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ADDED VALUE OF SCREENING FOR CHRONIC KIDNEY DISEASE AMONG ELDERLY OR PERSONS WITH LOW SOCIOECONOMIC STATUS

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Abstract

We compared three screening approaches on their ability to detect chronic kidney disease (CKD) cases, and to identify those CKD cases that have higher rate of incident cardiovascular disease (CVD) events and renal function decline. Approach 1 was the traditional CKD screening approach, targeting only persons with known diabetes mellitus, hypertension or CVD history. Approach 2 was defined as Approach 1 + elderly, and Approach 3, as Approach 1 + subjects with low SES. A prospective cohort of 3,411 subjects from the general population in the Netherlands was examined. Subjects aged >60 years were classified as elderly. SES was assessed based on educational level and classified as low, medium and high. CKD was diagnosed during examination at an outpatient clinic. Subjects were followed for 9.4 ± 2.6 years during 4 screening rounds. At baseline, 16%, 29%, and 25% of the general population was to be screened and 36%, 59%, and 51% of the CKD (n=263) cases were detected in Approaches 1, 2 and 3, respectively. The numbers of subjects needed to screen to detect one CKD case were nearly similar in all 3 approaches. In Approach 2 the rate of incident CVD events was significantly higher in detected as well as in undetected CKD cases compared to subjects without CKD, whereas in Approach 3 this rate was only significantly higher in detected CKD cases. The rate of decline in renal function was significantly higher in detected and undetected CKD cases compared to non-CKD subjects in Approach 2 and Approach 3, and tended to be higher in detected than undetected cases in both approaches. Adding persons with low SES, rather than adding elderly, to the traditional high risk groups may be of help for detecting more CKD cases that have a higher rate of, both, future CVD events and renal function decline.

INTRODUCTION

Chronic kidney disease (CKD) is a major public health problem. The prevalence of CKD is relatively high, and estimated to be around 10%-13% on a population level. Even mildly impaired kidney function and elevated albuminuria are associated with cardiovascular morbidity and mortality and with progression to end-stage renal disease (1, 2). Moreover, the costs of CKD management have increased substantially (3). As CKD often lacks symptoms in the early stages, the diagnosis is often delayed (4). Detection of CKD in earlier stages provides opportunities to start early treatment, thereby slowing the progression of CKD and reducing the incidence of cardiovascular complications.

For CKD detection, screening of selected high-risk groups is advised. The traditional CKD screening approach (as advocated in the Kidney Disease Improving Global Outcomes guidelines) recommends screening of patients with known hypertension, diabetes mellitus or a cardiovascular disease (CVD) history (5). When adopting such an approach still a large number of CKD cases remain undiagnosed. Therefore, adding other risk groups, such as elderly (>60 years), has been advised (6). Several studies have also shown an increased risk of CKD in subjects with low socioeconomic status (SES) and suggested screening for CKD among low SES groups (7-11). To date, however, it is not known whether adding elderly or subjects with low SES to the traditional CKD screening approach is effective with respect to their ability to detect CKD patients at risk for adverse health outcomes.

We hypothesized that adding elderly or subjects with low SES would increase the yield of screening when compared to the traditional screening approach. In this study we investigated therefore three screening approaches: Approach 1, the traditional approach, i.e. screening subjects with known diabetes mellitus, hypertension or CVD history; Approach 2, screening based on the traditional approach and additionally subjects older than 60 years; and Approach 3, screening based on the traditional approach and additionally subjects with low SES. SES was defined by educational level, because we previously found that low education has a stronger association with CKD in the Netherlands than low income (12). These screening approaches are compared regarding their ability to detect CKD cases. Furthermore, for each screening approach, the rate of incident CVD events and renal function decline during follow-up is assessed in detected and undetected CKD cases; to determine which screening approach best detects the CKD patients at risk for adverse health outcomes.

MATERIALS AND METHODS

Study design and population

For the present analyses data were used of Prevention of Renal and Vascular ENd-stage Disease (PREVEND) study participants. PREVEND is a prospective, observational cohort study designed to investigate the association of albuminuria with renal and cardiovascular outcomes in the general population. The PREVEND study comprised 8,592 community dwelling subjects and is enriched for subjects with higher albuminuria. This design may affect the findings of the different screening approaches. Therefore, a sub-cohort of the overall PREVEND cohort was used that is representative of the general population (n=3,432). Formation and characteristics of this sub-cohort have been reported in detail elsewhere (12). In the present study, 21 subjects with incomplete information on CKD status at baseline were excluded, leaving 3,411 subjects for analysis.

The PREVEND study was approved by the medical ethics committee of the University Medical Center Groningen and is conducted in accordance with the guidelines of the Declaration of Helsinki.

