

Original Article

Comparison of the yield of different screening approaches to detect chronic kidney disease

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Abstract

Background. Screening for chronic kidney disease (CKD) has been advised in high-risk populations. The present study aims to compare the yields of four approaches to select high-risk subjects for CKD screening, which are defined as follows: Approach 1, history of cardiovascular (CV) disease, diabetes mellitus or hypertension (=high CV risk); Approach 2, high CV risk or age >55 years; Approach 3, urinary albumin concentration (UAC) ≥ 20 mg/L; or Approach 4, UAC ≥ 10 mg/L at pre-screening.

Methods. The study population is a sample of the general population of Groningen, the Netherlands ($n = 3398$). UAC was measured (nephelometry) in a first morning void urine sample collected at home and sent to a laboratory by post. Information on demographics and the presence of CV risk factors was obtained by a questionnaire. The presence of CKD was determined during examination at an outpatient clinic.

Results. At baseline, 12% of the subjects met the criteria of Approach 1, 33% of Approach 2, 8% of Approach 3 and 25% of Approach 4. CKD was diagnosed in 370 subjects (11%). Approach 2 detected the most CKD patients (sensitivity 65%), while Approach 3 resulted in the lowest number needed to screen (1.9). During a follow-up of 7 years, only the UAC pre-screening approaches detected CKD patients who had both significantly accelerated renal function loss and increased CV risk compared to subjects without CKD. Only 28% of CKD patients detected by the UAC approaches used antihypertensive/angiotensin-converting enzyme inhibitor treatment prior to screening.

Conclusions. This study suggests that pre-screening based on UAC should be favoured in comparison to screening based on CKD risk factors to detect CKD patients at high renal and CV risk.

Keywords: cardiovascular risk; chronic kidney disease; population screening; renal function loss

Introduction

Chronic kidney disease (CKD) is a disease affecting ~11–12% [1–3] of the general population. CKD and its compli-

cations seriously affect patient health and well-being [4] and impose high costs on the health care system. CKD often lacks symptoms, which results in a high percentage of unawareness [5]. However, detection of CKD in an early stage offers possibilities to start early treatment and thereby to delay or prevent complications of CKD [6]. For this reason, screening for CKD has been advocated.

Various CKD screening approaches have been suggested [7]. Screening of selected high-risk groups has generally been preferred over screening of the general population to limit the costs and the psychological and physical burden of participants in such a screening programme [8,9]. Two possible ways to select high-risk groups are (i) selection based on medical history and demographic factors or (ii) selection based on urine abnormalities, i.e. elevated levels of albuminuria in a urine sample obtained at a pre-screening. The first method is adopted by the Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines, which recommend screening of patients with known hypertension, known diabetes mellitus (DM) and a cardiovascular (CV) disease history [4], whereas screening subjects of older age has also been suggested. This age cut-off to define 'elderly' is arbitrary, but Hallan *et al.* suggested that >55 years would be efficacious [4,10]. The possible merits of pre-screening on albuminuria has been advocated [7], but is not practiced yet. Traditionally, the cut-off of urinary albumin concentration (UAC) indicating abnormal albuminuria has been 20 mg/L. Recently, it has been suggested to lower that cut-off to 10 mg/L in order to lower the number of false-negative test results [11].

Results of previous studies considering the yield of screening by the various screening approaches are difficult to compare because of differences in populations that were included in these studies and the different definitions of CKD that were used [10,12–14]. Therefore, in the present study, the yield of various screening approaches will be compared in the same study population, using the widely accepted K/DOQI definition of CKD [4]. Four screening approaches will be compared: Approach 1, selection based on the presence of known non-insulin-dependent diabetes mellitus (NIDDM), CV disease history or hypertension;

Approach 2, selection based on Approach 1 and/or age >55 years; Approach 3, selection based on UAC of ≥ 20 mg/L at pre-screening; or Approach 4, UAC ≥ 10 mg/L at pre-screening. These approaches will be compared, first, on their ability to detect patients with CKD and, second, on their ability to identify those subjects with CKD that are at risk of accelerated renal function decline and CV events during follow-up.

Materials and methods

Population

This study is part of the Prevention of Renal and Vascular End-stage Disease (PREVEND) Study, a prospective cohort study that was designed to investigate the predictive value of albuminuria for renal and CV outcome in the general population. The study was initiated in 1997, when all 85 421 inhabitants of Groningen, the Netherlands, aged 28–75 years, were invited to fill out a brief questionnaire and to collect a urine sample (pre-screening). For this purpose, all subjects were sent a urine collection device including instructions to collect a first morning void urine sample, which could be returned by mail to a central laboratory. UAC level was measured at the central laboratory within 3 days, meanwhile keeping the samples refrigerated.

Insulin-dependent DM patients and pregnant females (defined by self-report) were excluded from the 40 856 (47.8%) responders. All remaining subjects with a UAC ≥ 10 mg/L were invited and 6000 participated. Furthermore, a randomly selected control group with a UAC of <10 mg/L was invited and 2592 participated. These 8592 subjects constitute the PREVEND cohort. Enrichment for subjects with higher albuminuria values in the PREVEND cohort may bias the comparison of the different screening approaches. Therefore, a sub-cohort representative of the Groningen population was composed. All subjects with a UAC of <10 mg/L who completed the first screening were included and a subset of subjects whose UAC was ≥ 10 mg/L was added by proportionally taking a computer-generated, random subset. After the exclusion of 34 participants who had incomplete information on CKD status at the first screening round, a cohort of 3398 participants was created. Measurements of renal and CV risk factors and outcome were repeated approximately every 3 years at an outpatient department. Detailed information on the study design and the fact that our study cohort is indeed representative for the overall general Groningen population has been published elsewhere [15].

