

# Screening strategies for chronic kidney disease in the general population: follow-up of cross sectional health survey

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## Abstract

**Objective** To find an effective screening strategy for detecting patients with chronic kidney disease and to describe the natural course of the disease.

**Design** Eight year follow-up of a cross sectional health survey (the HUNT II study).

**Setting** Nord-Trøndelag County, Norway

**Participants** 65 604 people (70.6% of all adults aged  $\geq 20$  in the county).

**Main outcome measures** Incident end stage renal disease (ESRD) and cardiovascular mortality monitored by individual linkage to central registries.

**Results** 3069/65 604 (4.7%) people had chronic kidney disease (estimated glomerular filtration rate  $< 60$  ml/min/1.73 m<sup>2</sup>), so we would need to screen 20.6 people (95% confidence interval 20.0 to 21.2) to identify one case. Restriction of screening to those with hypertension, diabetes, or age  $> 55$  would identify 93.2% (92.4% to 94.0%) of patients with chronic kidney disease, with a number needed to screen of 8.7 (8.5 to 9.0). Restriction of screening according to guidelines of the United States kidney disease outcomes quality initiative (US KDOQI) gave similar results, but restriction according to the United Kingdom's chronic kidney disease guidelines detected only 51.6% (49.6% to 53.4%) of cases. Screening only people with previously known diabetes or hypertension detected 44.2% (42.7% to 45.7%) of all cases, with a number needed to screen of six. During the eight year follow-up only 38 of the 3069 people with chronic kidney disease progressed to end stage renal disease, and the risk was especially low in people without diabetes or hypertension, women, and those aged  $\geq 70$  or with a glomerular filtration rate 45-59 ml/min/1.73 m<sup>2</sup> at screening. In contrast, there was a high cardiovascular mortality: 3.5, 7.4, and 10.1 deaths per 100 person years among people with a glomerular filtration rate 45-59, 30-44, and  $< 30$  ml/min/1.73 m<sup>2</sup>, respectively.

**Conclusion** Screening people with hypertension, diabetes mellitus, or age  $> 55$  was the most effective strategy to detect patients with chronic kidney disease, but the risk of end stage renal disease among those detected was low.

## Introduction

Currently, screening for chronic kidney disease is accepted practice only in patients with hypertension or diabetes.<sup>1,2</sup> More widespread screening is increasingly proposed,<sup>3-6</sup> including screening of all patients visiting general practitioners.<sup>7</sup> Recommendations, however, are based mostly on consensus procedures,<sup>5,8</sup> and the different screening strategies have not been compared for their ability to detect chronic kidney disease or their

efficiency. It has also been assumed that most patients with advanced renal insufficiency (stages 3-5) will eventually require renal replacement therapy,<sup>9</sup> but the natural course in those with newly detected disease (stages 3-5) is not well described.

We compared strategies for detecting patients with chronic kidney disease and examined the occurrence of end stage renal disease or cardiovascular death in these patients. We used data from the population based Nord-Trøndelag health study (HUNT study), Norway, and assessed different screening models. We also report on progression to end stage renal disease or cardiovascular death over the next eight years.

## Material and methods

### Study sample and design

During 1995-7, a large scale general health survey was conducted in Nord-Trøndelag County, Norway.<sup>10</sup> The population is ethnically homogenous and fairly representative of Norway. Everyone aged  $\geq 20$  ( $n = 92\ 939$ ) was invited to participate, and 70.6% did so. The survey comprised a questionnaire and clinical examination, including analysis of serum creatinine concentration. Three consecutive standardised blood pressure measurements were recorded. Participants were observed to 31 June 2004 or until advancement to end stage renal disease or death, by individual linkage to central registries with the unique identification number of every Norwegian citizen. See [bmj.com](http://bmj.com) for laboratory methods and estimation of glomerular filtration rate.