Measurements

The baseline screening of the PREVEND cohort took place in 1997-1998. Thereafter all subjects were invited for serial follow-up screenings with approximately 3 year intervals. During each screening round, subjects visited an outpatient clinic twice. Information on demographics, renal and cardiovascular disease history, and use of blood pressure, glucose and lipid lowering drugs was obtained by questionnaire and from pharmacy records (98% coverage). During the physical examination, weight and height were measured. Body mass index was calculated as weight divided by the square of height. Blood pressure was measured on both visits in supine position on the right arm every minute for 10 min, with an automatic Dinamap XL model 9300 series monitor (Johnson-Johnson Medical Inc., Tampa, FL, USA). Blood pressure was calculated as the mean of the last two measurements at both occasions. In addition, subjects collected two 24h urine samples for assessment of albuminuria, and fasting blood samples were obtained for measurement of creatinine, cystatin C, cholesterol and glucose on a Roche autoanalyzer. Serum creatinine was measured by an enzymatic method (Eastman Kodak, Rochester, NY, USA; IDMS traceable; intra- and interassay coefficient of variation (COV) 2.2% and 2.6%, respectively), serum cystatin C by a PETIA assay (Gentian, Moss, Norway; IFCC traceable; intra-and interassay COV 1.7 - 2.2% and 1.7 - 3.5%, respectively) and urinary albumin concentration by nephelometry (BNII; Dade Behring Diagnostic, Marburg, Germany, intra- and interassay COV less than 2.2% and 2.6%, respectively).

Diabetes, hypertension and cardiovascular disease history

Diabetes and hypertension were considered to be known when subjects used glucose or blood pressure lowering medication as per self-report or based on pharmacy records. Unknown diabetes was defined as a fasting glucose ≥126 mg/dL without use of glucose lowering medication in accordance with the American Diabetes Association criteria (13) and unknown hypertension as a systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg without use of blood pressure lowering medication in accordance with the JNC7 Criteria (14). Information on CVD history was obtained from questionnaires and defined as a previous hospital admission for a cardiovascular or cerebrovascular event.

Socioeconomic status (SES)

SES was defined by information on educational level, that was obtained from questionnaires at baseline as high (bachelor, master or doctorate graduate), medium (secondary education or non-tertiary or short-cycle tertiary education) and low (primary or below primary education). The high, middle and low educational levels are further denoted as the high, medium and low SES groups, respectively.

Chronic kidney disease (CKD)

CKD was defined as estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 or Urinary albumin excretion (UAE) ≥30 mg/24-hr or both (15). GFR was estimated involving both serum creatinine and cystatin C with the recently recommended CKD-EPI equation (16). Albuminuria was expressed as the average UAE in two 24hr urine samples.

Cardiovascular and renal outcomes at follow-up

During follow-up, information was obtained on CVD and renal outcome. CVD endpoints were defined as incidence of fatal and non-fatal myocardial infarction, stroke, ischemic heart disease, revascularization procedures or cardiovascular mortality or hospitalization. Data for mortality and cause of death were received from the Dutch Central Bureau for Statistics. Information for hospitalization for cardiovascular morbidity was obtained from Prismant (Utrecht, the Netherlands), the Dutch national registry of hospital discharge diagnoses. All data were coded according to the International Classification of Diseases, 10th Revision and the classification of interventions. As renal outcome, we used change in renal function per year, which was estimated by the slope of a linear regression line, fitted between the two or more serial eGFR values obtained over time using the least squares principle.

Statistical analysis

Continuous variables are presented as means ± standard deviations in case of a normal distribution or medians (interquartile ranges) in case of a skewed distribution. Categorical variables are presented as percentages. Comparison across groups was made for continuous variables using Student's t-test or Mann-Whitney's test (in case of skewed distribution), and for categorical variables using a Chi-square test.

To evaluate the yield of three screening approaches we calculated for each screening approach, first, the proportion of the overall population required screening, second, the proportion of CKD cases identified and, third, the number of subjects needed to screen to detected one CKD case. In addition, we evaluated detected and undetected CKD cases in each screening approach for incident CVD events and renal function decline during follow-up. Cox proportional hazard analysis, adjusted for age and gender, was used to calculate risk for incident CVD events. Survival time was defined as the period from the date of the baseline screening to the date of first CVD event or 1 January 2009 (end of follow-up). Subjects were censored in case of death other than CVD related, or when having moved to an unknown destination. Multilevel linear regression analysis was used to obtain the age and gender adjusted rate of eGFR decline which takes variance of individual slopes of renal function change into account.

In additional analyses we examined whether the yield of adding elderly and low SES subjects together is better than adding them individually, to the traditional CKD screening approach. To test whether the yield of additional screening would depend on the SES measure, we repeated the analyses using income as indicator of SES. Low income was defined as the lowest quintile of the Poverty Income Ratio (PIR) (12). The PIR is calculated by dividing family income by the poverty threshold income specific for family size and year, as provided by the Netherlands Institute for Social Research (18).

