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van Mil, Dominique; Kieneker, Lyanne M.; Evers-Roeten, Birgitte; Thelen, Marc H.M.; de Vries, Hanne; Hemmelder, Marc H.; Dorgelo, Annemiek; van Etten, Ronald W.; Heerspink, Hiddo J.L.; Gansevoort, Ron T.

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Participation rate and yield of two home-based screening methods to detect increased albuminuria in the general population in the Netherlands (THOMAS): a prospective, randomised, open-label implementation study

Dominique van Mil, Lyanne M Kieneker, Birgitte Evers-Roeten, Marc H M Thelen, Hanne de Vries, Marc H Hemmelder, Annemiek Dorgelo, Ronald W van Etten, Hiddo J L Heerspink, Ron T Gansevoort

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Department of Internal Medicine (D van Mil MD, L M Kieneker PhD, Prof R T Gansevoort PhD) **and Department of Clinical Pharmacy and Pharmacology** (D van Mil, Prof H J L Heerspink PhD), **University Medical Center Groningen, University of Groningen, Groningen, Netherlands; General Practice Tholos, Zevenbergen, Netherlands** (B Evers-Roeten MD); **Result Laboratory for Clinical Chemistry** (Prof M H M Thelen PhD) **and Department of Internal Medicine** (R W van Etten PhD), **Amphia Hospital, Breda, Netherlands; Radboud University, Nijmegen, Netherlands** (Prof M H M Thelen); **Department of Internal Medicine, Jeroen Bosch Hospital, 's-Hertogenbosch, Netherlands** (H de Vries MD); **Department of Internal Medicine, Division of Nephrology, Maastricht Universal Medical Center and Cardiovascular Research Institute University Maastricht, Maastricht, Netherlands** (Prof M H Hemmelder PhD); **Dutch Kidney Foundation, Bussum, Netherlands** (A Dorgelo MSc); **The George Institute for Global Health, Sydney, NSW, Australia** (Prof H J L Heerspink)

Summary

Background Chronic kidney disease (CKD) has a rising global prevalence and is expected to become the fifth leading cause of death by 2030. Increased albuminuria defines the early stages of CKD and is among the strongest risk factors for progressive CKD and cardiovascular disease. The value of population screening for albuminuria to detect CKD in an early phase has yet to be studied. We aimed to evaluate the effectiveness of two home-based albuminuria population screening methods.

Methods Towards Home-based Albuminuria Screening (THOMAS) was a prospective, randomised, open-label implementation study that invited Dutch adults aged 45–80 years for albuminuria screening. Individuals were randomly assigned (1:1) to screening by applying either a urine collection device (UCD) that was sent by post to a central laboratory for measurement of the albumin-to-creatinine ratio (ACR) by immunoturbidimetry or to screening via a smartphone application that measures the ACR with a dipstick method at home. Randomisation was done with a four-block method via a web-based system and was stratified by age, sex, and socioeconomic status. If two or more individuals per household were invited to participate, these individuals were randomly assigned to the same group. In case of confirmed increased albuminuria at home, participants were invited for an elaborate screening in a regional hospital (Amphia Hospital, Breda, Netherlands) for CKD and cardiovascular risk factors. When abnormalities were found, participants were referred to their general practitioner for treatment. The primary outcomes were the participation rate and yield of the home-based screening and elaborate screening. Participation rate was assessed in the intention-to-screen population (ie, all participants who were invited for the home-based screening or elaborate screening). Yield was assessed in the per-protocol population (ie, all individuals who participated in the home-based screening or elaborate screening). An exploratory analysis assessed the sensitivity and specificity of both home-based screening methods. To this end, an additional quantitative ACR test was performed among people participating in the elaborate screening, and a substudy was performed among participants with a first negative home-based screening test, who were invited for an additional test. The study is registered with ClinicalTrials.gov, NCT04295889.

Findings 15 074 participants were enrolled between Nov 14, 2019, and March 19, 2021. 7552 (50·1%) were randomly assigned to home-based albuminuria screening by the UCD method and 7522 (49·9%) were assigned to albuminuria screening by the smartphone application method. The participation rate of the home-based screening was 4484 (59·4% [95% CI 58·3–60·5]) of the 7552 invited individuals for the UCD method and 3336 (44·3% [43·2–45·5]) of 7522 invited individuals for the smartphone application method (p<0·0001). Increased ACR was confirmed by home-based testing in 150 (3·3% [95% CI 2·9–3·9]) of 4484 individuals for the UCD method and 171 (5·1% [4·4–5·9]) of 3336 indivduals for the smartphone application method. 124 (82·7% [95% CI 75·8–87·9]) of 150 individuals assigned to the UCD method and 142 (83·0% [76·7–87·9]) of 171 participants assigned to the smartphone application method attended the elaborate screening. Sensitivity to detect increased ACR was 96·6% (95% CI 91·5–99·1) for the UCD method and 98·1% (89·9–99·9) for the smartphone application method, and specificity was 97·3% (94·7–98·8) for the UCD method and 67·9% (62·0–73·3) for the smartphone application method, indicating that the test characteristics of only the UCD method were sufficient for screening. Albuminuria, hypertension, hypercholesterolaemia, and decreased kidney function were newly diagnosed in 77 (62·1%), 44 (35·5%), 30 (24·2%), and 27 (21·8%) of 124 participants for the UCD method, respectively. Of the 124 participants assigned to the UCD method who completed elaborate screening, 111 (89·5%) were referred to their general practitioner for treatment because of newly diagnosed CKD or cardiovascular disease risk factors or known risk factors outside the target range.

Interpretation Home-based screening of the general population for increased ACR using a UCD had a high participation rate and correctly identified individuals with increased albuminuria and yet unknown or known but outside target range CKD and cardiovascular risk factors. By contrast, the smartphone application method had a lower at-home participation rate than the UCD method and the test specificity was too low to accurately assess

individuals for risk factors during the elaborate screening. The UCD screening strategy could allow for an early start of treatment to prevent progressive kidney function loss and cardiovascular disease in patients with CKD.

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Correspondence to:
Prof Ron T Gansevoort, Department of Internal Medicine, University Medical Center Groningen, University of Groningen, 9713 GZ Groningen, Netherlands
r.t.gansevoort@umcg.nl

Introduction

More than 700 million people are estimated to have chronic kidney disease (CKD) worldwide, and prevalence of CKD is increasing.[1,2] Patients with CKD have an increased risk of progression to kidney failure, requiring dialysis or kidney transplantation. Additionally, even the earliest stages of CKD are associated with an increased risk of cardiovascular disease.[3,4] Thus, CKD contributes to a diminished quality of life, decreased life expectancy, and a high societal economic burden. To avoid CKD progression and related complications, early identification of CKD is needed to allow a timely start of preventive treatments.[5]

Previously, screening for CKD has focused on measuring the estimated glomerular filtration rate (eGFR), which means that intervention occurs at later stages of CKD when kidney function is already impaired. It is now acknowledged that increased albuminuria defines the early stages of CKD. Only few patients develop kidney failure without having increased albuminuria.[6] Moreover, during the past two decades, increased albuminuria has consistently been shown to be a strong predictor of progressive CKD and cardiovascular disease events, even in patients with higher eGFR.[4,7] In addition, the absolute benefits of cardioprotective and renoprotective preventive treatments such as RAAS inhibition and SGLT2 inhibition are better in patients with higher levels of albuminuria than in those with lower levels of albuminuria.[8,9]

Currently, most guidelines recommend screening for CKD only in individuals with established risk factors, such as diabetes, hypertension, or cardiovascular disease.[10–13] However, screening for CKD in these subgroups is currently suboptimal, and such a screening strategy will miss patients with unknown risk factors or absence of risk factors.[14,15] Therefore, population screening for albuminuria has been suggested as an alternative approach to identify patients with early stages of CKD. Population screening for albuminuria would allow the timely start of preventive treatments to reduce the burden of CKD.[10] However, such a strategy has not yet been investigated prospectively.