The PREVEND Study is approved by the medical ethics committee of our institution and conducted in accordance with the guidelines of the Declaration of Helsinki. All participants gave informed consent.

Pre-screening: definitions and measurements

Pre-screening was performed as a means to select high-risk subjects for actual screening. Pre-screening was performed *via post*, by sending all subjects a short questionnaire and a test tube to collect a sample of a first morning void urine. High-risk subjects were selected for the various screening approaches based on the following: Approach 1, high CV risk; Approach 2, high CV risk or age ≥ 55 years; Approach 3, UAC ≥ 20 at pre-screening; or Approach 4, a UAC ≥ 10 at pre-screening. To be selected as 'high CV risk' (Approaches 1 and 2), the subject had to fill in the pre-screening questionnaire to be acknowledged with a myocardial infarction, cerebrovascular accident, NIDDM or hypertension in need of medical treatment. Selection for Approaches 3 and 4 was based on the measurement of UAC in the first morning void urine samples, which were sent to a central laboratory by post and were measured within 3 days by nephelometry (Dade Behring Diagnostic, Marburg, Germany).

Actual screening: definitions and measurements

Participants were invited for the first screening round within 3 months after pre-screening. Baseline characteristics are based on information obtained at the first screening round. Each screening round consisted of two visits to an outpatient department separated within ~3 weeks. Participants filled in an extensive questionnaire on demographics, CV and renal his-

tory, lifestyle habits and the use of anti-diabetic and antihypertensive drugs. A subject was classified as smoker if the subject indicated to be a present smoker or if the subject had quit smoking <1 year ago. CV disease history was defined as a self-reported history of myocardial infarction or cerebrovascular accident. Information on drug use was also obtained from community pharmacies in Groningen.

During both study visits, blood pressure (BP) was measured in the right arm, every minute for 10 and 8 min, respectively, by an automatic Dinamap XL Model 9300 series device (Johnson & Johnson Medical Inc., Tampa, FL, USA). For systolic and diastolic blood pressure (SBP and DBP, respectively), the mean of the last two recordings from each of the two visits was used. Anthropometrical measurements were performed, and fasting blood samples were taken. In addition, subjects collected urine for two consecutive 24-h periods. Serum creatinine was measured by dry chemistry (Eastman Kodak, Rochester, NY, USA), which is an automated enzymatic method with intra- and inter-assay coefficients of variation of 0.9 and 2.9%, respectively. UAC was determined by nephelometry (Dade Behring Diagnostic, Marburg, Germany), and urinary albumin excretion (UAE) was given as the mean of the two 24-h urinary excretions. Laboratory personnel performing these tests were blinded to previous test results and clinical information. The presence of CKD was assessed at the first screening round. CKD was defined according to the KDOQI definition, by: estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m² (Stages 3–5) or eGFR ≥ 60 mL/min/1.73 m² with UAE ≥ 30 mg/24 h (Stages 1 and 2). Glomerular filtration rate (GFR) was estimated by the abbreviated MDRD formula [31].

Follow-up measurements

During follow-up, information was obtained on CV and renal endpoints. The CV endpoint was defined as the incidence of fatal and non-fatal CV first events after the first screening round. These data were obtained from the Dutch registry of hospital discharge diagnoses (Prismant) and from the Dutch Central Bureau of Statistics for causes of death. All data were coded according to the International Classification of Diseases, 9th Revision (ICD) and the classification of interventions. For this study, CV events were defined as: acute myocardial infarction (ICD Code 410), acute and sub-acute ischaemic heart disease (ICD Code 411), subarachnoid haemorrhage (ICD Code 430), occlusion or stenosis of the pre-cerebral (ICD Code 433) or cerebral arteries (ICD Code 434), coronary artery bypass grafting or percutaneous transluminal coronary angioplasty and other vascular interventions as percutaneous transluminal angioplasty or bypass grafting of aorta and peripheral vessels. Survival time of a subject was defined as the time between the date of UAE measurement to the date of first CV event or 31 December 2005. People who died of other causes, moved to an unknown destination or were lost to follow-up were censored from that time on. As renal endpoint, we used the rate of decline of renal function per year, which was estimated by the slope of a linear regression line, fitted between the two or three serial estimates of GFR, using the least squares principle.

Statistical analyses

Analyses were performed using the statistical package SPSS 14.0 (SPSS, Chicago, IL). A *P*-value ≤ 0.05 was adopted to indicate statistical significance. Normally distributed data are reported as means with standard deviation, whereas data with skewed distribution are given as medians with interquartile range. Differences between groups were tested by Student's *t*-test for continuous data. Differences in prevalence or incidence were tested with a chi-square test.

Subjects with missing data were not included in the analysis, since the number of subjects with missing data was small (<5% of the total) and appeared to be randomly missing.