RESULTS

Baseline characteristics

Table 1 shows the baseline characteristics of the overall population and of subjects selected to be screened and not to be screened per screening approach. In all three screening approaches, subjects to be screened were older, had higher BMI and higher total blood cholesterol levels compared to subjects not selected for screening. The prevalence of unknown hypertension was higher in subjects to be screened in Approaches 2 and 3 than in subjects identified for screening in Approach 1. In all three screening approaches, baseline eGFR was lower and UAE higher in subjects selected for screening when compared to subjects not selected for screening.

Table 1 | **Baseline characteristics of the overall study population and of subjects to be screened and not to be screened per screening approach**

		Screening approaches								
	All	**Approach 1** (CVD risk) Selected for screening			**Approach 2** (CVD risk or age>60 yr) Selected for screening			**Approach 3** (CVD risk or low SES) Selected for screening		
	N=3,411	Yes 527 (15)	No 2,884 (85)	p	Yes 978 (29)	No 2,433 (71)	p	Yes 855(25)	No 2,556 (75)	p
Age (years)	49 ± 12	59 ± 11	47 ± 12	<0.001	63 ± 9.0	43 ± 8.4	<0.001	58 ± 11	46 ± 11	<0.001
Male (%)	45	47	45	0.39	47	45	0.27	44	46	0.38
Caucasian (%)	95	94	95	0.53	96	95	0.25	95	95	0.75
BMI (kg/m^2)	26 ± 4.1	28 ± 4.2	25 ± 3.9	<0.001	28 ± 4.1	25 ± 3.9	<0.001	28 ± 4.3	25 ± 3.8	<0.001
Cholesterol (mmol/L)	5.6 ± 1.1	5.8 ± 1.0	5.6 ± 1.1	<0.001	6.0 ± 1.0	5.5 ± 1.1	<0.001	5.9 ± 1.1	5.5 ± 1.1	<0.001
Smoking (%)	35	27	36	<0.001	27	38	<0.001	34	35	<0.001
Known										
- Hypertension (%)	13	84	0.0	<0.001	45	0.0	<0.001	52	0.0	<0.001
- Diabetes Mellitus (%)	1.1	7.4	0.0	<0.001	4.0	0.0	<0.001	4.6	0.0	<0.001
- CVD history (%)	4.2	27	0.0	<0.001	15	0.0	<0.001	17	0.0	<0.001
Unknown										
- Hypertension (%)	16	5.7	18	<0.001	22	13	<0.001	16	14	0.16
- Diabetes Mellitus (%)	3.4	8.2	2.5	<0.001	6.5	2.1	<0.001	6.2	2.2	<0.001
eGFR (mL/min/1.73 m^2)	96 ± 16	85 ± 17	97 ± 15	<0.001	84 ± 15	100 ± 14	<0.001	88 ± 16	98 ± 15	<0.001
UAE (mg/24 hr)	7.1 (5.4-11)	8.5 (5.7-17)	6.9 (5.4-10)	<0.001	8.1 (5.7-15)	6.9 (5.4-10)	<0.001	8.4 (5.5-16)	6.9 (5.4-10)	<0.001

Normally distributed variables are presented as mean ± standard deviation. Skewed variables are presented as median (interquartile range). Categorical variables are presented as percentages. p <0.05 indicate statistically significant difference between screened and not-screened subjects per screening approach.

Abbreviations are: CVD=cardiovascular disease, SES=socioeconomic status, BMI=body mass index, eGFR=estimated glomerular filtration rate and UAE=urinary albumin excretion.

Characteristics of all CKD cases and of CKD cases that were detected or undetected by the three screening approaches are given in Table 2. For each approach, CKD cases that were detected were older and had lower baseline eGFR and higher UAE than CKD cases that remained undetected. The prevalence of undiagnosed hypertension and diabetes tended to be higher in undetected than in detected CKD cases in all three screening approaches, but in undetected CKD cases lower in Approaches 2 and 3 when compared to approach 1. In Approaches 2 and 3 detected CKD cases had a higher prevalence of unknown hypertension than in Approach 1 ($p < 0.001$ and $p < 0.001$, respectively). Detected CKD cases in Approach 3 had the lowest age, and highest GFR and UAE when compared to detected CKD cases in the other two approaches, although these differences did not reach statistical significance.

The number of subjects to be screened in different screening approaches is shown in Table 1. The number of subjects to be screened was highest in Approach 2 and lowest in Approach 1. Table 2 indicates that from a total of 263 CKD cases at baseline, the proportion of CKD cases detected in screening Approach 1 was 36% (95% Confidence Interval (CI): 30% - 42%), whereas in screening Approaches 2 and 3 the proportions were 59% (95% CI: 53% - 65%) and 51% (95% CI: 44% - 56%), respectively. Compared to Approach 1, the proportion of CKD cases detected was significantly higher in Approach 2 ($p < 0.001$) and in Approach 3 ($p < 0.001$). The identified cases with CKD were predominantly defined by albuminuria ≥30mg/24hr. The proportion of CKD subjects defined by an eGFR <60 mL/min/1.73 m^2 was relatively low (Table 2). The number needed to screen to identify one CKD case was roughly similar in the three screening approaches, although this figure tended to be slightly higher in Approaches 2 and 3 when compared to Approach 1, with values of 5.6, 6.5 and 6.5, respectively.