In the past decade, albuminuria screening tests have become available that make it possible to screen the general population for moderately increased

Research in context

Evidence before this study

We searched PubMed with the search terms "chronic kidney disease", "albuminuria", "screening", "early detection", and "cost-effectiveness analysis" for articles published between Jan 1, 2000, and July 1, 2022, in all languages that reported results on the effectiveness of screening for albuminuria and chronic kidney disease (CKD). Increased albuminuria defines the early stages of CKD. Emerging evidence supports a role for increased albuminuria as a robust predictor of progressive CKD and cardiovascular events. Available literature on the effectiveness of CKD screening suggests that screening for albuminuria is cost-effective when targeted to high-risk populations. There is an absence of prospective studies investigating the value of screening the general population for albuminuria.

Added value of this study

To our knowledge, Towards Home-based Albuminuria Screening (THOMAS) is the first study to prospectively assess the efficacy of screening the general population for increased albuminuria (albumin-to-creatinine ratio [ACR] >3 mg/mmol). We randomly assigned participants to two different home-based screening methods. Participants with confirmed elevated albuminuria were subsequently invited for an elaborate screening for renal and cardiovascular risk factors in a screening facility. Only individuals with increased albuminuria and newly diagnosed or poorly controlled risk factors were referred to their general practitioner. This study shows that home-based screening for increased albuminuria using a urine collection device results in a high participation rate (59·4%) and correctly identifies individuals with increased albuminuria and yet unknown CKD and cardiovascular risk factors or risk factors that were known, but outside target values. We referred 89·5% of the individuals with increased albuminuria attending the elaborate screening to their general practitioner for start or optimisation of preventive treatment. We found that 54·4% visited their general practitioner, of whom 66·1% received treatment.

Implications of all the available evidence

The present study shows the potential of home-based screening of the general population for increased ACR. The results suggest that the general population is willing to participate in a screening that identifies individuals who might benefit from an early start of preventive treatment or the optimisation of treatment already being administered. Future studies should investigate the cost-effectiveness and psychological impact of screening to prevent kidney and cardiovascular outcomes in patients with CKD.

albuminuria (ie, an albumin-to-creatinine ratio [ACR] >3 mg/mmol) in a home-based setting, which could provide an opportunity to improve early diagnosis of CKD. We aimed to prospectively investigate the participation rate and yield of two different home-based methods to screen the general population for increased albuminuria and to subsequently screen patients with confirmed positive results for the presence of renal and cardiovascular risk factors. We also aimed to assess the characteristics of participants and non-participants, the general practitioner follow-up rate, and the implementation of care by general practitioners.

See Online for appendix

Methods

Study design

Towards Home-based Albuminuria Screening (THOMAS) was a prospective, randomised, open-label implementation screening study done in the general population in Breda, the Netherlands. The study consisted of a home-based screening (ie, screening for albuminuria only), an elaborate screening (ie, a full screening for risk factors for progressive CKD and cardiovascular events, including smoking, overweight, blood pressure, total cholesterol, LDL cholesterol, HDL cholesterol, glucose, and eGFR) at a regional hospital (Amphia Hospital, Breda, Netherlands), and a general practitioner follow-up phase. An overview of the study design can be found in the appendix (p 4). The study protocol and methods have been published elsewhere.[16] The study protocol was approved by the Medical Ethics Committee of the University Medical Center Groningen (Groningen, Netherlands; 2018.687).

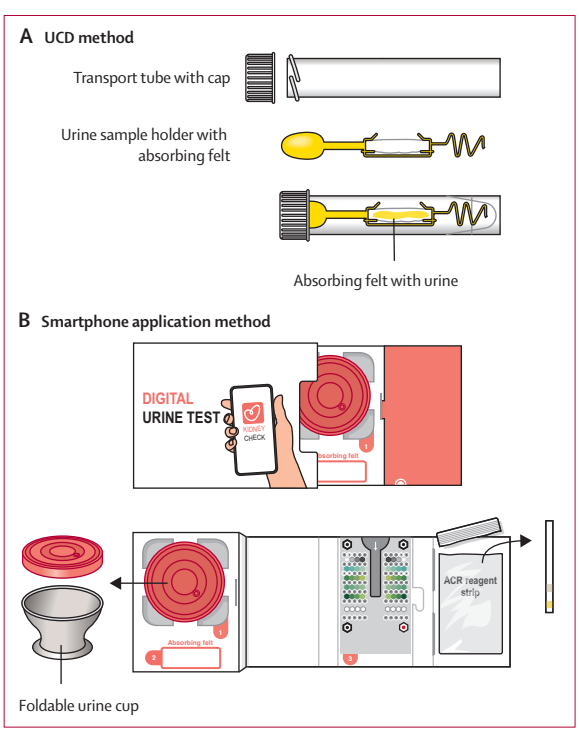

Figure 1: **Components of both home-based screening methods**
(A) UCD and its components. This CE-marked device consists of a holder containing a urine absorption pad in a transport tube. The urine absorption pad is a felt consisting of a dried hygroscopic polymer with preservatives that prevent bacterial growth for 4 days at room temperature. After receiving the sample in the laboratory, the tube is centrifuged to release urine with an albumin and creatinine recovery of 100%. The ACR is subsequently measured by standard laboratory methodology. (B) Smartphone application test kit and its components. This CE-marked test kit contains a foldable urine cup, an ACR dipstick, an absorbing pad, a colour board, and instructions to download a smartphone application. The downloaded application guides the participant through the process. After immersing the dipstick in urine, it is placed on the colour board. The smartphone application scans the dipstick by automatically taking a photo using the flashlight after 1 min. The smartphone application subsequently provides the ACR. Abbreviations: ACR=albumin-to-creatinine ratio. UCD=urine collection device.

Participants

A random sample of the general population aged 45–80 years living in the region of Breda, the Netherlands, was drawn by Statistics Netherlands, and these individuals were invited to take part in the study. This region was chosen because its population distribution concerning age, sex, and socioeconomic status closely reflects that of the Netherlands overall. Individuals living in institutions were excluded. All participants provided informed consent (written for the urine collection device [UCD] and via the app for the smartphone application) before participation.