Screening approach test characteristics were calculated. Sensitivity was defined as the number of subjects with a positive test at pre-screening who appeared to have CKD at baseline screening (true positive), divided by the total number of subjects with CKD at baseline screening. Specificity was defined as the number of subjects with a negative test result who appeared *not* to have CKD at baseline screening (true negative), divided by the total number of subjects without CKD at baseline screening. The positive predictive value was defined as the number of true-positive test results divided by the total number of positive test results; the negative predictive value was defined as the number of true-negative test results

Table 1. Baseline characteristics of the overall population and when subdivided according to whether one of the four screening criteria is present or absent

	Screening approaches								
	All (<i>n</i> = 3398)	Screening Approach 1: CV risk		Screening Approach 2: CV risk or >55 years		Screening Approach 3: UAC ≥20 mg/L		Screening Approach 4: UAC ≥10 mg/L	
		Present (<i>n</i> = 393)	Absent (<i>n</i> = 3005)	Present (<i>n</i> = 1112)	Absent (<i>n</i> = 2286)	Present (<i>n</i> = 270)	Absent (<i>n</i> = 3128)	Present (<i>n</i> = 833)	Absent (<i>n</i> = 2565)
Age (years)	49 (12)	60 (10)*	47 (12)	63 (7.5)*	42 (7.4)	54 (13)*	48 (12)	50 (13)*	48 (12)
Male (%)	45	50*	44	49*	43	54*	44	52*	43
Hypertension (%)	9.6	74*	1.2	28*	0.7	18.5*	8.8	13*	8.5
NIDDM (%)	1.1	8.9*	0.1	3.2*	0.0	2.6*	1.0	1.7	0.9
CVD history (%)	4.2	27*	1.2	12*	0.5	7.0*	4.0	6.2*	3.5
Smoking (%)	35	25*	36	27*	39	40	35	40*	33
BMI (kg/m ²)	26 (4.1)	28 (4.0)*	26 (4.0)	27 (4.0)*	25 (3.9)	27 (4.7)*	26 (4.0)	26 (4.3)*	26 (4.0)
SBP (mmHg)	126 (18)	141 (20)*	124 (17)	137 (20)*	121 (15)	138 (23)*	125 (18)	132 (21)*	124 (17)
DBP (mmHg)	73 (9)	78 (9)*	72 (9)	77 (9)*	71 (9)	77 (10)*	72 (9)	75 (10)*	72 (9)
BP-lowering medication (%)	12	80*	4.2	35*	2.7	26*	13	19*	12
ACEi/ARB (%)	3.7	31*	0.4	12*	0.2	9.9*	3.9	6.7*	3.7
Cholesterol (mmol/L)	5.6 (1.1)	5.9 (1.0)*	5.6 (1.2)	6.0 (1.0)*	5.4 (1.1)	5.9 (1.1)*	6.0 (1.1)	5.6 (1.1)*	5.6 (1.1)
Lipid-lowering medication (%)	4.6	20*	2.2	11*	1.1	6.3*	4.4	6.7	3.9
Glucose (mmol/L)	4.7 (1.0)	5.4 (1.5)*	4.6 (0.9)	5.1 (1.2)*	4.6 (0.8)	5.2 (1.5)	4.7 (0.9)	5.0 (1.2)*	4.6 (0.9)
Glucose-lowering medication (%)	1.1	7.5*	0.1	2.8*	0.2	3.6*	0.8	2.0*	0.7
Uric acid (mmol/L)	0.30 (0.08)	0.34 (0.09)*	0.29 (0.08)	0.32 (0.08)*	0.29 (0.07)	0.33 (0.09)*	0.29 (0.08)	0.31 (0.09)*	0.29 (0.08)
eGFR (mL/min/1.73 m ²)	80 (14)	74 (14)*	81 (14)	74 (13)*	84 (13)	78 (16)*	81 (14)	81 (15)	80 (14)
UAC (mg/L)	5.7 (3.4–9.9)	6.7 (3.7–13)*	5.6 (3.3–9.4)	5.9 (3.3–11)*	5.6 (3.4–9.1)	32 (24–62)*	5.3 (3.2–8.2)	14 (12–24)*	4.5 (2.9–6.4)

Mean (SD), median (interquartile range). NIDDM, non-insulin-dependent diabetes mellitus; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; UAC, urinary albumin concentration; CKD, chronic kidney disease; CV, cardiovascular; DM, diabetes mellitus.

**P* < 0.05 compared to those with that screening criterion absent.

divided by the total number of negative test results. The positive likelihood ratio was defined as sensitivity divided by 1 – specificity; the negative likelihood ratio was defined as 1 – sensitivity divided by specificity. Number needed to screen was defined as the number of subjects that participated in the actual screening approach divided by the number of subjects that were detected with CKD.

Cox proportional hazards analysis was used to calculate the hazard ratio (HR) and 95% confidence interval (95% CI) for CV events. Linear regression analysis was used to obtain the age- and sex-adjusted rate of eGFR decline. The purpose of the present study is to evaluate the yield of different screening approaches. When evaluating prognostic factors for a screening test, a causal association between the prognostic factor and outcome is not necessary. Consequently, adjustment for confounders is not needed [16]. However, adjustment for age and sex was incorporated, since age and sex are non-modifiable variables and are, therefore, not eligible for intervention.

