²)	24·9 (4·5)	24·8 (4·4)	26·0 (6·1)
Systolic blood pressure (mm Hg)	121 (18)	120 (17)	135 (24)
Diastolic blood pressure (mm Hg)	78 (11)	78 (11)	84 (12)
Mean arterial pressure (mm Hg)	93 (12)	92 (12)	101 (15)
Fasting blood glucose (mmol/L)	5·1 (2·0), n=38 630	5·1 (2·0), n=34 943	5·6 (2·3), n=3687
Total cholesterol (mmol/L)	4·7 (1·1), n=59 425	4·7 (1·1), n=58 721	5·1 (1·2), n=704
Triglycerides (mmol/L)	1·6 (1·1–2·1), n=57 467	1·6 (1·1–2·1), n=56 764	1·3 (0·9–1·9), n=703
Serum creatinine (µmol/L)	85·7 (27·4)	86·6 (27·4)	92·8 (61·0)
eGFR (mL/min per 1·73 m²)	88·4 (21·4)	88·0 (21·2)	81·6 (31·9)
Urine albumin-to-creatinine ratio (mg/g)	7·7 (0·7–19·8), n=19 634	7·1 (0·7–19·3), n=19 052	21·4 (10·1–77·0), n=582
Urine proteins dipstick ≥1+	2025/69 872 (3%)	1661/67 514 (2%)	364/2358 (15%)

Data are mean (SD), number of participants (%), or median (IQR), unless stated otherwise. Variable denominators indicate the number of available records. eGFR=estimated glomerular filtration rate. *Calculated only for patients with disease diagnosis by objective criteria. †Includes any of the following: stroke, ischaemic heart disease, or peripheral artery disease.

Table 1: **Characteristics of participants**

hypertension, and BMI. We stratified the 10-year risk of developing cardiovascular disease into three categories, low (<10%), medium (10% to <20%), and high (≥20%),[28] irrespective of existing chronic kidney disease or a related risk factors disorder.

Statistical analysis

We did not impute missing values into the study database or do case-wise deletion; therefore, the total number of participants differed by variable of interest. We tabulated descriptive statistics by count or percentage and used 95% CIs for categorical variables and either mean and SD or median and IQR (when appropriate), for continuous data. To investigate the possible association between risk factors and chronic kidney disease in the general population cohorts, we used univariable and multiple logistic regression. The predictors we included in the multiple logistic regression models were dichotomous risk factors for kidney damage (hypertension, diabetes, obesity, hypercholesterolaemia), cohort, and their interaction. We further adjusted the above models by age (change by 10 years) and sex. We judged p less than 0·05 significant. We did all statistical analyses with R.

Role of the funding source

The funder had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

Figure 1 shows the process for selection of cohorts for the ISN-KDDC study. After exclusion of non-eligible records, 75 058 participants were included; 70 774 (94%) study participants were from seven general population cohorts and one healthy population cohort (Iran[19]) and the remaining 4284 (6%) individuals were from four high-risk population cohorts. Sociodemographic and clinical characteristics of the participants are listed in table 1. Mean age was 44·5 years (SD 13·8) and 46 664 (62%) participants were men. 8168 (11%) individuals were from eastern Asia and 25 757 (34%) were from southern Asia; the ethnic origin of 1934 (3%) participants was black African and 35 793 (48%) people were white. Participants in general population cohorts were younger, more likely to be men, more educated, and less active smokers than were individuals in high-risk population cohorts. The screened general population also had lower blood pressure, a higher eGFR, and a lower prevalence of albuminuria (table 1). No prominent sex differences were recorded, except that men were more educated, more frequently employed, and more likely to be active smokers compared with women, both in general and in high-risk cohorts (appendix pp 1, 2).

Figure 2 shows the prevalence of chronic kidney disease in all 12 countries of low and middle income included in the ISN-KDDC study, and table 2 presents prevalence data adjusted by country, ethnic origin, and sex. In general population cohorts, the prevalence of chronic kidney disease was 14·3% (95% CI 14·0–14·5), with a prominent difference by ethnic origin. Women had a higher prevalence of chronic kidney disease than did men. In screened general populations, the overall prevalence of decreased eGFR (<60 mL/min per 1·73 m²) was 9·8% (95% CI 9·6–10·0) and of albuminuria was 5·5% (5·4–5·7). However, in general population cohorts from China, Mongolia, India, Moldova, and Bolivia, the prevalence of albuminuria was higher than the prevalence of decreased eGFR. In high-risk populations, the overall prevalence of chronic kidney disease was 36·1% (95% CI 34·7–37·6), with albuminuria having a greater effect than in general populations, with a prevalence of 32·6% (31·2–34·0); the prevalence of decreased eGFR was 8·3% (7·5–9·1; table 2). The overall prevalence of chronic kidney disease in high-risk cohorts was greater in men than in women. According to the KDIGO classification, in the general population, fewer than 1% of individuals had severely increased albuminuria (category A3), and among those defined as having albuminuria (categories A2 and A3), one in five participants had decreased eGFR (figure 3A). However, in high-risk populations, severely increased albuminuria (category A3) was detected in 3% of patients, and among those with increased albuminuria (categories A2 and A3) every seventh patient had decreased eGFR (figure 3B). The appendix (pp 4–9) shows the prevalence of chronic kidney disease in general population cohorts by world subregion.