Randomisation and masking

Individuals were randomly assigned (1:1) for home-based screening with either a novel UCD or an electronic health method based on a smartphone application and dipstick. Randomisation was done with a four-block method via a web-based system and was stratified by age (<65 years or ≥65 years), sex (male or female), and socioeconomic status (low, middle, or high). If two or more individuals per household were invited to participate, these individuals were randomly assigned to the same group. Because of the applied screening methodology, masking the participants and study personnel to group assignment was impossible.

Procedures

Individuals randomly assigned to the UCD method received a test kit with a CE-marked PeeSpot Urine Collection Device (Hessels+Grob, Deventer, Netherlands; figure 1A).[17] Participants were instructed to collect midstream urine from an early morning void and send their urine sample to a central laboratory at the Amphia Hospital. Urinary albumin and creatinine concentrations were measured, and the ACR was reported following the Kidney Disease Improving Global Outcomes (KDIGO) categorisation (A1 [normal; <3 mg/mmol], A2 [moderately increased; 3–30 mg/mmol], or A3 [severely increased; >30 mg/mmol]). Individuals randomly assigned to the App method received the ACR | EU test kit, a CE-marked home-based albuminuria screening self-test (Healthy.io, Tel Aviv-Yafo, Israel; figure 1B).[18,19] Participants

were instructed to collect midstream urine from an early morning void and to use a urine dipstick to be analysed with a smartphone application, which returned results to the participant for the ACR following the KDIGO categorisation. Results were also automatically returned to the secured research data platform when the dipstick was analysed by the smartphone application. If the first test result for both methods indicated increased albuminuria (eg, KDIGO categorisation ≥A2), participants were sent a second test kit of the assigned screening method. If the result of the second test was negative, a third test was sent. If the initial increased albuminuria result was confirmed by either the second or third positive test, the participant was considered to have confirmed increased albuminuria and invited for an elaborate screening.

During the elaborate screening at the Amphia Hospital, participants were screened for CKD and cardiovascular disease risk factors using a questionnaire, physical examination, and blood and urine samples. Risk factors assessed were smoking status, overweight, hypertension, type 2 diabetes, hypercholesterolaemia, and impaired kidney function. Participants and their general practitioner received the results of the elaborate screening by post. If no risk factors were found besides albuminuria, participants were recommended to visit their general practitioner 1 year later to repeat screening for albuminuria and CKD and cardiovascular disease risk factors. If participants smoked or had overweight, regardless of their albuminuria status, they were advised to stop smoking or lose weight, or both, and to contact their general practitioner if they needed support with these lifestyle changes. When hypertension, hypercholesterolaemia, type 2 diabetes, or impaired kidney function was found that warranted lifestyle advice, medical treatment, or both, according to the prevailing guidelines, participants were referred to their general practitioner to be prescribed these measures. 6 months after the entire screening project had ended, general practitioners and pharmacists of participants who were referred to their general practitioner for treatment (lifestyle advice or medication) were approached to confirm whether participants visited their general practitioner, and whether this visit led to the start of or changes in treatment of CKD and cardiovascular disease risk factors.

To define the presence of risk factors during the elaborate screening, definitions were used in accordance with prevailing national guidelines for Dutch general practitioners or in accordance with international guidelines when Dutch guidelines were not available, as described previously[16] (appendix p 5). For the UCD method, urinary albumin concentrations were measured by immunoturbidimetry and urinary creatinine concentrations were measured enzymatically in a central laboratory at Amphia Hospital on a Cobas c502 analyser (Roche Diagnostics, Almere, Netherlands). For the smartphone application method, urinary albumin and creatinine concentrations were measured by a colorimetric assay using the ACR | EU test kit. Increased albuminuria was defined following the KDIGO categorisation (A2 or A3). Demographic information, including age, sex, and socioeconomic status, was provided by Statistics Netherlands. Socioeconomic status was based on postal codes (low socioeconomic status area, middle socioeconomic status area, or high socioeconomic status area). Ethnicity and level of education were self-reported by participants through a paper questionnaire that participants completed at home before visiting the screening facility, and level of education was based on the International Standard Classification of Education.

Outcomes

The primary outcomes were the participation rate and yield of the home-based screening and the elaborate screening. These outcomes were assessed for each of the two home-based screening methods. Participation rate was calculated separately for the home-based screening, and for the entire screening programme (including the home-based screening and the elaborate screening in case of increased albuminuria). The yield of the home-based screening was defined as the number of individuals who tested positive for albuminuria (at least two positive tests). The yield of the elaborate screening was defined as the number of individuals with increased albuminuria and newly diagnosed or known (outside the target range) risk factors for cardiovascular disease or CKD. Risk factors were classified as newly diagnosed if a participant stated that they had no medical history of the risk factor, and risk factors are were defined as known but outside the target range if a participant stated that they had a medical history of the risk factor but the risk factor was classified as not regulated according to targets described in national or international guidelines.

Secondary outcomes were characteristics of participants and non-responders of the home-based screening, elaborate screening, and general practitioner follow-up; the general practitioner follow-up rate and implementation of care; numbers of participants needed to screen to identify one participant with increased albuminuria, one participant with newly diagnosed albuminuria, and one participant with increased albuminuria and a newly diagnosed risk factor or known risk factor outside the target range; and test usability as assessed by a self-administered questionnaire.

In a preplanned exploratory analysis, we assessed the false-positive and false-negative test rates to explore the test characteristics of both home-based albuminuria screening methods. To assess the false-negative test rate, we aimed to invite 500 participants assigned to each home-based screening method who had a negative first home-based albuminuria screening test for an additional test. The false-positive test rate was defined as the ratio between the number of participants of the elaborate

screening who did not have increased albuminuria at the elaborate screening, and the total number of participants of the elaborate screening. This additional test was done with quantitative measurement of urinary albumin via immunoturbidimetric methods and urinary creatinine via enzymatical methods to provide a quantitative ACR value. Subsequently, the false-negative rate was calculated as the ratio between the number of participants in the substudy with a positive quantitative ACR measurement and the total number of participants in the substudy. These false negative and positive rates enabled us to calculate the true negative and true positive rates, required to calculate the sensitivity and specificity (appendix p 3).

Statistical analysis

The analytical approach for the study's sample size has been published previously.[16] The sample size was calculated to be able to detect a significant difference between both screening methods for finding a participant with at least one newly diagnosed risk factor. The sample size was calculated on the basis of several assumptions: a participation rate of 47·5% for the UCD method and 52·5% for the smartphone application method; that 8% of the participants would have elevated ACR, of whom 90% will have confirmed elevated ACR by the confirmatory tests; a participation rate in the elaborate screening of 90%; and 71% of participants using the UCD method and 51% of participants using the smartphone application method would have a newly diagnosed risk factor for cardiovascular disease or CKD. This calculation led to a minimum of 15 032 individuals who were to be invited to take part in the study, which also allowed detection of a 5% difference in participation rate between the two study methods. Continuous variables are reported as mean (SD) or median (IQR). Categorical variables are reported as numbers with proportions, with main proportions reported with 95% CIs. The outcomes were assessed separately for each of the two home-based screening methods.