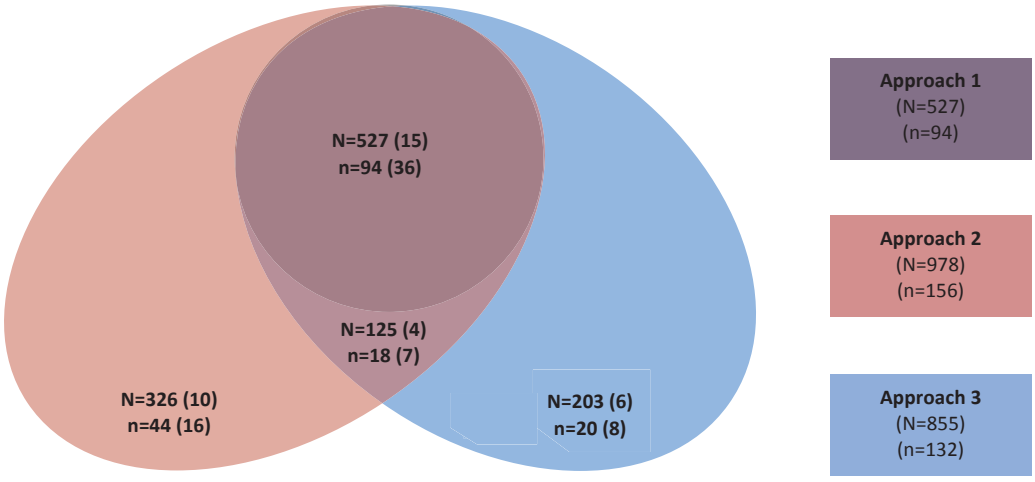
The distribution of subjects to be screened and the distribution of detected CKD cases for the three screening approaches is shown in Figure 1. 451 subjects have to be screened additionally in Approach 2 and 328 subjects in Approach 3. Of these subjects, 125 were to be screened in Approach 2 as well as Approach 3. The additional number of CKD cases identified in Approach 2 and Approach 3 was 64 and 38, respectively, of which 18 were identified by both approaches.

Table 2 | **Characteristics of all chronic kidney disease (CKD) cases and of CKD cases that were detected or undetected by the three screening approaches**

	Screening approaches								
	All	Approach 1 (CVD risk)			Approach 2 (CVD risk or age>60 yr)			Approach 3 (CVD risk or low SES)		
	N=263	Detected n=94 (36)	Undetected n=169 (64)	p	Detected n=156 (59)	Undetected n=107 (41)	p	Detected n=132 (51)	Undetected n=131 (49)	p
Age (years)	57 ± 12	64 ± 8.5	53 ± 13	<0.001	66 ± 6.8	45 ± 8.9	<0.001	63 ± 9.4	55 ± 14	<0.001
Male (%)	57	62	54	0.21	62	50	0.05	61	52	0.14
Caucasian (%)	95	95	95	0.27	95	95	0.33	95	95	0.96
BMI (kg/m^2)	28 ± 4.7	28 ± 3.9	27 ± 5.0	0.64	28 ± 4.1	27 ± 5.3	0.09	28 ± 4.4	27 ± 4.8	0.004
Cholesterol (mmol/L)	5.9 ± 1.1	5.9 ± 1.1	5.9 ± 1.1	0.74	6.0 ± 1.1	5.8 ± 1.1	0.06	5.9 ± 1.0	5.9 ± 1.2	0.86
Smoking (%)	39	25	46	0.001	30	50	0.003	35	42	0.08
Known										
- Hypertension (%)	25	68	0.0	<0.001	42	0.0	<0.001	49	0.0	<0.001
- Diabetes Mellitus (%)	2.4	6.5	0.0	0.001	4.0	0.0	0.039	4.7	0.0	0.015
- CVD history (%)	11	27	0.0	<0.001	18	0.0	<0.001	21	0.0	<0.001
Unknown										
- Hypertension (%)	35	11	48	<0.001	32	36	0.08	29	41	0.031
- Diabetes Mellitus (%)	9.7	6.4	12	0.17	6.6	14	0.048	7.6	12	0.26
eGFR (mL/min/1.73 m^2)	83 ± 22	72 ± 18	89 ± 22	<0.001	72 ± 18	97 ± 19	<0.001	75 ± 19	90 ± 22	<0.001
eGFR<60mL/min/1.73m^2(%)	27	38	18	<0.001	41	3.0	<0.001	33	18	<0.001
UAE (mg/24 hr)	48 (35-247)	60 (37-128)	55 (37-93)	0.015	58 (36-115)	56 (38–99)	<0.001	62 (37-127)	55 (37–93)	0.05
UAE ≥30 mg/24 hr (%)	83	74	88	0.19	74	92	0.039	78	87	0.21