Awareness of chronic kidney disease was very low in both the general and high-risk cohorts: 409 (6%) of 6631 individuals in general populations and

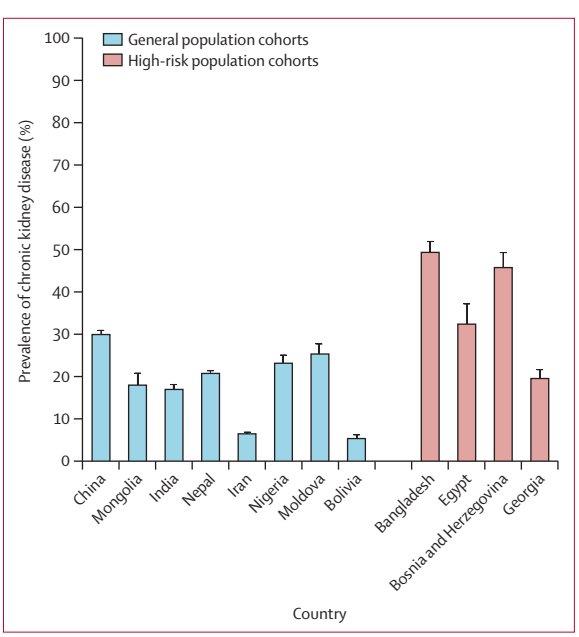

Figure 2: **Prevalence of chronic kidney disease, by country**
Data are prevalence (95% CI).

See Online for appendix

	Participants (n)	Men (%)	Age (years)	Prevalence (95% CI)		
				eGFR <60 mL/min per 1·73 m²	ACR >30 mg/g	Chronic kidney disease
General population cohorts						
Eastern Asia	..	..	..	..	..	..
China	7340	25·9%	53·4 (10·2)	13·0% (12·2–13·8)	19·6% (18·7–20·5)	29·9% (28·9–31·0)
Mongolia	832	22·8%	41·1 (13·6)	9·6% (7·7–11·9)	11·3% (9·3–13·7)	18·0% (15·5–20·8)
Southern Asia	..	..	..	..	..	..
India	3196	42·9%	50·1 (13·4)	2·5% (2·0–3·1)	15·4% (14·1–16·7)	16·8% (15·5–18·1)
Nepal	21066	38·6%	40·8 (15·6)	16·2% (15·7–16·7)	5·8% (5·5–6·2)	20·1% (19·6–20·6)
Middle East	..	..	..	..	..	..
Iran	31615	98·4%	43·8 (11·3)	5·8% (5·5–6·0)	0·6% (0·5–0·7)	6·3% (6·1–6·6)
Africa	..	..	..	..	..	..
Nigeria	1912	36·6%	44·3 (13·2)	20·7% (18·9–22·6)	3·9% (3·1–4·9)	23·0% (21·2–25·0)
Eastern Europe	..	..	..	..	..	..
Moldova	1403	29·4%	50·7 (14·3)	11·2% (9·6–13·0)	17·1% (15·2–19·2)	25·5% (23·3–27·9)
Latin America	..	..	..	..	..	..
Bolivia	3410	36·1%	41·6 (13·7)	1·7% (1·3–2·2)	4·5% (3·9–5·3)	5·5% (4·7–6·3)
Ethnic origin	..	..	..	..	..	..
Eastern Asian	8168	25·6%	52·1 (11·2)	12·6% (11·9–13·4)	18·8% (17·9–19·6)	28·7% (27·7–29·7)
Southern Asian	24244	39·1%	42·0 (15·7)	14·4% (13·9–14·8)	7·1% (6·8–7·4)	19·7% (19·2–20·2)
Black African	1934	37·1%	44·3 (13·2)	20·5% (18·7–22·4)	4·0% (3·2–5·0)	23·0% (21·1–24·9)
White	33022	95·5%	44·1 (11·5)	6·0% (5·8–6·3)	1·3% (1·2–1·4)	7·1% (6·9–7·4)
Other	3406	36·1%	41·6 (13·7)	1·7% (1·3–2·2)	4·5% (3·8–5·2)	5·5% (4·7–6·3)
Sex	..	..	..	..	..	..
Men	45041	..	44·2 (13·1)	7·3% (7·1–7·6)	3·0% (2·9–3·2)	9·7% (9·5–10·0)
Women	25733	..	44·1 (14·3)	14·2% (13·8–14·6)	9·9% (9·5–10·3)	22·2% (21·7–22·7)
Overall	70774	63·6%	44·2 (13·5)	9·8% (9·6–10·0)	5·5% (5·4–5·7)	14·3% (14·0–14·5)
High-risk population cohorts						
Southern Asia	..	..	..	..	..	..
Bangladesh	1511	43·3%	47·2 (15·9)	8·5% (7·1–10·0)	45·4% (42·9–48·0)	49·3% (46·8–51·9)
Middle East	..	..	..	..	..	..
Egypt	412	56·3%	39·1 (14·3)	7·5% (5·3–10·6)	29·6% (25·3–34·3)	32·3% (27·8–37·1)
Eastern Europe	2361	31·2%	53·2 (15·3)	8·3% (7·2–9·5)	24·9% (23·2–26·8)	28·3% (26·5–30·2)
Bosnia and Herzegovina	798	42·6%	57·0 (15·0)	14·9% (12·6–17·6)	39·1% (35·7–42·6)	45·9% (42·4–49·4)
Georgia	1563	25·3%	51·2 (15·0)	4·9% (3·9–6·1)	17·7% (15·9–19·7)	19·4% (17·5–21·5)
Ethnic origin	..	..	..	..	..	..
Southern Asian	1513	43·3%	47·2 (15·9)	8·5% (7·1–10·0)	45·3% (42·8–47·9)	49·2% (46·7–51·8)
White	2771	34·9%	51·1 (15·9)	8·2% (7·2–9·3)	25·7% (24·0–27·3)	28·9% (27·3–30·7)
Sex	..	..	..	..	..	..
Men	1623	..	49·7 (16·7)	6·4% (5·3–7·7)	37·6% (35·3–40·1)	40·0% (37·7–42·5)
Women	2661	..	49·7 (15·6)	9·4% (8·3–10·6)	29·5% (27·8–31·3)	33·7% (31·9–35·5)
Overall	4284	37·9%	49·7 (16·0)	8·3% (7·5–9·1)	32·6% (31·2–34·0)	36·1% (34·7–37·6)