The primary outcome of the participation rate of the home-based screening and elaborate screening was assessed in the intention-to-screen population, which included all participants who were invited for the study phase concerned (ie, home-based screening, elaborate screening, or general practitioner referral). The yield of the home-based screening and elaborate screening was assessed in the per-protocol population, which included all individuals who participated in the respective study phase (home-based screening, elaborate screening, or general practitioner referral).

Differences between groups for categorical data were tested with a χ^2 test; differences between groups for continuous data were tested by Student's *t* test or a Mann-Whitney test in case of skewed distribution.

The secondary outcomes of participant characteristics and non-responders were compared with a χ^2 test for categorical data, with Student's *t* test for continuous data, or a Mann-Whitney test in case of skewed distribution. Implementation of care and general practitioner follow-up rate was assessed in the per-protocol population, including all individuals who had a reported visit to their general practitioner after referral. The number needed to screen to identify one individual was calculated using the inverse of the detection rate derived from the total number of participants in the home-based screening. In a preplanned exploratory analysis, test characteristics of the UCD and smartphone application methods were calculated. The sensitivity and specificity of the methods were reported as percentages with 95% CIs.

p values of less than 0·05 were considered to indicate significance. IBM SPSS (version 28) was used to analyse the data.

THOMAS is registered with ClinicalTrials.gov, NCT04295889.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, writing of the report, or the decision to submit for publication.

Results

Among 15 500 people assessed for eligibility, 15 074 individuals were invited between Nov 14, 2019, and March 19, 2021. Of these 15 074 individuals, 7552 (50·1%) were randomly assigned to home-based albuminuria screening by the UCD method and 7522 (49·9%) were assigned to albuminuria screening by the smartphone application method, and these individuals subsequently received the assigned home-based screening method.

The participation rate for the home-based albuminuria screening was 59·4% (95% CI 58·3–60·5; 4484 of 7552 invited individuals) for the UCD method and 44·3% (43·2–45·5; 3336 of 7522 invited individuals) for the smartphone application method (figure 2). Compared with all invited individuals, those who completed albuminuria screening using the UCD method were, on average older, whereas those who completed screening using the smartphone application method were younger (table 1; appendix p 6). The participation rate was significantly higher for the UCD method than for the smartphone application method overall and across all strata of sex, age, and socioeconomic status (table 2). For both methods, the participation rate was significantly higher among women than among men and significantly lower among people living in a low socioeconomic status area than among people living in a middle or high socioeconomic status area. For the UCD method, the participation rate was significantly higher among individuals 65 years or older than among individuals younger than 65 years, whereas for the smartphone application method, the participation rate among older individuals was significantly lower than among younger individuals. In both age strata,

participation rate was higher for the UCD method than the smartphone application method, and this difference was larger in the older age stratum than in the younger age stratum (appendix p 7).

Of the 4507 participants assigned to the UCD method who responded to the first test, 239 (5·3% [95% CI 4·7–6·0]) had a first positive test. Ultimately, in 150 (3·3% [2·9–3·9]) of 4484 participants who completed the home-based albuminuria screening, the positive test was confirmed (figure 2). For the smartphone application method, 451 (13·3% [12·2–14·5]) of 3398 participants had a positive first test. After confirmatory tests, 171 (5·1% [4·4–5·9]) of 3336 participants had a confirmed positive test. Compared with participants with a negative test, participants with a confirmed positive albuminuria test during the home-based screening both with the UCD method and with the smartphone application method were significantly more likely to be male than female, to live in a low socioeconomic status area than in a middle or high socioeconomic status area, and to be

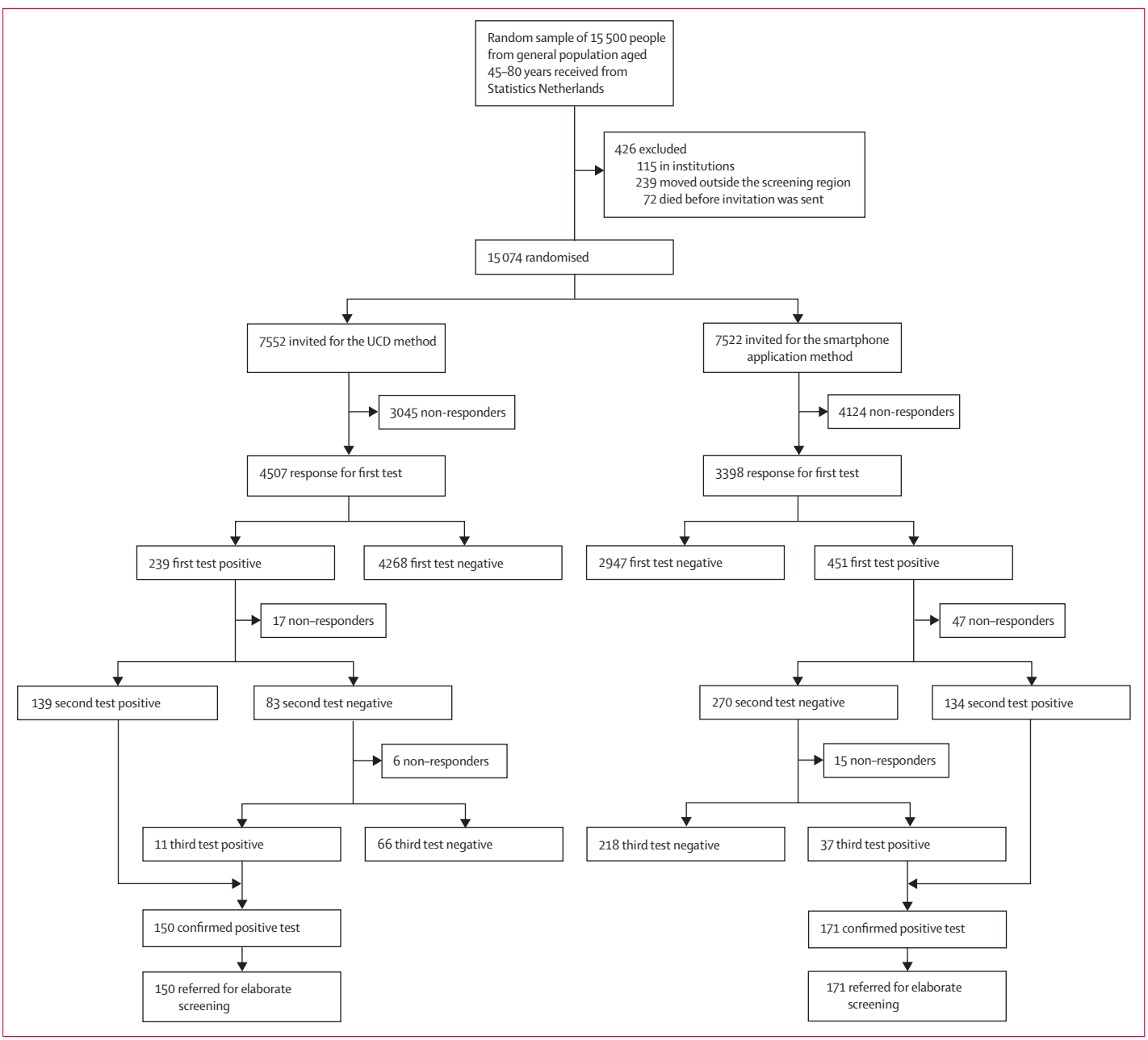

Figure 2: **Participation rates and yield of home-based albuminuria screening**
UCD=urine collection device.