Normally distributed variables are presented as mean ± standard deviation. Skewed variables are presented as median (interquartile range). Categorical variables are presented as percentages. p <0.05 indicate statistically significant difference between detected and undetected CKD cases by a screening approach.
Abbreviations are: CVD=cardiovascular disease, BMI=body mass index, eGFR=estimated glomerular filtration rate and UAE=urinary albumin excretion

Figure 1 | **Number, percentage and distribution of subjects to be screened for chronic kidney disease (CKD) (N) and of CKD cases (n) detected according to the three screening approaches**
(Note: Total study population=3,411 and total number of CKD cases=263)

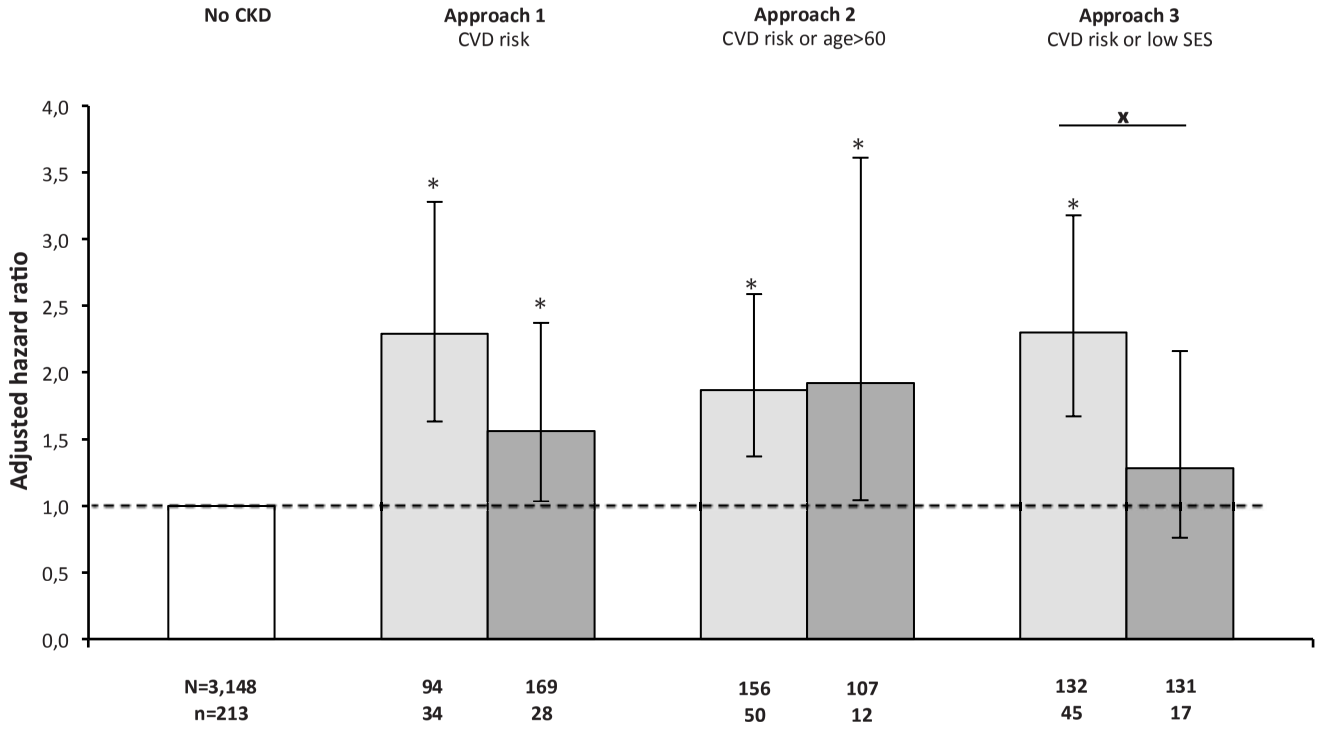


Outcomes in CKD cases

During a follow-up of 9.4 ± 2.6 years, 275 incident CVD events occurred. Figure 3 illustrates that CKD patients, detected or undetected by the different approaches, in general had a higher risk of incident CVD events when compared to non-CKD subjects of the same age and gender. Only undetected CKD cases in Approach 3 did not have a higher CVD risk when compared to non-CKD subjects. Finally, detected CKD cases had a higher risk for CVD than undetected CKD cases in Approaches 1 and 3, but not in approach 2.