### Statistical analysis

We assessed the established model of screening only people with previously known diabetes mellitus or treated hypertension. We evaluated models that included people with other risk factors like higher age groups, obesity, smoking, cardiovascular disease, or family history of hypertension or diabetes. Finally, we assessed screening models proposed by international authorities: a modification of the UK chronic kidney disease guidelines (screening people with diabetes/hypertension/cardiovascular disease/moderate to severe lower urinary tract symptoms/autoimmune disease); a modification of the US kidney disease outcomes quality initiative guidelines (screening people with diabetes/hypertension/age  $> 60$ /autoimmune disease); and the International Society of Nephrology (screening everybody). When appropriate, we used receiver operating characteristics curves

Editorial by Clase

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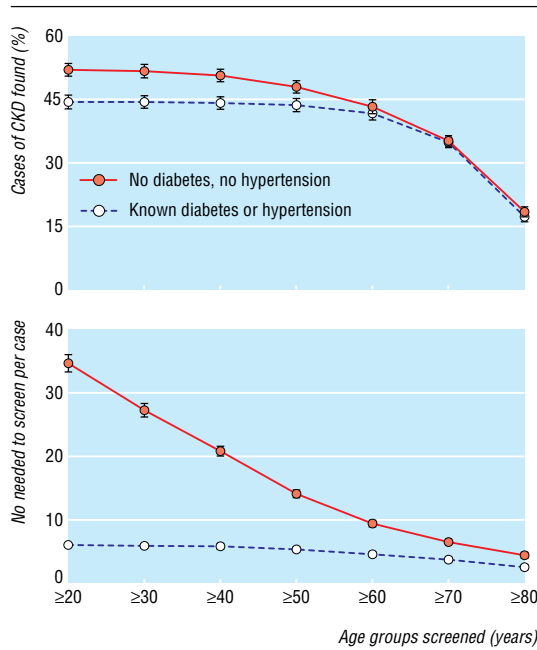
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**Fig 1** Effect of age restriction on screening people with (n=8368) and without (n=56 825) diabetes or hypertension. Top: proportion of people with chronic kidney disease (CKD) stage 3-5 identified by screening. Bottom: number needed to screen to find one person with chronic kidney disease stage 3-5. Error bars represent 95% confidence intervals

(ROC) to find the cut-off with the highest sum of sensitivity and specificity.

We evaluated the strategies as percentage of all patients with chronic kidney disease stage 3-5 (glomerular filtration rate < 60 ml/min/1.73 m<sup>2</sup>) and stage 4-5 (glomerular filtration rate < 30 ml/min/1.73 m<sup>2</sup>) in the general population identified with a particular strategy (“detection rate”); percentage of total adult population included for screening; and the number of people we need to screen to find one case. For this we calculated 95% confidence intervals as the inverse of the 95% confidence intervals of the prevalence estimates. We evaluated the clinical importance of detecting patients with chronic kidney disease stage 3-5 with Kaplan Meier analysis for survival without end stage renal disease and cardiovascular

mortality. We used Cox proportional hazard regression analysis to evaluate the influence of level of glomerular filtration rate, age, sex, diabetes, and hypertension on progression to end stage renal disease among those with chronic kidney disease. For all analyses we weighted data to reflect the actual population age distribution.

## Results

### Screening models for chronic kidney disease stage 3-5

Glomerular filtration rate could be estimated in 65 193 people—that is, 99.4% of the participants. Median age was 49.0 (range 20-103), 3.0% reported having diabetes mellitus, and 11.1% were taking medication for hypertension. The prevalence of chronic kidney disease stage 3-5 (glomerular filtration rate < 60 ml/min/1.73 m<sup>2</sup>) was 4.7% (n = 3069). See [bmj.com](http://bmj.com) for baseline characteristics.

Restriction of screening to everyone with known hypertension or diabetes mellitus identified 44.2% (95% confidence 42.7% to 45.7%) of all cases of chronic kidney disease, and 5.9 people (5.7 to 6.2) were screened to find one case. Because this high risk model detected less than half of all cases, we also evaluated screening in people without previously known diabetes or hypertension. In this group, which included the remaining 55.8% of chronic kidney disease cases, the number needed to screen was 34.6 (33.3 to 36.0) per case, and we considered various selection criteria for improving effectiveness. Figure 1 illustrates that the detection rate started to fall when we increased the age cut-off to 50-60 years. Age restriction, however, dramatically reduced the number needed to screen for people without diabetes or hypertension, while the effect was small for those with diabetes or hypertension. Age restriction therefore seemed most relevant for people without diabetes or hypertension, and in this group analysis of receiver operating characteristics curves indicated that maximum sensitivity plus specificity would be achieved by testing those aged >55.