	UCD method			Smartphone application method			p value for participation*	p value for positive tests*
	Invited	Participated†	Positive test	Invited	Participated†	Positive test		
All individuals	7552	4484	150	7522	3336	171	<0·0001	0·0007
Age, years	60·5 (9·8)	61·4 (9·4)	68·5 (9·0)	60·3 (9·6)	59·7 (9·1)	61·2 (10·2)	<0·0001	<0·0001
Age group							<0·0001	<0·0001
45 to <65 years	4867 (64·4%)	2753 (61·4%)	43 (28·6%)	4915 (65·3%)	2262 (67·8%)	98 (57·3%)	..	..
65 to 80 years	2685 (35·6%)	1713 (38·2%)	107 (71·3%)	2607 (34·7%)	1074 (32·2%)	73 (42·7%)	..	..
Sex							0·73	0·41
Women	3887 (51·5%)	2379 (53·1%)	62 (41·3%)	3777 (50·2%)	1757 (52·7%)	63 (36·8%)	..	..
Men	3665 (48·5%)	2105 (46·9%)	88 (58·7%)	3745 (49·8%)	1579 (47·3%)	108 (63·2%)	..	..
Socioeconomic status area							0·026	0·31
Low	2513 (33·3%)	1382 (30·8%)	68 (45·3%)	2475 (32·9%)	938 (28·1%)	66 (38·6%)	..	..
Middle	2688 (35·6%)	1610 (35·9%)	42 (28·0%)	2700 (35·9%)	1216 (36·5%)	61 (35·7%)	..	..
High	2342 (31·0%)	1487 (33·2%)	40 (26·7%)	2335 (31·0%)	1173 (35·2%)	44 (25·7%)	..	..

Data are mean (SD) or n (%). UCD=urine collection device. *UCD method versus the smartphone application method. †Participants completing the home-based screening.

Table 1: **Characteristics of individuals invited for the home-based albuminuria screening, participating individuals, and individuals with a confirmed increased albuminuria result according to both screening methods**

	UCD method	Smartphone application method	p value for UCD *vs* smartphone application method	p value within subgroups of UCD	p value within subgroups of smartphone application
Overall	4484/7552 (59·4%; 58·3–60·5)	3336/7522 (44·3%; 43·2–45·5)	<0·0001	..	..
Sex				0·0009	0·0001
Women	2379/3887 (61·2%; 59·7–62·7)	1757/3777 (46·5%; 44·9–48·1)	<0·0001	..	..
Men	2105/3665 (57·4%; 55·8–59·0)	1579/3745 (42·2%; 40·6–43·8)	<0·0001	..	..
Age group				<0·0001	<0·0001
45 to <65 years	2753/4867 (56·6%; 55·2–58·0)	2262/4915 (46·0%; 44·6–47·4)	<0·0001	..	..
65 to 80 years	1731/2685 (64·5%; 62·6–66·3)	1074/2607 (41·2%; 39·3–43·1)	<0·0001	..	..
Socioeconomic status area				<0·0001	<0·0001
Low	1382/2513 (55·0%; 53·0–56·9)	938/2475 (37·9%; 36·0–39·8)	<0·0001	..	..
Middle	1610/2688 (59·9%; 58·0–61·8)	1216/2700 (45·0%; 43·2–46·9)	<0·0001	..	..
High	1487/2342 (63·5%; 54·4–58·2)	1173/2335 (50·2%; 48·2–55·3)	<0·0001	..	..

Data are n/N (%; 95% CI) unless otherwise specified. UCD=urine collection device.

Table 2: **Participation rate according to the two home-based screening methods overall and in subgroups defined by sex, age, and socioeconomic status**

65 years or older than younger than 65 years (appendix p 8).

124 (82·7% [95% CI 75·8–87·9]) of the 150 participants assigned to the UCD method and 142 (83·0% [76·7–87·9]) of the 171 participants assigned to the smartphone application method invited for the elaborate screening in the central screening facility attended this screening (table 3; appendix p 9). Individuals participating in the elaborate screening for the UCD method were significantly older than individuals participating in the elaborate screening for the smartphone application method (68·5 years [SD 8·9] *vs* (60·9 years [10·1]; table 3). For both methods, the majority of the participants were male and had a medium level of education. The use of antihypertensive drugs, glucose-lowering drugs, and lipid-lowering drugs was significantly higher in participants who used the UCD method than in participants who used the smartphone application method. Participants younger than 65 years who used the UCD method were more likely to be current smokers, have hypertension, and have diabetes than participants younger than 65 years who used the smartphone application method. Participants who were 65 years or older who used the UCD method had higher systolic blood pressure, were more likely to have used lipid-lowering drugs, and had a lower eGFR than participants who were 65 years and older who used the smartphone application method (appendix pp 10–11).

Increased albuminuria was present in 113 (91·1%) of 124 participants identified by the UCD method who completed elaborate screening and 52 (36·6%) of 142 participants identified by the smartphone application