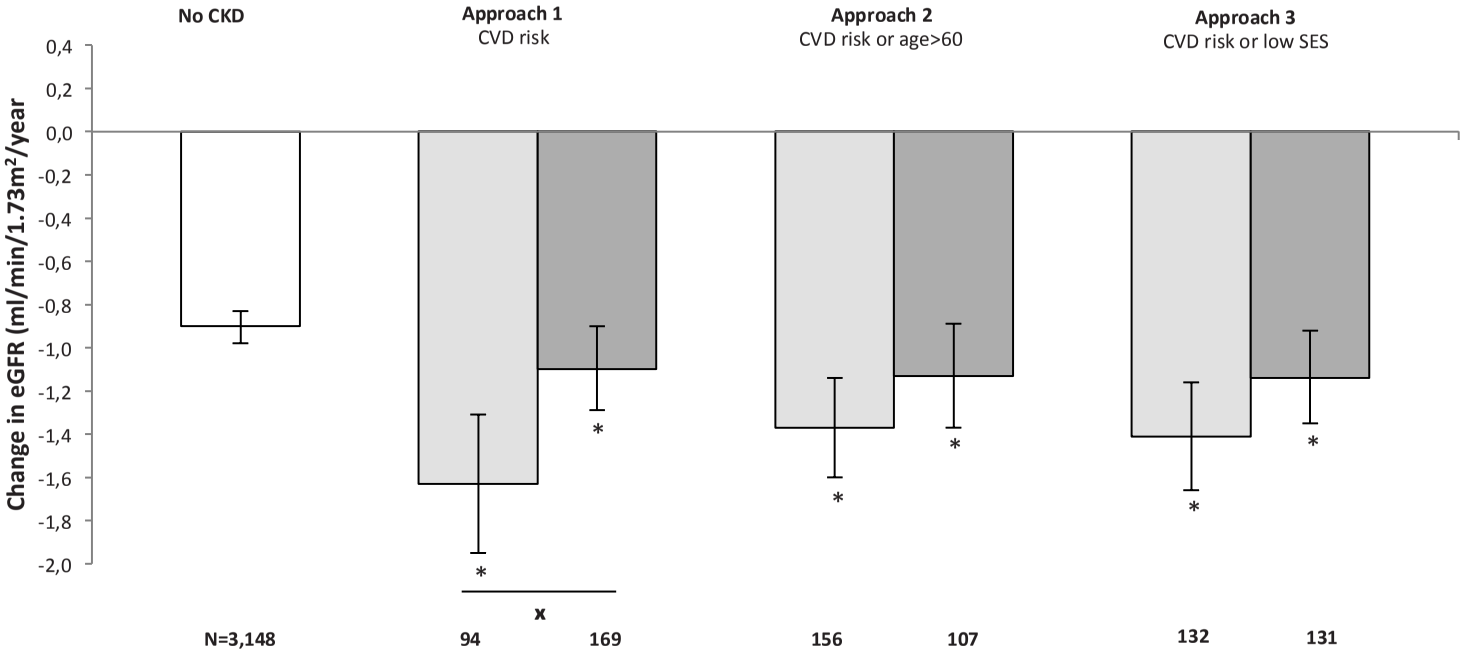
Serial follow-up with respect to eGFR was available in 80% of the overall population with on average of 3.1 eGFR measurements. In non-CKD cases these figures were 82% and 3.1, and in CKD cases 79% and 2.8, respectively. Figure 4 shows that the rate of renal function decline was significantly higher in detected and undetected CKD cases compared to non-CKD subjects in all three screening approaches. Rate of renal function decline tended to be higher in detected than undetected cases in both approaches though it did not reach statistical significance (p=0.17 and p=0.11, respectively), whereas in Approach 1 this difference achieved statistical significance (p=0.001).

Figure 2 | **Age- and gender- adjusted hazard rates (with 95% Confidence Interval) for CVD events in subjects with CKD that are detected (light grey bars) or not detected (dark grey bars) per screening approach, with subjects without CKD at baseline (white bar) as reference**



Abbreviations are: N=number of subjects; n=number of events; CVD=cardiovascular disease; CKD=chronic kidney disease, SES=socioeconomic status.
*p <0.05 indicate statically significant difference between CKD and non-CKD subjects.
[x]p <0.05 indicate statically significant difference between detected CKD and undetected CKD cases for the same approach.

Figure 3 | **Age- and gender- adjusted rates of eGFR decline (with 95% Confidence Interval) in subjects with CKD that are detected (light grey bars) or not detected (dark grey bars) per screening approach, with subjects without** CKD at baseline (white bar) as reference



Abbreviations are: N=number of subjects; CVD=cardiovascular disease; CKD=chronic kidney disease; eGFR=estimated glomerular filtration rate
*p <0.05 indicate statically significant difference between CKD and non-CKD subjects.
xp <0.05 indicate statically significant difference between detected CKD and undetected CKD cases for the same approach.