The table lists effectiveness data. Extension of screening beyond people with diabetes or hypertension by including other risk factors for chronic kidney disease, such as family history, previous cardiovascular disease, obesity, or smoking, increased the detection rate to 81.4%. The number needed to screen, however, increased significantly to 19.1, and models with a high detection rate and a low number needed to screen are more desirable. The UK and US guidelines resulted in a similar number needed to screen but the UK guidelines had a detection rate of only 51.6% (49.7% to 53.4%). Theoretically, the International Society of Nephrology’s guidelines would identify 100% of cases, but the number needed to screen was 20.6 (20.0 to 21.2). The ranking of strategies was quite similar with glomerular filtration rate < 30 ml/min/1.73 m<sup>2</sup> as outcome, but the number needed to screen was twentyfold higher.

### Progression to end stage renal disease or cardiovascular death

During a median follow-up of 8.0 years (range 0.1-8.9) 51 of 65 604 participants progressed to end stage renal

Effectiveness of different screening strategies for detecting people with chronic kidney disease (CKD)

Screening strategy	CKD stage 3-5 (GFR <60 ml/min/1.73 m <sup>2</sup> )		
	% found*	% included†	NNTS‡ (95% CI)
DM/HT	44.2	12.0	5.9 (5.7 to 6.2)
DM/HT/family§	59.8	41.8	15.3 (14.8 to 15.9)
DM/HT/CVD	57.5	16.0	6.1 (5.9 to 6.3)
DM/HT/CVD/obesity/smoking	73.8	50.0	15.8 (15.2 to 16.3)
DM/HT/CVD/obesity/smoking/family§	81.4	66.9	19.1 (18.5 to 19.8)
DM/HT/>55	93.2	37.1	8.7 (8.5 to 9.0)
UK CKD guidelines	51.6	17.5	8.9 (8.5 to 9.3)
US KDOQI guidelines	89.3	29.0	8.7 (8.4 to 9.0)
ISN guidelines (everybody)	100.0	100.0	20.6 (20.0 to 21.2)

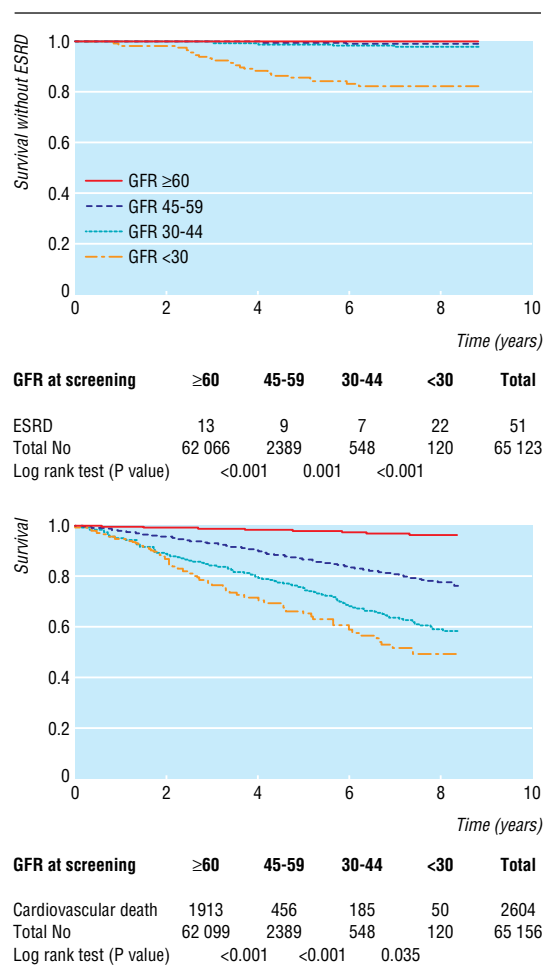
GFR=glomerular filtration rate; DM=diabetes mellitus; HT=hypertension; CVD=cardiovascular disease; KDOQI=kidney disease outcomes quality initiative; ISN=International Society of Nephrology.