	UCD method (n=124)	Smartphone application method (n=142)	p value
Demographics			
Sex	..	..	0·36
Men	70 (56·5%)	88 (62·0%)	..
Women	54 (43·5%)	54 (38·0%)	..
Age, years	68·5 (8·9)	60·9 (10·1)	<0·0001
Ethnicity	..	..	0·52
White	111 (89·5%)	132 (93·0%)	..
Black	1 (0·8%)	0	..
Asian	8 (6·5%)	8 (5·6%)	..
Unknown	4 (3·2%)	2 (1·4%)	..
Socioeconomic status area	..	..	0·16
Low	58 (46·8%)	52 (36·7%)	..
Middle	33 (26·6%)	52 (36·7%)	..
High	33 (26·6%)	38 (26·8%)	..
Level of education			0·010
Low	40 (32·3%)	28 (19·7%)	..
Medium	52 (41·9%)	60 (42·3%)	..
High	28 (22·6%)	54 (38·0%)	..
Risk factors for CKD and cardiovascular disease			
Cardiovascular history*	29 (23·4%)	25 (17·6%)	0·24
Current smokers	24 (19·4%)	16 (11·3%)	0·069
BMI, kg/m^2	27·0 (5·2)	27·5 (4·6)	0·37
Overweight	59 (47·6%)	87 (61·3%)	0·017
Obesity	31 (25·0%)	40 (28·2%)	0·52
Systolic blood pressure, mm Hg	142 (20)	130 (17)	<0·0001
Diastolic blood pressure, mm Hg	83 (12)	82 (10)	0·60
Use of antihypertensive drugs	67 (54·0%)	48 (33·8%)	0·0007
Hypertension	111 (89·5%)	88 (62·0%)	<0·0001
HbA_{1c}, mmol/mol	45·9 (15·7)	40·8 (9·3)	0·0020
Glucose, mmol/L	..	..	..
Fasting glucose	7·2 (2·8)	6·3 (1·2)	0·44
Non-fasting glucose	7·8 (4·3)	6·5 (2·2)	0·0061
Unknown fasting status†	26·0	8·7	..
Use of glucose-lowering drugs	33 (26·6%)	17 (12·0%)	0·0023
Diabetes	39 (31·5%)	24 (16·9%)	0·0054
Total cholesterol, mmol/L	4·6 (1·2)	4·7 (1·0)	0·21
LDL cholesterol, mmol/L	2·4 (1·0)	2·6 (0·9)	0·098
HDL cholesterol, mmol/L	1·3 (0·5)	1·3 (0·4)	0·99
Triglycerides, mmol/L	1·9 (1·3)	1·7 (1·0)	0·24
Use of lipid-lowering drugs	64 (51·6%)	41 (28·9%)	<0·0001
Hypercholesterolaemia	95 (76·6%)	91 (64·1%)	0·036
Serum creatinine, µmol/L	91·6 (32·4)	85·8 (57·4)	0·32
eGFR, mL/min per 1·73 m^2	70·9 (21·8)	82·2 (18·2)	<0·0001
eGFR category	..	..	0·0006
eGFR <60 mL/min per 1·73 m^2	36 (29·0%)	17 (12·0%)	..
eGFR ≥60 mL/min per 1·73 m^2	88 (71·0%)	125 (88·0%)	..
ACR, mg/mmol	10·8 (6·0–30·5)	1·7 (0·7–6·5)	<0·0001
ACR category‡			<0·0001
<3 mg/mmol	8 (6·5%)	89 (62·7%)	..
3–30 mg/mmol	82 (66·1%)	39 (27·5%)	..
>30 mg/mmol	31 (25·0%)	13 (9·2%)	..

(Table 3 continues in next column)

(Continued from previous column)

Data are n (%), mean (SD), or median (IQR). ACR=albumin-to-creatinine ratio. CKD=chronic kidney disease. eGFR=estimated glomerular filtration rate. UCD=urine collection device. *Cardiovascular history is defined as having had a stroke, myocardial infarction, or heart failure. †SD could not be calculated. ‡Laboratory ACR values were missing for three participants using the UCD method and one participant using the smartphone application method.

Table 3: **Characteristics of the participants of the elaborate screening according to the two home-based screening methods**

method who completed elaborate screening (table 3). The ACR at the elaborate screening was significantly higher in those identified by the UCD method than by the smartphone application method (p<0·0001; table 3). Among participants identified by the UCD method, albuminuria was moderately increased (ACR >3 mg/mmol) in 82 (66·1%) of 124 participants who completed elaborate screening or severely increased (ACR >30 mg/mmol) in 31 (25·0%) of 124 participants who completed elaborate screening. By contrast, among participants identified by the smartphone application method, albuminuria was moderately increased in 39 (27·5%) of 142 participants who completed elaborate screening or severely increased in 13 (9·2%) of 142 participants who completed elaborate screening. Of the 124 participants identified by the UCD method, 77 (62·1%) reported that they did not know that they had increased albuminuria, compared with 119 (83·8%) of 142 participants identified by the smartphone application method.

For the preplanned exploratory analysis, due to the temporary halt of the study during the COVID-19 pandemic, we were able to invite 326 participants assigned to the UCD method and 220 participants assigned to the smartphone application method. Eight (6·6%) of 121 participants had false-positive results with the UCD method and 89 (63·1%) of 141 participants had false-positive results with the smartphone application method. For examining the false-negative rates, 292 (89·6%) of 326 invited individuals assigned to the UCD method

	UCD method (n=124)
Total individuals with any risk factors	120 (96·8%)
Individuals with one or more newly diagnosed risk factor	79 (63·7%)
Individuals with one or more known risk factor	89 (71·8%)
Outside target range	68 (54·8%)
Within target range	58 (46·8%)
Total risk factors	279
Newly diagnosed	104/279 (37·3%)
Known	175/279 (62·7%)
Known, outside target range	87/279 (31·2%)
Known, within target range	76/279 (27·2%)
Known, decreased eGFR	12/279 (4·3%)
Hypertension	111 (89·5%)
Newly diagnosed	44 (35·5%)
Known	67 (54·0%)
Known, outside target range	50 (40·3%)
Known, within target range	17 (13·7%)
Type 2 diabetes	39 (31·5%)
Newly diagnosed	3 (2·4%)
Known	36 (29·0%)
Known, outside target range	25 (20·2%)
Known, within target range	11 (8·9%)
Prediabetes during screening and no history of diabetes	47 (37·9%)
Hypercholesterolaemia	95 (76·6%)
Newly diagnosed	30 (24·2%)
Known*	65 (52·4%)
Known, outside target range	12 (9·7%)
Known, within target range	48 (38·7%)
Decreased eGFR	36 (29·0%)
Newly diagnosed	27 (21·8%)
Known	9 (7·3%)

Data are n (%). Percentages are expressed as proportion of total participants of elaborate screening (n=124), unless stated otherwise. CKD=chronic kidney disease. eGFR=estimated glomerular filtration rate. UCD=urine collection device. *Five participants knew that they had hypercholesterolaemia, but laboratory cholesterol values from the elaborate screening were missing.

Table 4: **Risk factors for the progression of CKD and cardiovascular disease detected during the elaborate screening in participants assigned to the UCD method**

participated and 189 (85·9%) of 220 invited individuals assigned to the smartphone application method participated. Four (1·4%) of 292 participants had false-negative results with the UCD method, and one (0·5%) of 189 participants had false-negative results with the smartphone application method. Consequently, the UCD method showed high sensitivity (96·6% [95% CI 91·5–99·1]) and specificity (97·3% [95% CI 94·7–98·8], whereas the smartphone application method showed high sensitivity (98·1% [89·9–99·9]) but low specificity (67·9% [62·0–73·3]; appendix p 12).

In terms of usability, 106 (85·5%) of 124 individuals assigned to the UCD method who participated in the elaborate screening would recommend the method to others and 93 (75·0%) of 124 individuals preferred the UCD method over a standard urine test (ie, sending a urine sample by post to a central laboratory instead of bringing a urine sample to the general practitioner's office during working hours). 132 (93·0%) of 142 individuals assigned to the smartphone application method would recommend the method to others, and 108 (76·1%) of 142 individuals preferred the smartphone application method over a standard urine test (appendix p 13). In both groups, most of the participants found the assigned screening test very easy to perform (appendix p 13).

In total, 279 CKD and cardiovascular risk factors were present in 120 (96·8%) of 124 participants assigned to the UCD method during the elaborate screening. In four (3·2%) participants, no risk factors were found. Moreover, 79 (63·7%) participants had at least one newly diagnosed risk factor (table 4). Known risk factors were more often outside the target range than within the target range. Hypertension was the most common newly diagnosed risk factor among 44 (35·5%) of 124 participants. 47 (37·9%) participants were classified as having prediabetes, and 27 (21·8%) were newly diagnosed with decreased kidney function (eGFR <60 mL/min per 1·73 m²). In participants aged 65 years or older, most of the risk factors (140 [67·3%] of 208) were known, of which more than half of the risk factors were outside the target range (appendix p 14). In participants younger than 65 years, percentage wise, risk factors were more often newly diagnosed than in older participants (36 [50·7%] of 71 risk factors found *vs* 68 [32·7%] of 208). Because more risk factors were found in older participants than in younger participants (208 *vs* 71 risk factors), the absolute number of newly diagnosed risk factors was higher in older participants than in younger participants (68 *vs* 36 risk factors).