Results

Baseline characteristics of the study population are shown in Table 1. A flowchart of the follow-up of the study cohort is shown in Figure 1. The characteristics of the subjects that would be selected by a certain screening approach ('present') are compared with the characteristics of those who would not be selected by that same approach ('absent'). In general, the subjects selected by the four screening approaches are older, more often male, have higher BP, higher cholesterol and higher glucose levels when compared to non-selected subjects. Subjects selected by Approaches 1 (CV risk factors) and 2 (CV risk factors

or age >55 years) are, on average, older than subjects selected by Approaches 3 (UAC ≥20 mg/L) and 4 (UAC ≥10 mg/L), they more often use BP- and lipid-lowering medication, have lower baseline eGFR and lower UAC.

In total, 370 patients appeared to have CKD at the first screening round, with 47 (13%) patients having Stage 1 CKD, 139 (38%) Stage 2, 183 (49%) Stage 3 and 1 (0.3%) Stage 4. Figure 2 shows how many patients with CKD were detected per screening approach, including the number needed to screen to find one case of CKD (Figure 2, cross-sectional data). Approach 1 (CV risk factors) detected the lowest number of CKD patients (*n* = 104), whereas Approach 2 (CV risk factors or age >55 years) detected the highest number of CKD patients (*n* = 240), which was 65% of the total number of CKD patients (*n* = 370). However, applying Approach 2 also results in the highest number of subjects that need to be screened, namely, 33% of the total population of 3398 subjects, resulting in a number needed to screen to identify one patient with CKD of 4.6. Approach 3 (UAC ≥20 mg/L) results in the lowest number needed to screen compared to the other approaches, but leaves more than half of the CKD patients undetected. Approach 4 (UAC ≥10) yields a lower number needed to screen compared to Approach 2, but still detects the majority of CKD patients.

Table 2 shows the characteristics of the CKD patients, comparing those who were detected ('true positives') by

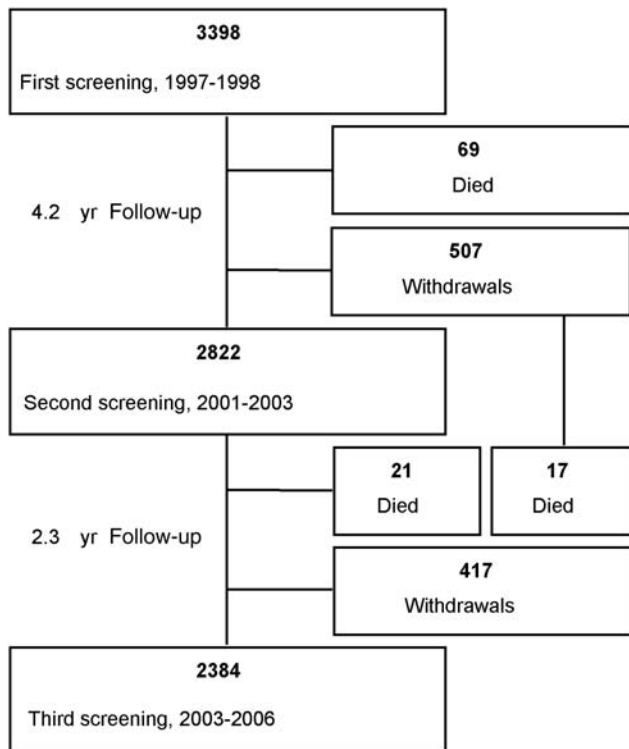


Fig. 1. Flowchart of the study cohort.

the different screening approaches with those who were left undetected ('false negatives') by that approach. CKD patients who were detected by Approaches 1 or 2 were older, had lower baseline eGFR and were more often treated with antihypertensive medication than the subjects with

CKD that are detected by Approaches 3 and 4: 83% of CKD patients detected by Approach 1 received BP-lowering medication *versus* ~28% of CKD patients detected by elevated levels of UAC. Patients detected by Approach 1 and used angiotensin-converting enzyme inhibitors (ACEis)/angiotensin receptor blockers (ARBs) three times more often compared to patients detected by Approach 3 or 4.

The screening approach test characteristics to detect CKD at baseline are shown for the four different screening approaches in Table 3. In accordance with the results described above, Approach 2 has the highest sensitivity, whereas Approach 3 has the highest specificity. This latter approach stands out with its likelihood ratio for a positive test of 10.08 and its positive predictive value of 55%.

Figure 1 shows that ~70% of the study subjects still participated in the third screening ($n = 2384$). Figures 3 and 4 show the outcome of the CKD patients during follow-up, separated for CKD subjects that would have been detected and CKD subjects that would not have been detected by the different screening approaches. Follow-up for incidence of CV events ($n = 186$) in the overall population was 7.3 ± 1.5 years. No differences were observed in duration of follow-up between the various groups. The cumulative incidence of CV events during follow-up in the CKD subjects that were detected per risk group were 21% (=22/104) in the CV risk group (Approach 1), 19% (=46/240) in the CV risk or age >55 years group (Approach 2), 23% (=34/149) in the UAC ≥ 20 mg/L group (Approach 3) and 20% (=43/216) in the UAC ≥ 10 mg/L group (Approach 4), whereas the cumulative incidence of CV events in subjects without CKD was 4.4% (=133/3028) during follow-up. The age- and sex-adjusted HRs for a CV event for CKD subjects that were detected *versus* those who were not detected are shown in Figure 3 for which subjects