\*Proportion of valid cases with GFR <60 ml/min/1.73 m<sup>2</sup> or GFR <30 ml/min/1.73 m<sup>2</sup> from the HUNT II cohort detected with screening strategy.

†Proportion of valid subjects selected for screening with strategy.

‡Number needed to screen to find one case.

§First degree relative with hypertension or diabetes.



**Fig 2** Survival without end stage renal disease (ESRD) and cardiovascular death by glomerular filtration rate (GFR) (ml/min/1.73 m<sup>2</sup>) at screening

disease, and 2604 of 5640 deaths were from cardiovascular disease. More than 99% of those with glomerular filtration rate 45-59 ml/min/1.73 m<sup>2</sup> were free from end stage renal disease after eight years (fig 2). Among those with rate 30-44 ml/min/1.73 m<sup>2</sup> 98% were free from end stage renal disease. The corresponding proportion among people with glomerular filtration rate <30 ml/min/1.73 m<sup>2</sup> was only 80%. Incidence rates of end stage renal disease were 0.04, 0.2, and 2.6 per 100 patient years in these groups, respectively. Full analysis of those with glomerular filtration rate <60 ml/min/1.73 m<sup>2</sup> (n = 3049) showed that the risk of progression to end stage renal disease was influenced by several variables: glomerular filtration rate was of major importance (hazard ratio 1.0 for rate 45-59; 4.2 (1.5 to 11) for rate 30-44; 68.5 (30 to 156) for rate <30 ml/min/1.73 m<sup>2</sup>), but there was also an increased risk in men (3.2 (1.6 to 6.4)), in people aged <70 years (5.7 (2.8 to 11)), and in those with diabetes or hypertension (3.1 (0.98 to 10)). Smoking, body mass index, and prevalent cardiovascular disease were not of significance.

Cardiovascular death accounted for 56% of the total number of deaths among people with chronic kidney disease compared with 44% in those without chronic kidney disease. Cardiovascular mortality among those without chronic kidney disease was 0.4

per 100 person years. Mortality, however, was much higher among people with chronic kidney disease and increased with decreasing glomerular filtration rate: 3.5 for rate 45-59, 7.4 for rate 30-44, and 10.1 for rate <30 ml/min/1.73 m<sup>2</sup>.

## Discussion

A high risk screening model targeting only those with diabetes or hypertension would identify less than half of those with chronic kidney disease. A model that also targeted those aged >55 would identify 93%, with only a few more people needed to screen than for the high risk strategy (nine versus six per case). The incidence rate of end stage renal disease was low among people with glomerular filtration rate 30-60 ml/min/1.73 m<sup>2</sup> at screening, while cardiovascular mortality was much higher (0.1 and 4.2 per 100 person years, respectively). Cases with glomerular filtration rate <30 ml/min/1.73 m<sup>2</sup> had a high risk for both outcomes (incidence of end stage renal disease 2.6 and cardiovascular mortality 10.1 per 100 person years).

### Strengths and weaknesses of the study

Our use of death certificates to ascertain cause of death and reliance on one creatinine measurement might have led to misclassification. We had no data on the effect of intervention or costs of screening and follow-up. We did not know how many prevalent cases of chronic kidney disease were already known to the health services, but studies from several countries indicate that the number is low (5-25%). Our study, however, was based on data from a large survey with a high participation rate. We minimised the risk of underestimating glomerular filtration rate by thorough adjustment of serum creatinine values. Linkage to accurate and complete central registries for information on renal replacement therapy and mortality was possible in all cases. Comprehensive cost effectiveness studies are needed to show whether screening is justified or not. The optimal screening interval also remains to be found.