Additional analysis

Compared to the other screening approaches, adding elderly as well as subjects with low SES to be screened for CKD detected the highest percentage of CKD cases (68%), but also required the highest percentage of the overall population to be screened (35%), resulting in a number to be screened to detect 1 CKD case of 7. The results with respect to the risk for future CVD events and renal function decline were essentially similar to the results obtained in screening Approach 3 (Appendix). Compared to adding subjects with low SES defined by low education, adding subjects with low SES defined by low income to the traditional target population for CKD screening required a similar number of participants to be screened (n=872 versus n=855, respectively and p for difference=0.68), but detected less CKD cases (n=113 versus n=132, respectively and p for difference=0.048). The results with respect to the risk for future CVD events and renal function decline were essentially similar when low SES was defined on income instead of educational status (Appendix).

DISCUSSION

In this study we examined the added value of screening for CKD among elderly or subjects with low SES. Our results show that the number of subjects needed to screen to detect one CKD case were similar in both approaches and similar to the traditional approach of screening only subjects with known hypertension, known diabetes or a history of CVD. Adding persons with low SES rather than adding elderly to these traditional high risk groups detected more CKD cases that have a high risk for both future CVD events and decline in renal function.

Some earlier studies have also reported on the outcomes of CKD screening when adding elderly as risk group to the traditional CKD screening approach. One of these studies was performed using data from the same cohort as the present study, and examined CKD screening among elderly and subjects with a high urinary albumin concentration (UAC) during a prescreening (19). Results of that study favoured additional screening using the UAC based screening approach to detect CKD cases, but the problem with this approach is that a prescreening on UAC leads to extra work and costs. Another study from Norway showed that screening elderly, along with individuals of known CVD risk factors, was effective in detecting more CKD cases, but that the risk for end-stage renal disease among those detected CKD cases was low (20). The yield of adding subjects with low SES to the traditional CKD screening target populations has never been examined before.

Elderly are at high risk of developing CKD (21), and screening for CKD among elderly has been shown to be effective in detecting large numbers of CKD cases (19, 20). However, it is also known that a decline in eGFR occurs with aging (21, 22). Therefore, adding elderly to the traditional CKD

screening approach may be efficient to detect subjects with mildly impaired GFR, but at the same time may not be the most efficient approach to detect those CKD cases that are at increased risk for CKD complications. Indeed we found that adding elderly to the population to be screened identified additionally 23% of all CKD subjects present in the general population. However, these subjects were at relatively low risk for future CVD events, as can be deduced from our observation that adding these subjects led to a non-significant hazard ratio for CVD events in detected CKD cases (Figure 2).

In our study, adding subjects with low SES to the traditional target population for CKD screening led to detection of more than half of all CKD cases (51%). In addition, extending screening to include also subjects with low SES not only detected CKD cases that were at high risk for CKD related complications, but also resulted in delineating a group of undetected CKD cases with a relatively good prognosis when compared to non-detected CKD cases in the screening approach that added elderly, particularly for CVD complications. The higher percentage of smokers amongst those subjects identified by Approach 3 might be one of the reasons for a better prediction of CVD complications in this screening approach compared to the other screening approaches. Identifying a higher percentage of smokers is therefore an additional benefit of Approach 3. It should be noted that defining low SES based on low education levels might also identify more elderly people for CKD screening, because older individuals and particularly older women might be expected to have a lower educational status than younger individuals.

In an additional analysis we examined the yield of screening when adding low income individuals instead of low education individuals to the traditional target population for CKD screening. This led to essentially similar results, except that adding subjects with low education led to detection of more CKD cases than adding subjects with low income. In addition, we also examined the yield of adding elderly as well as subjects with low SES to the traditional target population for CKD screening. The number of subjects needed to screen to identify one CKD case in this approach was similar to the Approach 3 (i.e. 7 and 6.5 respectively). Although this approach also makes as good distinction with respect to prognosis among detected and undetected CKD cases as Approach 3, it seems unlikely that, given the current debate on CKD screening where there is reluctance to add new high risk groups to be screened for CKD, in the near future two risk groups will be added simultaneously for CKD screening.

In this study we found that identified CKD cases were predominantly defined based on increased albuminuria, and that these subjects in general had relatively high eGFRs. Identifying such CKD cases may be of particular interest from a screening perspective because even moderately increased albuminuria is already a marker of increased risk for mortality and adverse renal outcomes, independent of renal function (23, 24). Furthermore, intervening in subjects

with still preserved kidney function has the potential to delay renal failure more efficiently than in CKD subjects with already impaired kidney function.

Another finding in this study was that the proportion of unknown hypertension was higher in undetected than in detected CKD cases in all three screening approaches. Importantly, this difference was particularly large in the traditional CKD screening approach, offering an additional motivation to add elderly or low SES groups to the traditional high risk groups to be screened for CKD. In addition, this finding also suggests that in these high risk groups it may be worthwhile to measure not only eGFR and albuminuria, but also blood pressure. In this scenario also people identified as having hypertension could receive appropriate treatment.