Data are adjusted prevalence (95% CI) or mean (SD), unless otherwise stated. ACR=albumin-to-creatinine ratio approximate equivalent. eGFR=estimated glomerular filtration rate.

Table 2: **Prevalence of decreased eGFR, albuminuria, and chronic kidney disease, adjusted for country, ethnic origin, and sex**

150 (10%) of 1524 participants from high-risk populations were aware of their condition (table 1). A more detailed map of awareness about chronic kidney disease by eGFR and albuminuria categories (figure 4) shows that some people with severe chronic kidney disease had very low awareness. In the general population, of 2783 individuals with albuminuria stages A2 and A3, 239 (9%) were aware they had chronic kidney disease, and of 905 with eGFR less than 45 mL/min per 1·73 m² (categories G3b, G4, and G5), 70 (8%) were aware of their condition. Corresponding awareness for high-risk populations was 10% (139/1376) and 18% (28/156), respectively. Of patients who were aware of their chronic kidney disease, 170 (42%) of 409 in general populations and 72 (48%) of 150 in high-risk populations were reported as having any treatment for the condition.

Awareness of disorders representing major risk factors for chronic kidney disease was higher than for chronic kidney disease (table 1). In the general population, 7151 (56%) of 12751 individuals knew they had hypertension, but only half (3485/7151 [49%]) were taking antihypertensive drugs. Awareness of hypertension was higher in high-risk populations (2002/2710 [74%]), but even among this group, almost one in four individuals did not know about elevated blood pressure and 1815 (91%) of 2002 were prescribed appropriate treatment (appendix pp 1, 2). With respect to diabetes, 2157 (69%) of 3130 individuals in the general population and 588 (80%) of 738 in the high-risk population were aware of existing disease. Only 1544 (72%) of 2157 patients in general cohorts and 514 (87%) of 588 in high-risk populations who were aware of existing diabetes reported taking anti-diabetes drugs.

Several risk factors were associated with chronic kidney disease in the general population cohorts, at overall study population level or adjusted by cohort, and adjusted for cohort, age, and sex (table 3). In multiple logistic regression analyses, hypertension, diabetes, obesity, and high cholesterol were all associated independently with chronic kidney disease (overall, and for almost all regions). Overall, the odds of detecting chronic kidney disease were increased significantly in individuals with hypertension (adjusted odds ratio 1·68, 95% CI 1·60–1·76), diabetes (1·75, 1·62–1·89), obesity (1·07, 1·01–1·14), and high serum cholesterol (1·22, 1·13–1·31). Data for the prevalence of risk factors for chronic kidney disease in individuals in the general population cohort who have chronic kidney disease are presented in the appendix (p 3).