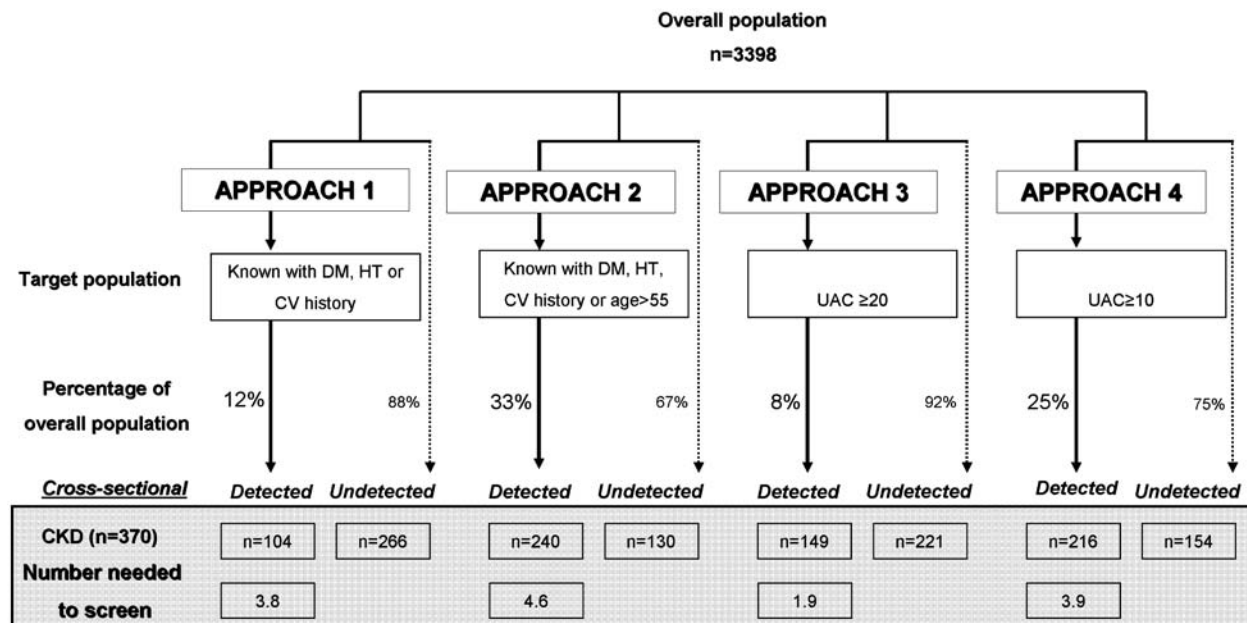


Fig. 2. Cross-sectional and longitudinal outcome of different screening approaches; *P < 0.05 compared to no CKD.

Table 2. Comparison of the characteristics of CKD patients that were detected ('true positives') by each screening approach *versus* those who were left undetected ('false negatives')

	Screening approaches								
	All (n = 370)	Screening Approach 1: CV risk		Screening Approach 2: CV risk or age >55 years		Screening Approach 3: UAC ≥20 mg/L		Screening Approach 4: UAC ≥10 mg/L	
		Present (n = 104)	Absent (n = 266)	Present (n = 240)	Absent (n = 130)	Present (n = 149)	Absent (n = 221)	Present (n = 216)	Absent (n = 154)
Age (years)	58 (12)	65 (59–70)*	56 (46–68)	66 (61–70)*	46 (39–51)	59 (48–68)	62 (50–69)	59 (48–69)	57 (54–59)
Male (%)	44	56*	39	48*	33	63*	31	58*	24
Hypertension (%)	22	74*	2.3	34*	0.8	22	23	20	25
NIDDM (%)	1.6	5.8*	0	2.5	0	3.4*	0.5	2.3	0.6
CVD history (%)	36	28*	2.6	15*	0	11.4	8.6	12	6.5
Smoking (%)	35	23*	39	29*	45	44*	28	41*	26.0
BMI (kg/m ²)	27 (4.5)	28 (3.9)	27 (4.6)	28 (3.9)*	27 (5.2)	28 (4.8)*	27 (4.2)	28 (4.6)*	27 (4)
SBP (mmHg)	140 (22)	146 (21)*	137 (22)	146 (21)*	128 (19)	146 (22)*	135 (21)	143 (22)*	134 (21)
DBP (mmHg)	77 (8)	79 (9)*	77 (10)	79 (9)*	75 (10)	80 (10)*	75 (9)	80 (10)*	74 (9)
BP-lowering medication (%)	31	83*	7.7	43*	5.7	29	32	28	34
ACEi/ARB (%)	12	35*	1.4	18*	0	10	12.6	10	12
Cholesterol (mmol/L)	6.0 (1.1)	5.9 (1.0)	6.0 (1.2)	6.1 (1.1)*	5.8 (1.2)	6.1 (1.1)	5.9 (1.1)	6.0 (1.1)	6.0 (1.1)
Lipid-lowering medication (%)	11	26*	4.5	16*	1.9	7.9	13	9.7	13
Glucose (mmol/L)	5.1 (1.4)	5.3 (1.1)	5.1 (1.4)	5.2 (1.1)	5.1 (1.7)	5.5 (1.6)*	4.9 (1.1)	5.4 (1.6)*	4.7 (0.7)
Glucose-lowering medication (%)	2.2	7.2*	0	3.3	0	3.9	1.1	3.2	0.8
eGFR (mL/min/1.73 m ²)	68 (17)	59 (54–69)*	64 (56–84)	59 (54–70)*	78 (59–90)	76 (62–87)*	58 (55–69)	75 (60–87)*	57 (54–59)
eGFR <60 mL/min/1.73 m ² (%)	184 (50)	59 (57)	125 (50)	143 (60)	41 (32)	32 (22)	152 (69)	54 (25)	130 (84)
UAE (mg/24 h)	35 (8.2–68)	34 (7.2–79)	36 (8.9–63)	33 (7.7–65)	41 (11–70)	71 (43–142)*	5.8 (11–35)	53 (37–94)*	5.2 (7.4–13)
UAE ≥30 mg/24 h (%)	59	56	61	53	72	96	34	89	17