Due to the high number of false-positive tests in participants who used the smartphone application method (table 3), the results of the elaborate screening at the central screening facility of these participants are not considered to reflect the characteristics of a population with increased albuminuria that we aimed to identify in the current study. The CKD and cardiovascular disease risk factors found in individuals assigned to the smartphone application method who completed elaborate screening (n=142) are therefore only shown in the appendix (pp 15–17).

73 (58·7%) of 124 individuals assigned to the UCD method were advised to stop smoking, lose weight, or both. In total, 111 (89·5%) of 124 participants assigned to the UCD method were referred to their general practitioner after the elaborate screening visit because of the presence of newly diagnosed risk factors or known risk factors that were outside the target range (table 4). The general practitioners and pharmacists of 103 (92·8%) of 111 participants responded. Of the 103 participants for

whom we had information on implementation of care, 56 (54·4%) actually visited their general practitioner, and treatment was started or changed in 37 (66·1%) of these 56 participants (appendix p 18). Participants who did not visit their general practitioner were likely to live in a low socioeconomic status area, had a higher BMI, and were more likely to have diabetes or a decreased eGFR than participants who did visit their general practitioner (appendix p 19).

When screening the general population aged between 45 years and 80 years with the UCD method, the number needed to screen to identify one participant with increased albuminuria was 30, whereas the number needed to screen to identify one participant with newly diagnosed increased albuminuria was 58. The number needed to screen to identify one participant with increased albuminuria and a newly diagnosed risk factor or known risk factor that is outside target range was 45 (appendix p 20).

Discussion

THOMAS was a prospective, randomised, open-label implementation study to evaluate the effectiveness of two home-based population screening methods to detect increased albuminuria and associated renal and cardiovascular risk factors. The study showed that the participation rate using a UCD sent to a central laboratory was significantly higher than a smartphone application-based method (4484 [59·4%] of 7552 invited individuals *vs* 3336 [44·3%] of 7522 invited individuals). It was established that the UCD method had high specificity and sensitivity. Using the UCD method, increased albuminuria was confirmed by a second or third positive test in 150 (3·3%) of 4507 participants, resulting in a number needed to screen of 30. Of the 124 participants assigned to the UCD method who completed elaborate screening, 111 (89·5%) participants were referred to their general practitioner because at least one newly diagnosed renal or cardiovascular risk factor or a known risk factor was outside the target range of treatment (ie, hypertension, hypercholesterolaemia, diabetes, or decreased eGFR). In total, 56 (54·4%) of 103 participants for whom we received a response from general practitioners or pharmacists visited their general practitioner, of whom 37 (66·1%) received new treatment or a treatment change.

A participation rate of 59·4% was found for the UCD method in our implementation study. This participation rate is high and similar to the participation rates of the first home-based faecal occult screening studies to detect colorectal cancer in the Netherlands, which ranged between 46·9% and 59·6%.[20] When home-based faecal occult blood testing changed from implementation research to actual population screening, participation increased to more than 70·0%.[21] An increase in participation rate for ACR testing with the UCD method could therefore also be expected if it became part of an official population screening programme. The participation rate of the smartphone application method was significantly lower than that of the UCD method overall and among all strata of sex, age, and socioeconomic status. Importantly, the participation rate for the smartphone application method was significantly lower among older participants than among younger participants. The participation rate for the smartphone application method was also significantly lower for participants living in a low socioeconomic status area than for participants living in a higher socioeconomic status area. Older individuals and individuals with a low socioeconomic status are known to be at higher risk of increased albuminuria.[22] The lower access that these populations have to smartphones could change over time if smartphones become more widely used.

The study examined two different home-based screening methods. By incorporating confirmation tests during the home-based screening with a subsequent ACR measurement at the elaborate screening, we were able to assess test characteristics. For the smartphone application method, we established a low specificity of the test and a low positive predictive value. Consequently, participants identified by the smartphone application method did not reflect a population with increased albuminuria, which we aimed to identify, because of too many false-positive tests and too few true-positive tests. Agreement of test results measured with the smartphone application method was high when compared with another semi-quantitative ACR test.[18] Unfortunately, to our knowledge, there is no published evidence on the sensitivity and specificity of the smartphone application test compared with measuring the ACR with gold standard methodology in a central clinical chemistry laboratory.[19] The manufacturer now has an improved version of the product that has been approved for home use by the US Food and Drug Administration.[23] By contrast, the UCD method had high sensitivity and specificity, and a description of the results associated with screening using the UCD method was, therefore, the main focus of this study.

The data from our study suggest a prevalence of increased albuminuria of approximately 3·3% in our population. By contrast, Okpechi and colleagues reported an albuminuria prevalence in population-based studies of 11·2%, varying considerably across countries.[24] In the Netherlands, the baseline screening of the PREVEND study, which was performed in 1997 in the city of Groningen, showed that 5·6% of the general population had confirmed increased albuminuria.[25] The lower albuminuria prevalence in our study might reflect regional differences but can also be explained by improved screening among high-risk populations and enhanced treatment of cardiovascular and renal risk factors since the start of the PREVEND study.[5,26] Notwithstanding, the results of our study highlight that of the individuals identified by population screening to have increased albuminuria, there is a considerable percentage in whom increased albuminuria was not known yet.

Our study investigated the effect of albuminuria screening on the early detection of CKD in the general population. It appeared that 79 (63·7%) of 124 participants assigned to the UCD method who completed elaborate screening had one or more newly diagnosed cardiovascular disease or CKD risk factors that would require the initiation of preventive treatment. In addition, 68 (54·8%) of 124 participants with increased albuminuria had a risk factor that was known to their general practitioner but outside target range. Although population screening has been put forward as the most complete approach to reduce the burden of kidney disease, the evidence before this study suggested that only CKD screening targeted to high-risk subpopulations is effective. This evidence was provided by cost-effectiveness analyses that differ in three essential points from our initiative. First, these analyses were modelled and not studied prospectively, whereas we conducted a prospective analysis. Second, these analyses were based on screening for decreased eGFR or severely increased albuminuria (ACR >30 mg/mmol) only. By contrast, we screened for moderately increased albuminuria (ACR >3 mg/mmol), leading to more individuals being identified and treated. Third, screening in these previous analyses was performed in the general practitioner setting, which contrasts with our home-based screening method that would be associated with lower costs than the general practitioner setting. Importantly, these previous analyses took only benefits concerning the prevention of kidney failure into account, whereas the prevention of cardiovascular events should also be considered. These differences result in fewer benefits with respect to disease prevention and higher screening costs than our approach.[27,28] Our study results suggest that, even in a high-income country such as the Netherlands, screening more individuals than just high-risk populations is required, because this excludes the screening of individuals with unknown risk factors. Furthermore, it is known that in many countries, screening for CKD in specific high-risk subgroups is currently suboptimal.[14,15] Many people with known hypertension, known diabetes or a known cardiovascular disease history are not screened for albuminuria or eGFR, although guidelines recommend this. Screening the general population could also be beneficial for individuals in these subgroups. Of note, we kept our screening broad and also included individuals who stated that they were aware of having increased albuminuria. Reasons to do so were, first, that some of these individuals were identified with increased albuminuria in the past (eg, during pregnancy) but were not under medical attention anymore. Second, in individuals who are under medical attention, risk factor treatment might not be optimal. Therefore, both groups could benefit from starting or optimising risk factor treatment.