In the general population cohort (n=67 009), 50 033 (75%) individuals were at low risk, 10 587 (16%) were at medium risk, and 6389 (10%) were at high risk of developing cardiovascular disease in the next 10 years. In the high-risk population cohort (n=4250), 2084 (49%) participants were at low risk, 770 (18%) were at medium risk, and 1396 (33%) were at high risk. Figure 5 shows the proportion of the population at high risk of developing cardiovascular disease in the next 10 years, by eGFR and albuminuria categories. Individuals in a higher category of albuminuria (A2 and A3) or decreased eGFR (G3a to G5) had a striking increase in 10-year risk, and the risk was even higher for individuals with both markers of kidney damage and dysfunction.

***Figure 3*: Prevalence of chronic kidney disease by eGFR and albuminuria categories, overall and stratified by sex**

Data are %. Chronic kidney disease-related risk defined as: green, low risk (if no other markers of kidney disease, no chronic kidney disease); yellow, moderately increased risk; orange, high risk; red, very high risk.[3] eGFR was calculated with the CKD-EPI equation:[21] G1, normal or high (≥90 mL/min per 1·73 m²); G2, mildly decreased (60–89 mL/min per 1·73 m²); G3a, mildly to moderately decreased (45–59 mL/min per 1·73 m²); G3b, moderately to severely decreased (30–44 mL/min per 1·73 m²); G4, severely decreased (15–29 mL/min per 1·73 m²) and G5, kidney failure (<15 mL/min per 1·73 m²). Albuminuria categories were defined as ACR approximate equivalent: A1, normal to mildly increased (ACR <30 mg/g); A2, moderately increased (ACR ≥30 mg/g to <300 mg/g); A3, severely increased (ACR ≥300 mg/g). ACR=albumin-to-creatinine ratio. eGFR=estimated glomerular filtration rate.

Discussion

The findings of the ISN-KDDC study are estimates for the prevalence of chronic kidney disease in populations of 12 low-income and middle-income countries in six regions of the world belonging to the ISN-KHDC and affiliated programmes. In the general population, the overall prevalence of chronic kidney disease was 14·3%, ranging from 5·5% in Bolivia to 29·9% in China. The mean prevalence of chronic kidney disease across all 12 countries was similar to the figure of 10–13% recorded by high-quality screening programmes in high-income countries.[6,29]

The specific features of the studied population could account for the variability in prevalence of chronic kidney disease we noted in the general cohorts. One of the lowest values for prevalence of chronic kidney disease was recorded in predominantly healthy, young (mean age 44 years), male taxi drivers in Iran,[19] whereas the highest prevalence was detected in China, where participants were older (mean age 53 years), 30% had elevated blood pressure, and 6% had diabetes.[15] Moreover, we recorded differences in ethnic origin, with a much lower prevalence of chronic kidney disease in white populations compared with people from Asian and black African backgrounds, which could be related to the known effect of ethnic origin on development of chronic kidney disease.[30] Nevertheless, it should be taken into account that the main objective of the ISN KHDC-based screening programmes,[14] established in 2005, was not to estimate the true prevalence of chronic kidney disease by repeat testing, as recommended by KDIGO guidelines published in 2012,[3] but to identify individuals at risk of or with kidney disease and to include them in follow-up programmes aimed at limiting morbidity and mortality related to complications of renal and cardiovascular disease in countries of low and middle income. Moreover, these ISN programmes provided an integrated view on the assessment of non-communicable diseases, which included detection of kidney abnormalities in the context of a wide range of risk factors and chronic diseases.

Screening for chronic kidney disease in high-risk populations (people with diabetes or hypertension, or who are older than 60 years) is recommended by the latest KDIGO guidelines[3] and most,[31] but not all,[32] cost-effectiveness studies. Conversely, screening for chronic kidney disease in the general population is not recommended by the US Preventive Task Force[33] because of the absence of high-quality data that can forecast its effectiveness in preventing complications. However, evidence shows that screening for chronic kidney disease