Mean (SD), median (interquartile range). ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; UAE, urinary albumin excretion; CV, cardiovascular; DM, diabetes mellitus.

*P < 0.05 compared to those with that screening criterion absent.

with no CKD were used as reference. Figure 3 illustrates that the approach that detects most CKD patients (Approach 2) does not detect the patients at highest CV risk. Although the absolute number of CV events during follow-up is highest in the group selected by Approach 2 (Figure 2), the group that was left undetected by this approach had even a higher risk of CV events, after adjustment for age and sex, than those who were detected (HR = 2.2 *versus* HR = 1.8, P = NS). In contrast, the patients who were undetected by Approaches 3 and 4 are not at increased risk of CV events when compared to subjects without CKD (HR = 1.2 and HR = 0.9, respectively).

The decline in eGFR for those with no CKD was, on average, -0.4 ± 1.6 mL/min/1.73 m²/year. Only CKD patients detected by both UAC approaches (UAC ≥20 and UAC ≥10) had a rate of eGFR loss that differed significantly from those with no CKD (P = 0.001 and P = 0.008, respectively; Figure 4). Although pre-screening on UAC ≥20 leaves more than half of the CKD patients undetected (as shown in Figure 2), Figure 4 shows that these subjects are not at increased risk of renal function loss and even have a mean rate of GFR loss that is less than those without CKD (-0.1 mL/min/1.73 m²/year, P = 0.005). The same holds true for CKD subjects who are undetected by the UAC ≥10 approach (eGFR, 0.1 mL/min/1.73 m²/year; P < 0.001). CKD subjects detected by Approaches 1 and 2 had a rate of eGFR loss that was not different from those

who were undetected (P = 0.10 and P = 0.28, respectively). Of note, the rate of eGFR loss did not change after adjustment for age and sex.

A sensitivity analysis has been performed for the risk of CV events and rate of renal function loss during follow-up, which included only patients who did not use antihypertensive medication at baseline. This did not essentially change the results.

Discussion

The present study has compared different approaches to screen for CKD on their ability to detect CKD patients, who are not yet treated for CKD and are thereby eligible for intervention, and who are at increased risk of CKD-associated adverse events. The 'CV risk or age >55 years' approach detects most patients with CKD but had the disadvantages of yielding the largest number needed to screen, not detecting those CKD patients who were at increased risk of renal function loss during follow-up and leaving CKD patients at increased risk of CV events undetected. In contrast, the UAC ≥20 approach yielded the lowest number needed to screen, with the majority of CKD patients detected by this approach not being on antihypertensive/ACE-inhibiting medication yet. CKD patients detected by either UAC approach were at increased risk of

Table 3. Screening approach test characteristics to detect CKD

	Approach 1: CV risk	Approach 2: CV risk or age >55 years	Approach 3: UAC ≥ 20 mg/L	Approach 4: UAC ≥ 10 mg/L
Sensitivity (%)	28	65	40	58
Specificity (%)	90	71	96	81
Positive predictive value (%)	26	22	55	28
Negative predictive value (%)	91	94	93	94
Likelihood ratio positive test	2.95	2.25	10.08	3.12
Likelihood ratio negative test	0.79	0.49	0.62	0.51

UAC, urinary albumin concentration; CV, cardiovascular.

CV events and had a significantly increased rate of renal function loss during follow-up, whereas CKD patients that remain undetected were not at increased risk of such events.

Previous studies evaluating the detection of CKD by screening high-risk groups are the HUNT II study, the KEEP programme and the PolNef study [10,17,18]. The latter two do not have data available on how many CKD patients are missed by these approaches and they have not shown follow-up data. We can only compare our findings to the HUNT II study by Hallan *et al.*, which shows us how many CKD patients (eGFR < 60 mL/min/1.73 m²) are missed by their approach (subjects with age ≥ 55 years or a history of DM or hypertension are screened): only 7% of CKD patients is left undetected. In contrast, the result of the present study shows that 35% of CKD patients are left undetected by this approach, partly explained by the inclusion of Stages 1 and 2 CKD in the present study, as opposed to the study by Hallan *et al.* When we use the same definition of CKD, being an eGFR < 60 mL/min/1.73 m², 22% is left undetected by this approach in the present study.

The present study has shown that, although the UAC pre-screening approaches do not detect the most CKD patients, these approaches are the only approaches which

detect CKD patients who are both at increased renal and CV risk. A combined approach, for example, Approach 2 with Approach 3 or 4, meaning that only high CV risk subjects are pre-screened for urinary albumin level, could be an interesting approach to investigate in future studies.