Implementation of additional screening for CKD among elderly or low SES groups necessitates the collection of information on age and SES of subjects. Information on age is routinely collected and its operationalization is straightforward. Information on SES measures can also be collected relatively easy, in particular when measuring it by educational level as we did. However, SES can be defined and measured in various ways, e.g. by income, education, occupation and neighbourhood characteristics (25). We have previously shown that the optimal SES measure to identify CKD cases may vary regionally depending on circumstances such as costs of access to health care (12). Moreover, there is no established threshold to define low SES (25, 26). These considerations indicate that region-specific, careful operationalization of SES will be needed to obtain an optimal yield from a screening approach involving subjects with low SES.

Important strengths of our study are, first, that we assessed eGFR and albuminuria using the gold standards for population studies, i.e. serum creatinine and cystatin C to estimate GFR, and 24-hr urinary albumin excretion to assess albuminuria. This triple marker approach has been shown to be the most accurate in defining CKD. Second, we used an optimized SES measure (i.e. education) to define low SES. Finally, to assess future adverse health outcomes, we followed subjects for a relatively long period (almost 10 years).

Our study has also some limitations. First, the power of our study to detect differences in prognosis between detected and undetected CKD cases was relatively limited. Second, our study population may not be representative of populations of other countries, for instance populations can differ across countries socioeconomically, racially/ethnically and with respect to the prevalence of known versus unknown hypertension and diabetes mellitus. Our findings should therefore be confirmed in other populations. However, that we found in a representative sample of the Dutch population that is characterized by a relatively high average SES and a high percentage of known hypertension and diabetes, suggests that the present encouraging results may even be better in other populations. Third, subjects examined in this study were those who volunteered to participate in an observational study. Such subjects are usually healthier than people who do not participate. Therefore, there might be an underestimation of the yield of screening and of the risk for adverse outcomes that we found. However, this scenario exists

likewise for actual population screening programmes (27), and is therefore unlikely to have biased our results to a large extent.

For CKD screening, adding elderly or low SES groups to the traditional target populations for CKD screening will lead to an increase in workload for health services as the number of subjects needed to be screened increases. Moreover, the CKD cases that are detected require intervention to prevent progression of CKD and cardiovascular complications. Dedicated, comprehensive cost-effectiveness analyses are needed to assess whether the associated costs are in balance with the benefits regarding CVD and CKD events that are prevented. Our data provide important information to start such studies, as well as information for public health policy makers regarding optimisation of strategies for detecting CKD.

In conclusion, our study shows that adding subjects with low SES rather than adding elderly to the traditional target population for CKD screening might be helpful in detecting more CKD cases that have a high risk for future CVD events as well as renal function decline. Confirmation of these results in other populations and dedicated cost-effectiveness studies are needed to indicate whether screening elderly or subjects with low SES for CKD is justified.

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APPENDIX

1. The result of adding elderly and low SES individuals, together, to the traditional CKD screening approach

1 | Population screened

Number=1,181

Percentage=35

2 | CKD cases detected

Number=178

Percentage=68 (95% confidence Interval (CI): 62 - 73)

3 | Rate of incident cardiovascular disease events (age and gender adjusted)

In detected CKD cases compared to non-CKD subjects:

[Hazard Ratio (HR) =1.90, 95% CI: 1.38 - 2.62, p <0.001]

In undetected CKD cases compared to non-CKD subjects):

[HR=1.74, CI: (0.82 - 3.72), p=0.15]

P for difference between detected and undetected CKD cases (p <0.001)

4 | Rate of renal function decline (age and gender adjusted)

In detected CKD cases vs. non-CKD subjects:

-1.30 ml/min/1.73 m^2 vs. -0.90 ml/min/1.73 m^2 (p <0.001)

In undetected CKD cases vs. non-CKD subjects:

-1.18 ml/min/1.73 m^2 vs. -0.90 ml/min/1.73 m^2 (p <0.001)

P for difference between detected and undetected CKD cases (p=0.103)

2. The result of adding low SES individuals when defined using income levels, to the traditional CKD screening approach

1 | Population screened

Number=872

Percentage=26

2 | CKD cases detected

Number=113

Percentage=43 (95% CI: 37 - 49)

3 | Rate of incident cardiovascular disease events (age and gender adjusted)

In detected CKD cases compared to non-CKD subjects:

[Hazard Ratio (HR) =2.36, 95% CI: 1.64 - 3.41, p <0.001]

In undetected CKD cases compared to non-CKD subjects):

[HR=1.48, CI: (0.98 - 2.26), p=0.07]

P for difference between detected and undetected CKD cases (p=0.07)

4 | Rate of renal function decline (age and gender adjusted)

In detected CKD cases vs. non-CKD subjects:

-1.56 ml/min/1.73 m^2 vs. -0.90 ml/min/1.73 m^2 (p <0.001)

In undetected CKD cases vs. non-CKD subjects:

-1.07 ml/min/1.73 m^2 vs. -0.90 ml/min/1.73 m^2 (p <0.001)

P for difference between detected and undetected CKD cases (p=0.092)