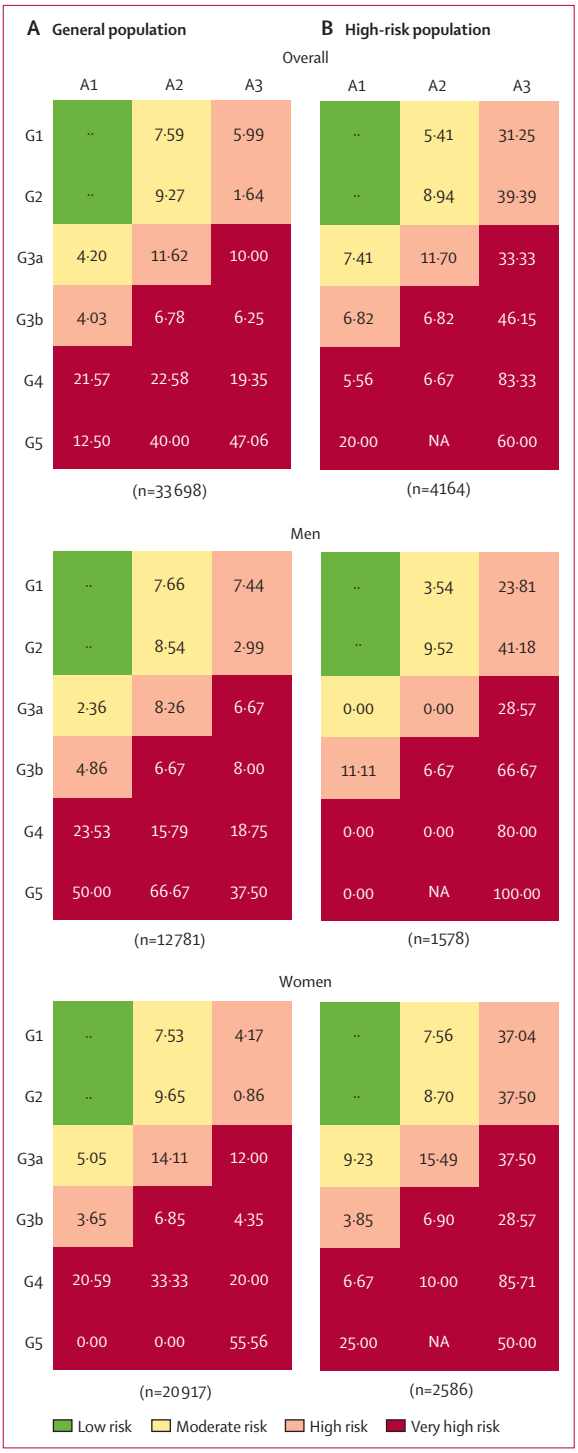

Figure 4: **Awareness of chronic kidney disease by eGFR and albuminuria categories, overall and stratified by sex**

Data are %. Chronic kidney disease-related risk defined as: green, low risk (if no other markers of kidney disease, no chronic kidney disease); yellow, moderately increased risk; orange, high risk; red, very high risk.[3] eGFR was calculated with the CKD-EPI equation:[21] G1, normal or high (≥90 mL/min per 1·73 m^2); G2, mildly decreased (60–89 mL/min per 1·73 m^2); G3a, mildly to moderately decreased (45–59 mL/min per 1·73 m^2); G3b, moderately to severely decreased (30–44 mL/min per 1·73 m^2); G4, severely decreased (15–29 mL/min per 1·73 m^2) and G5, kidney failure (<15 mL/min per 1·73 m^2). Albuminuria categories were defined as ACR approximate equivalent: A1, normal to mildly increased (ACR <30 mg/g); A2, moderately increased (ACR ≥30 mg/g to <300 mg/g); A3, severely increased (ACR ≥300 mg/g). ACR=albumin-to-creatinine ratio. eGFR=estimated glomerular filtration rate. NA=no data available.

	Hypertension		Diabetes		Obesity		Hypercholesterolaemia	
	Odds ratio (95% CI)	p	Odds ratio (95% CI)	p	Odds ratio (95% CI)	p	Odds ratio (95% CI)	p
Overall (univariable logistic regression)*	2·88 (2·76–3·01)	<0·001	2·43 (2·25–2·62)	<0·001	1·32 (1·25–1·39)	<0·001	1·49 (1·39–1·59)	<0·001
World subregions†	..	..	..	..	..	..	..	..
Eastern Asia (China, Mongolia)	1·25 (1·09–1·43)	0·001	1·81 (1·38–2·38)	<0·001	1·62 (1·23–2·12)	<0·001	2·06 (1·36–3·09)	<0·001
Southern Asia (India, Nepal)	2·58 (2·42–2·75)	<0·001	3·14 (2·87–3·44)	<0·001	1·67 (1·54–1·81)	<0·001	2·21 (1·89–2·59)	<0·001
Middle East (Iran)	2·44 (2·17–2·75)	<0·001	NA	..	1·18 (1·03–1·35)	0·019	1·91 (1·71–2·13)	<0·001
Africa (Nigeria)	1·43 (1·15–1·77)	0·001	1·71 (1·13–2·55)	0·009	1·24 (0·94–1·63)	0·116	1·93 (1·49–2·48)	<0·001
Eastern Europe (Moldova)	1·93 (1·49–2·49)	<0·001	2·74 (1·97–3·78)	<0·001	1·40 (1·09–1·80)	0·009	2·49 (1·83–3·39)	<0·001
Latin America (Bolivia)	6·17 (4·56–8·38)	<0·001	8·22 (4·89–13·42)	<0·001	1·77 (1·28–2·43)	<0·001	NA	..
Overall (multiple logistic regression)‡	1·68 (1·60–1·76)	<0·001	1·75 (1·62–1·89)	<0·001	1·07 (1·01–1·14)	0·019	1·22 (1·13–1·31)	<0·001
World subregions§	..	..	..	..	..	..	..	..
Eastern Asia (China, Mongolia)	1·01 (0·88–1·15)	0·940	1·44 (1·09–1·91)	0·010	1·58 (1·20–2·08)	0·001	1·90 (1·25–2·87)	0·002
Southern Asia (India, Nepal)	1·57 (1·47–1·69)	<0·001	2·25 (2·04–2·48)	<0·001	1·43 (1·31–1·55)	<0·001	1·64 (1·38–1·94)	<0·001
Middle East (Iran)	1·73 (1·54–1·95)	<0·001	NA	..	1·21 (1·05–1·38)	0·007	1·73 (1·54–1·93)	<0·001
Africa (Nigeria)	1·01 (0·81–1·27)	0·909	1·29 (0·85–1·95)	0·217	1·03 (0·78–1·36)	0·837	1·29 (0·98–1·68)	0·060
Eastern Europe (Moldova)	1·07 (0·82–1·40)	0·604	2·13 (1·52–2·97)	<0·001	1·13 (0·87–1·46)	0·374	1·98 (1·42–2·74)	<0·001
Latin America (Bolivia)	3·93 (2·89–5·37)	<0·001	4·58 (2·69–7·58)	<0·001	1·25 (0·89–1·72)	0·186	NA	..