Furthermore, it appeared that Approach 3 could be the most efficient screening approach, reflected by the lowest number needed to screen, meaning that the lowest number of subjects had to undergo actual screening to find one case of CKD. One might argue that the whole population is actually screened because of the pre-screening, which was done by receiving and returning questionnaires and a urine collection device by post. Given that the present study evaluates a population-screening approach, identifying high-risk groups is necessary to be able to invite these high-risk subjects for actual screening. Both the pre-screening by questionnaire (to identify subjects with known hypertension, known diabetes, a CV disease history and/or age ≥ 55 years) and the pre-screening based on UAC are relatively low in cost and not a burden to participants. Therefore, these pre-screening procedures should not be regarded as part of the actual screening itself. In line with this, the number needed to screen is based on the number of subjects participating in actual screening, not pre-screening.

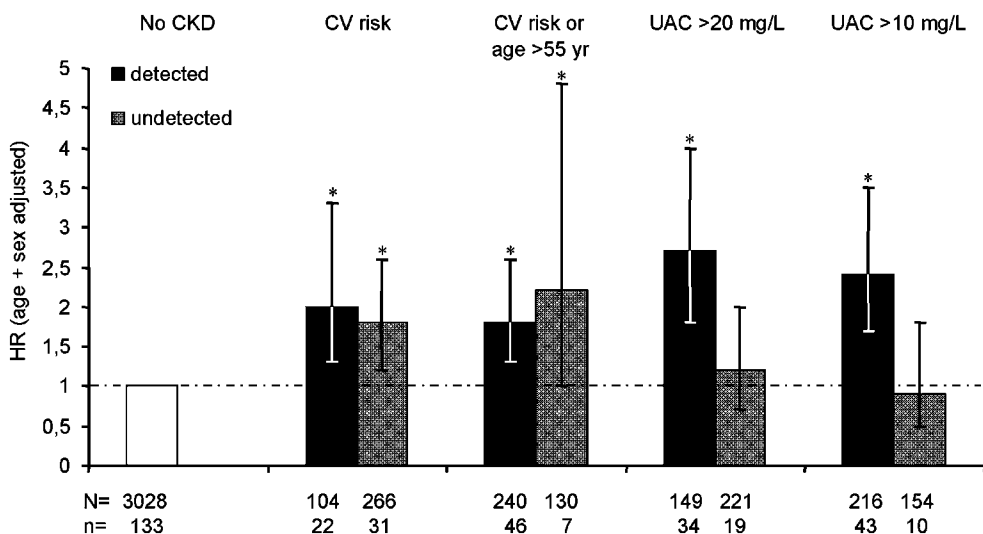


Fig. 3. Age- and sex-adjusted hazard rates (with 95% CI) for CV events in patients without CKD at baseline (open bar) and in those CKD patients that are detected (black bars) or not detected (grey bars) per screening approach; *P < 0.05 compared to no CKD.

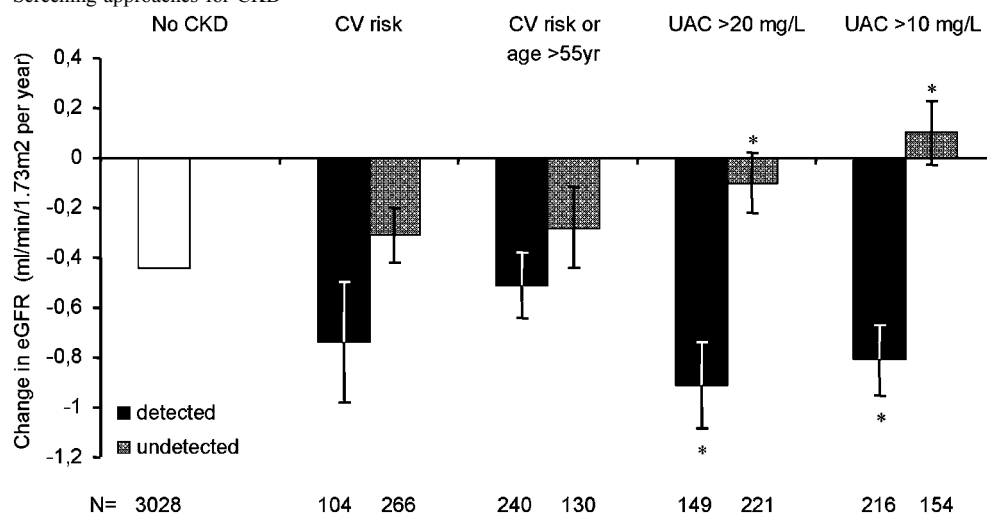


Fig. 4. Rate of renal function decline during follow-up in patients without CKD at baseline (open bar) and in those CKD patients that are detected (black bars) or not detected (grey bars) per screening approach (with 95% CI); * $P < 0.05$ compared to no CKD.

Some may argue that it seems circular to use albuminuria as a potential pre-screener when albuminuria is also part of the definition of the outcome measure, being CKD. However, urinary albumin levels for pre-screening are measured in a different way than the albuminuria measure that is used to define the outcome variable CKD. At pre-screening, a relatively simple, inexpensive and non-invasive method was used by obtaining a first morning void urine sample that was collected at home and sent to a central laboratory by post. For the actual screening, UAE was measured in two 24-h urine collections, which is considered to be the gold standard of assessing albuminuria.