Whereas the home-based screening resulted in a high participation rate of approximately 60%, only 56 (54·4%) of 103 participants for whom we received responses from general practitioners or pharmacists visited the general practitioner after referral, of whom 37 (66%) participants received the proposed treatment. Although there might be several reasons why the screening uptake was suboptimal, one crucial factor could be CKD awareness. Individuals at risk for CKD generally have a low perceived risk of CKD.[29] Studies have shown that awareness is low, even among those patients with CKD.[30,31] Low awareness might be caused by an absence of symptoms, especially early in the disease, but perhaps also by low awareness among health-care providers, resulting in the absence of necessary discussion between patients and clinicians about the severity and need for treatment of kidney disease. Whatever might have caused some participants who received referrals to not visit their general practitioner and receive the suggested treatment, improving the implementation of care deserves attention for an albuminuria screening programme to have an optimal effect on the population level.

The present study underlines the importance of albuminuria screening, which has become even more relevant since more interventions have become available to improve the prognosis of renal and cardiovascular outcomes. Lifestyle interventions and various pharmaceutical treatments, including GLP-1 analogues, SGLT2 inhibitors, and non-steroidal mineralocorticoid receptor antagonists, have recently shown cardioprotection and renoprotection when given in addition to renin–angiotensin system inhibitors in individuals with albuminuria.[6,32–34] Future studies should address remaining knowledge gaps. First, the reasons why individuals do not participate in the screening and do not visit their general practitioner after referral, and the role of socioeconomic status and (electronic) health literacy herein, should be explored. Lessons learned should improve the yield of screening. Second, the yield of repeat screening and the optimal time interval for repeat screening should be investigated. Third, at present, the study results are generalisable to similar high-income countries such as the Netherlands. Screening studies should be expanded to low-income countries and racially diverse countries. It is known that both low-income and racially diverse countries have a higher prevalence of increased ACR and that fewer people are already screened for ACR even when they have risk factors, such as known hypertension or diabetes, than in high-income countries. Therefore, the cost-effectiveness of home-based ACR screening could even be better in low-income countries than in high-income countries.

We recognise several limitations to our study. First, the screening approach focused on the early identification of individuals with CKD characterised by increased albuminuria. Consequently, not all individuals with CKD risk factors were identified. However, previous epidemiological analyses showed that individuals with increased albuminuria and newly discovered cardiovascular risk factors are especially at risk of progressive CKD and

cardiovascular disease, which merits the start of preventive treatment. Start of such preventive treatment might be less warranted in people with newly discovered CKD and cardiovascular risk factors but no increased albuminuria. It has been shown that, on average, such individuals have an absolute risk for CKD progression and cardiovascular disease that does not merit the start of cardioprotective treatment.[25] Screening for albuminuria might therefore identify a subgroup of people who could particularly benefit from treatment to prevent CKD progression and cardiovascular disease. Second, due to the COVID-19 pandemic, which reached the Netherlands in February, 2020, and caused a high burden on the health-care system, our screening study had to be put on hold temporarily. Despite efforts to re-invite all individuals, the pandemic might have led to underestimation of the participation rate, although the participation rate with the UCD method was already satisfactory. Third, test characteristics were calculated in subgroups instead of the entire study population. We therefore report sensitivity and specificity with a 95% CI to indicate that there is some uncertainty about their exact value. Finally, our study does not show the actual benefits of preventing renal and cardiovascular events. However, the present results lay a firm foundation to start prospective, large-scale studies to formally investigate the effect of albuminuria screening with subsequent treatment to prevent these outcomes. In February, 2022, we received a large grant from the Dutch Government to start such a study in the Netherlands.[35] Moreover, the possible effects and costs of albuminuria screening on the incidence of cardiovascular and kidney outcomes can be modelled using the present data in a formal cost-effectiveness analysis. A detailed description of such an analysis is beyond the scope of the present paper and will be published separately. This analysis will also investigate what the cost-effectiveness is of screening for albuminuria in specifically younger and older individuals within the target age range (45–80 years) that we included in our study. Last, we do not present the results of the smartphone application method in detail because of the many false-positive results. Of note, the limited specificity of the smartphone application that we used might be due to the fact that it was developed for screening individuals at high risk, such as people with hypertension or type 2 diabetes, whereas we applied it in a low-risk population. The manufacturer now has an improved method, applying a different dipstick and a different algorithm to calculate ACR that is approved by the Food and Drug Administration,[23] and its initial results[18] merit further study.

In conclusion, in this first prospective study to investigate the value of population-based screening for chronic kidney disease by albuminuria, we showed that home-based screening of the general population using a device to collect urine at home to be sent to a central laboratory for albuminuria measurement has a high participation rate. Moreover, such a strategy identifies individuals with increased albuminuria and yet unknown renal and cardiovascular risk factors or risk factors that are known, but outside the target range for treatment. These individuals could benefit from the early start of lifestyle measures and treatments to prevent the progression of chronic kidney and cardiovascular disease.

Contributors

LMK, RTG, BE-R, MHMT, MHH, and RWvE designed the study's protocol. LMK, RTG, DvM, BE-R, MHMT, HdV, and RWvE were involved in the conduct of the study, data collection, and data interpretation. DvM, LMK, and RTG wrote the first draft of the manuscript, which was revised with input from BE-R, MHMT, MHH, AD, RWvE, and HJLH. All authors had full access to all data in the study. All authors reviewed the manuscript drafts and provided approval of the final version. DvM, LMK, and RTG directly assessed and verified the data, and all authors took responsibility for the decision to submit for publication.

Declaration of interests

In the past 5 years, RTG has received fees for consultancy or grants, or both, for research from AbbVie, AstraZeneca, Baxter, Bayer, Healthy.io, Roche, and Sandoz. In the past 5 years, HJLH has received fees for consultancy or grants, or both, for research from AbbVie, AstraZeneca, Boehringer Ingelheim, Bayer, Chinook, CSL Behring, Dimerix, Gilead, Goldfinch, Janssen, Merck, Mitsubishi Tanabe, MundiPharma, NovoNordisk, and Travere Therapeutics. All other authors declare no competing interests.

Data sharing

De-identified and anonymised participant data generated during the study are available upon reasonable request to the corresponding author, approval by the joint investigators, and with a signed data access agreement.

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