Odds ratios are for prediction of chronic kidney disease. NA=no data available in the subset for the corresponding predictor. *Univariable logistic regression included risk factor only. †Multiple logistic regression included risk factor, cohort, and risk factor:cohort interaction. ‡Multiple logistic regression included risk factor, age, and sex. §Multiple logistic regression included risk factor, age, sex, cohort, and risk factor:cohort interaction.

Table 3: **Risk factors associated with chronic kidney disease in general population cohorts**

in the general population is plausible even for healthy individuals older than 50 years when done once every 10 years, which strikingly increases its cost-effectiveness.[34] Almost all recommendations—both for and against screening for chronic kidney disease—are based on data from the developed world.

Although our study is not a cost-effectiveness analysis, our data provide important insights into the usefulness of screening for chronic kidney disease and its risk factors, both in general population and high-risk cohorts in countries of low and middle income. In particular, we found that in screened individuals, awareness of chronic kidney disease, hypertension, or diabetes was low: more than 90% of individuals did not know they had chronic kidney disease, almost every second screened patient did not know about his or her hypertension, and close to every third screened individual was unaware of his or her diabetes. These findings parallel those of a large-scale screening programme in Brazil,[35] where more than four-fifths of individuals with detected proteinuria were unaware of chronic kidney disease and roughly a quarter of the screened population with recorded high blood pressure did not know they had hypertension. In India,[36] only 2% of screened participants diagnosed with chronic kidney disease had a self-reported history of kidney disease, and in China,[29] a third of the rural and two-thirds of the urban population were unaware of their diabetes.

Our estimated awareness of chronic kidney disease (6% and 10%, for general and high-risk population cohorts, respectively) in low-income and middle-income countries seems comparable with data from developed countries. In US Kidney Early Evaluation Program (KEEP) screening programmes, the prevalence of patients aware of their existing chronic kidney disease was 7%[37] or 9%.[38] However, in a smaller cohort of KEEP participants with presumed chronic kidney disease, based on one measurement of renal function, awareness of chronic kidney disease was higher, up to 23%.[39]

Furthermore, our study highlights that, in general populations, almost half of patients with high blood pressure did not take antihypertensive drugs and a third of people known to have diabetes did not receive antidiabetes drugs, which indicates that, in countries of low and middle income, a substantial number of patients have no access to appropriate treatment, even though both diabetes and hypertension are major risk factors for development and progression of chronic kidney disease,