The four screening approaches have been compared with respect to their yield to detect subjects with CKD, with CKD being defined according to the present K/DOQI guidelines. Of note, these guidelines are under debate [19]. It has especially been under discussion whether subjects with Stage 3 CKD, but without the presence of elevated levels of albuminuria, should be considered to have CKD. The findings of our study form an additional argument for including albuminuria in the classification of CKD.

An important feature of the screening approaches is that it should detect patients which are eligible for intervention. In a recent editorial, concerns were expressed with regard to limiting screening to subjects with known hypertension, known DM and/or a CV disease history because these patients often already receive medical treatment [20]. This concern is supported by our data. When patients who do not receive BP-lowering medication are considered to be eligible for intervention, only 17% of CKD patients detected by Approach 1 is eligible for intervention, compared to 57% detected by Approach 2 and 71% versus 72% for Approaches 3 and 4, respectively. Again, this information favours pre-screening for albuminuria instead of screening patients at high CV risk and/or age >55 years to identify subjects with CKD.

Whether pre-screening for UAC levels will serve its ultimate goal, i.e. reducing the number of people with progressive kidney disease and its associated comorbidities, depends on more factors. A number of criteria have to

be fulfilled in order for a screening programme to be of benefit [21–24]. One of them is that there should be a screening test available, which makes a clear distinction between those at high risk of CKD and those at low risk. The present study shows that Approach 2 (CV risk or age >55 years) had the highest sensitivity and Approach 3 (UAC ≥ 20 mg/L) had the highest specificity (Table 2). Interpretation of these results depends on the importance of the occurrence of false-positive and false-negative tests. Since it has been shown that CKD patients who are not detected by the UAC approaches (= false negative) are not at increased risk of progressive renal disease nor at increased CV risk, it seems not so important that the sensitivity of Approach 3 is lower than Approach 2.

Another important criterion for a successful screening programme is the availability of appropriate treatment to prevent or delay the onset of disease. Although it is well accepted that the cornerstones of treatment of CKD are reducing BP and reducing albuminuria, especially with ACEis and/or ARBs [25], these studies have all been performed in patients with known advanced CKD and not in subjects detected by screening. Efficacy of treatment in subjects detected by screening has to be investigated in future studies, which should also investigate the cost-effectiveness of the screening programme and consequent treatment. Of note, a recent study has shown that, when taking into account all personnel, laboratory and overhead costs (including pre-screening on albuminuria) and the costs of subsequent treatment with an ACEi, pre-screening on albuminuria is cost-effective in the prevention of CV events [26,27].

The present study is an observational study. Therefore, the outcome during follow-up of the subjects detected by the different screening approaches should be regarded as their natural courses. We can only assume that, if the patients would be optimally treated after detection, it would be of benefit to them and decrease the risk of adverse outcomes. For the same reason, it is hard to estimate at what time interval screening should be repeated. However, Brantsma *et al.* suggested that screening for albuminuria

should be repeated every 5 years, based on its prognostic value for CV events [28].

The limitations of the present study are that this study population may not be representative of populations in other countries since 95% of the study population is of the Caucasian race and since the prevalence of NIDDM was low, although consistent with other national reports at the time of start of the first screening [29]. On the other hand, although there are racial differences, the current study population had, for example, a mean decline in eGFR that was comparable to the Japanese population [30]. Furthermore, pre-screening by collecting a first morning urine void at home, pouring it in a tube and sending it by post to a central laboratory may not be easy to achieve in some areas. In that case, it can be preferred to invite the subjects to an outpatient clinic and deliver a urine sample there, which would limit the benefits of pre-screening. Furthermore, the present study has been performed in subjects who volunteered to participate in the PREVEND study. People who volunteer for screening programmes are usually healthier than people who do not want to participate, which may lead to selection bias. The outcomes that are reported by this study, being the number of CKD patients detected, the risk of CV events and the rate of renal function loss, are, therefore, likely to be underestimated. The same is true for loss to follow-up, which is most likely higher among higher-risk groups. Of note, one has to realize that, when screening programmes are implemented, a certain group of subjects will always decline participation. Our findings reflect, therefore, the real-life situation. Furthermore, since we compared four screening approaches among the same study population, non-participation bias will influence all screening approaches to the same extent and will, therefore, not influence our results. To increase the yield of CKD screening, strategies should be developed that try to increase participation rates, especially under higher-risk groups, such as subjects with lower socio-economic status.

Conclusion

In conclusion, pre-screening by UAC level was the most efficient screening approach to detect CKD patients and also the only screening approach that detected CKD patients with increased risk of CV disease and renal function loss during follow-up, compared to subjects without CKD. CKD patients that were left undetected by this approach were not at increased risk of adverse events during follow-up. Also, only a minority of CKD patients detected by pre-screening on a UAC level was treated with BP-lowering medication (including ACEi) and, therefore, most CKD patients detected by this approach were still eligible for intervention. Thus, the results of this study suggest that pre-screening on UAC should be favoured in comparison to screening based on demographic and CKD risk factors to detect CKD patients at high renal and CV risk.

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Conflict of interest statement. None declared.

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