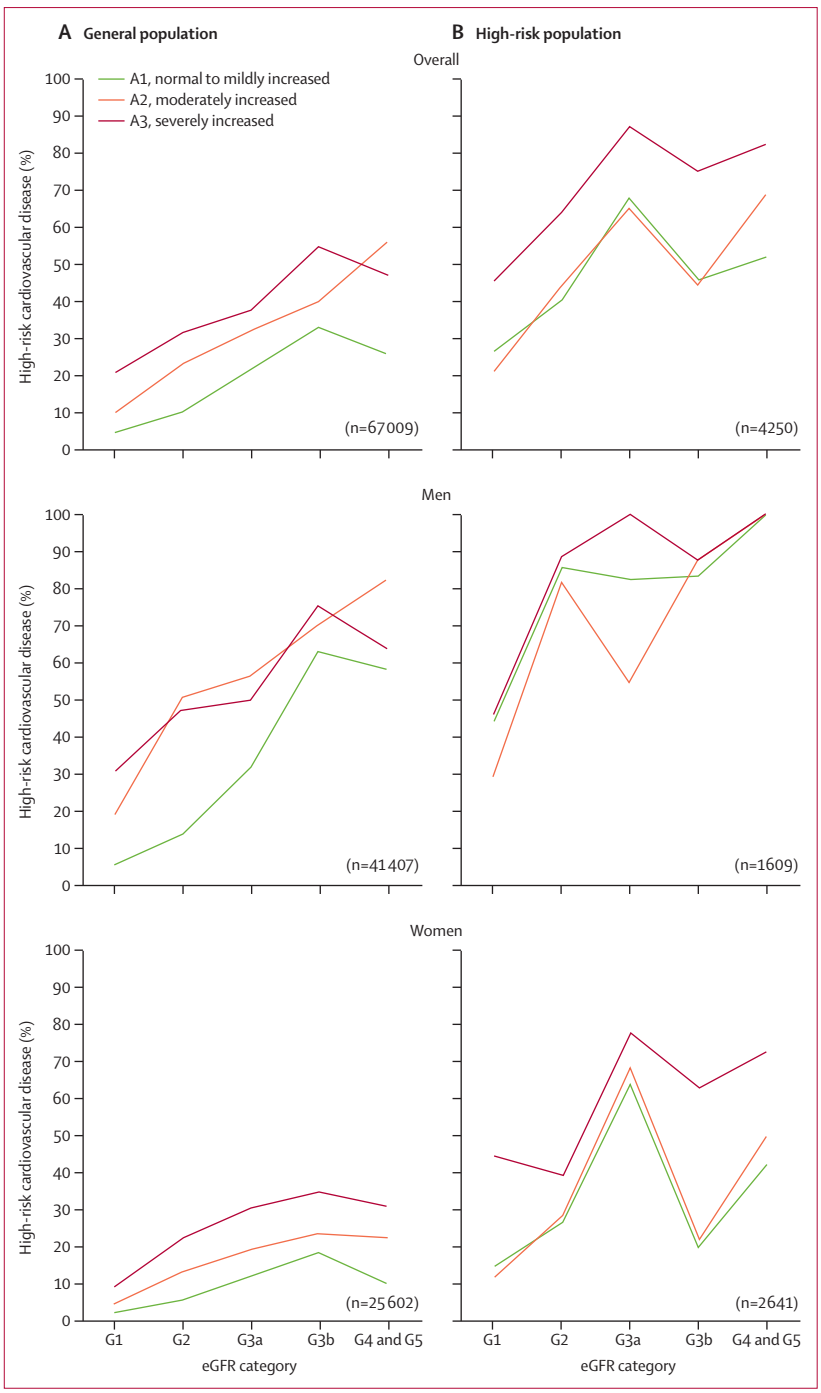

Figure 5: **Proportion of population at high risk of developing cardiovascular disease in the next 10 years by eGFR and albuminuria categories, overall and stratified by sex**

Risk calculated according to the simpler risk prediction Framingham risk score equation based on non-laboratory predictors (sex, age, diabetes, and smoking status, treated or untreated hypertension, and body-mass index).[26] High risk defined as a probability greater than 20%. eGFR was calculated with the CKD-EPI equation:[21] G1, normal or high (≥90 mL/min per 1·73 m²); G2, mildly decreased (60–89 mL/min per 1·73 m²); G3a, mildly to moderately decreased (45–59 mL/min per 1·73 m²); G3b, moderately to severely decreased (30–44 mL/min per 1·73 m²); G4, severely decreased (15–29 mL/min per 1·73 m²) and G5, kidney failure (<15 mL/min per 1·73 m²). Albuminuria categories were defined as ACR approximate equivalent: A1, normal to mildly increased (ACR <30 mg/g); A2, moderately increased (ACR ≥30 mg/g to <300 mg/g); A3, severely increased (ACR ≥300 mg/g). ACR=albumin-to-creatinine ratio. eGFR=estimated glomerular filtration rate.

and for complications and mortality from chronic kidney disease.[40,41] Indeed, our analysis confirmed the increased odds of detecting chronic kidney disease in patients with elevated blood pressure, diabetes, obesity, and high amounts of cholesterol in serum. In a subset of patients, we also detected a high prevalence of smoking, in either general (22%) or high-risk (34%) population cohorts, which is known as one of the risk factors for development of chronic kidney disease, not only during adult life[42] but also via epigenetic modification and mitochondrial dysfunction during fetal programming.[43]

According to the latest nephrology[44] and cardiology[40,41] guidelines, all people with chronic kidney disease should be judged at high risk of complications from chronic kidney disease. However, no markers of chronic kidney disease (eg, decreased eGFR and increased albuminuria) are included in risk scores for cardiovascular disease, including the Framingham risk score—the non-laboratory-based version of which[26] we used to calculate the 10-year risk for developing cardiovascular disease in our study. Nevertheless, we reported an incremental increase in cumulative effect of reduced eGFR and increased albuminuria on the Framingham risk score, but the risk was substantially underestimated for most patients with chronic kidney disease. 35% of individuals in eGFR category 3B, and 20% and 31% of those in albuminuria category A2 and A3, respectively, would have been recognised by the Framingham risk score as being at high risk of cardiovascular disease, whereas all these patients are classified as high risk by KDIGO guidelines.[3] These findings suggest that timely recognition of chronic kidney disease could provide additional key information to appropriately estimate risk of cardiovascular disease in screened individuals in general populations in low-income and middle-income countries.

Our study has several limitations. First, individuals were screened based on convenience sampling with active referral from advertisements, or on specific geographical areas; thus, participants were not randomly selected from the whole population. Therefore, we cannot infer per country representativeness of renal abnormalities. This selection bias could have led us to overestimate the prevalence of chronic kidney disease in some regions, because we assessed people who volunteered to be tested.[45] Such bias has been proven in a US study comparing random selection in the NHANES study with active referral in the KEEP study,[37] in which the prevalence of chronic kidney disease was 13·1% and 28·7%, respectively. Similarly, in our screening programme in India, the prevalence of chronic kidney disease was 16·8%, but in another study in which random multistage cluster sampling was used,[36] prevalence was only 7·5%. Second, laboratory methods for measurement of creatinine were not standardised, which could introduce bias both for comparison of the prevalence of low eGFR between study sites and for adequate calculation of eGFR with the CKD-EPI

formula,[21] which assumes creatinine standardisation (with a costly reference standard that is unaffordable for most countries of low and middle income). However, in every country of low and middle income, creatinine measurement was calibrated according to manufacturer guidelines, which should have prevented major bias. Third, in most individuals, determinants of chronic kidney disease were based on one measurement of creatinine in serum and albuminuria, which could have contributed to overdiagnosis of chronic kidney disease in some screened individuals with transient changes in these variables. This approach is widespread in published literature on the epidemiology of chronic kidney disease: urinalysis and measurement of serum creatinine to calculate eGFR was done only once in studies of the prevalence of chronic kidney disease in the general population of high-income European countries[46–48] and the USA[39,49] and in nationally representative screening for chronic kidney disease in China.[29] Although at the population level, one-time measurement of markers of chronic kidney disease is common and could be acceptable for estimation of prevalence, on the individual patient level, obligatory confirmation of initial abnormalities should be done. To better discriminate the management strategy at population and individual levels, findings obtained during screening—in which one calculation for eGFR and one evaluation of urinalysis was done—could be described more precisely as the prevalence of a positive screening test for chronic kidney disease, to which we refer in our analysis, while using the generally accepted term chronic kidney disease. Although there is a risk of false-positive results with this approach,[6] the main screening goal, particularly in countries of low and middle income, is to avoid false-negative findings. Therefore, in case of a positive result after initial detection, confirmatory assessment should be set up before any intervention treatment is started or the patient is referred to a specialist. Finally, eGFR was calculated with the CKD-EPI equation,[21] which was developed for the US population, and although this formula includes a coefficient for ethnic origin, it could indicate eGFR imprecisely in multiethnic cohorts. Several different coefficients have been proposed for Asian and black populations,[44,50,51] but currently they are neither widely recommended nor validated.[52] Moreover, in Chinese populations, the CKD-EPI two-level race equation was proven better than the Modification of Diet in Renal Disease (MDRD) study equation and the CKD-EPI four-level race equation.[53] Thus, in our multiethnic cohort, we used the recommended[3] two-level race CKD-EPI equation.

Although formal comparison across different populations is prevented by variable sampling strategies, our use of identical cutoffs for clinical and laboratory variables, the same screening protocol, one web-based database for data entry and centralised data monitoring in most cases, and inclusion of both urban and rural populations in screening and the programmes makes our analysis a unique opportunity to study the prevalence of chronic kidney disease and other non-communicable diseases in countries of low and middle income. In conclusion, decreased eGFR and increased albuminuria—and the resulting prevalence of chronic kidney disease—are common in the general populations of countries of low and middle income. Our results not only suggest the feasibility of screening in poor-resource settings but also underline that, without local screening programmes, most individuals in these regions remain unaware of existing chronic kidney disease and its risk factors. This sparse knowledge precludes any appropriate prevention, follow-up, and treatment programmes for patients in need. In view of the major effect renal abnormalities have on cardiovascular disease, such screening programmes—complemented by sustainable management of patients who screen positive—should be implemented urgently with adjustments for local settings, along with generally strengthening the health-care workforce and making cheap drugs accessible to local populations. Prospective studies are warranted to quantify the potential benefits of this type of prevention strategy in countries of low and middle income.

Contributors

BE-I, GR, NP, and BB developed the idea for the study. NI, RFB, MA-H, HZ, LZ, ZG, IT, GA, MM-M, MG, IC, AT, SKS, PK, SU, and IU were principal investigators, responsible for the screening programmes in their respective countries, and participated in data collection. BE-I, SC, and AR contributed to setting up the ISN-KDDC database. BE-I and SC assessed the quality of data entry and did analyses. BE-I, NP, BB, AP, and GR contributed to data analyses and interpretation. BE-I wrote the first draft, and together with NP and BB, the final version of the report. All authors approved the final manuscript.

Declaration of interests

We declare no competing interests.

Acknowledgments

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