### Comparison of strategies

We are aware of only one other study reporting on the performance of similar screening strategies.<sup>11</sup> It reported that seven people with diabetes or hypertension or with first degree relatives with diabetes, hypertension, or kidney disease need to be screened for one case of chronic kidney disease to be found. We found we needed to screen 15 people when we used similar criteria. Other risk factors, however, such as obesity and African descent are more prevalent in the US. Effectiveness of strategies targeting high risk subgroups could therefore be different. A significant proportion of patients, however, could still escape detection.

An extensive cost effectiveness analysis of screening for proteinuria in US adults showed that maximising sensitivity was more important than maximising specificity.<sup>12</sup> According to this, the US guidelines or the simple strategy of targeting people with diabetes, hypertension, or age >55 would be good choices.

Our data show that progression to end stage renal disease among patients with chronic kidney disease stage 3-5 is rare, contrary to the previous assumption

### What is already known on this topic

Knowledge of the disease, the test, and effectiveness are important for screening programmes, but this information is partly missing for chronic kidney disease

Currently, screening for chronic kidney disease is established for patients with hypertension or diabetes, but UK and US guidelines recommend expanding these criteria

### What this study adds

A simple screening strategy targeting people with diabetes, hypertension, or age > 55 had the highest detection rate for chronic kidney disease combined with a low number needed to screen

Most patients detected had a low risk of progression to end stage renal disease

Whether screening is cost effective needs further research, and extending screening to people without diabetes or hypertension cannot yet be recommended

that most of these patients will eventually require renal replacement treatment.<sup>9</sup> The lower risk in our study may be explained by the inclusion of truly unselected cases, while other studies included individuals seeking medical advice.

### Health policy and clinical implications

Efficient screening for chronic kidney disease might lead to an increase in workload for the health services as the patients detected are at high risk and need intensive intervention to prevent progression to end stage renal disease and cardiovascular complications. The costs of detecting patients and treating them might not be economically balanced in relation to possible expenditure on medical care as a whole.

We have shown that finding cases of chronic kidney disease can be done effectively, and that most patients with a glomerular filtration rate of 30–60 ml/min/1.73 m<sup>2</sup> at screening had a low incidence of end stage renal disease, at least in the first eight years, while their risk of cardiovascular mortality was high. This could be important for planning an optimal follow-up.

The HUNT study is a collaboration between HUNT Research Center, Faculty of Medicine, Norwegian University of Science and Technology, Verdal; Norwegian Institute of Public Health, Oslo; Nord-Trøndelag County Council; and Central Norway Regional Health Authority. We thank the health service and people of Nord-Trøndelag for their endurance and participation and Stephen Lock for his help in preparing the manuscript. Contributors: See [bmj.com](http://bmj.com)

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Competing interests: None declared.

Ethical approval: Regional committee for medical research ethics, health region 4, Norway. Additional permissions for linking data registries and for handling the health data was

given by the Health Department and by the Data Inspectorate, respectively.

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### Corrections and clarifications

*Eastern Mediterranean Association of Medical Editors*

We introduced two errors into this letter by Arash Etemadi and colleagues (*BMJ* 2006;333:862, 21 Oct). Firstly, somehow we moved Akbar Fotouhi's name from fourth place to second—the correct order is Arash Etemadi, Asieh Golozar, Jane Nicholson, Akbar Fotouhi. Secondly, we should have described Arash Etemadi as an epidemiologist.

*Self management of arthritis in primary care: randomised controlled trial*

In this research paper by Marta Buszewicz and colleagues (*BMJ* 2006;333:879–82, 28 Oct), the authors meant, but forgot, to acknowledge Lisa Cotterill, Gill Dorer, Jeannett Martin, Claire Newland, Gloria Randall, and Tom Sensky, who are all members of the trial steering committee.

*Pulmonary artery catheters*

An incomplete reference in this editorial by Simon Finfer and Anthony Delaney (*BMJ* 2006;333:930–1, 4 Nov) might have caused readers difficulty in searching for the cited report. Reference 3 (*Health Technol Assess* 2006;10:1–150) should have included the issue number (29). The link on [bmj.com](http://bmj.com) was also wrong but has now been corrected.

*Measles in the United Kingdom: can we eradicate it by 2010?*

The wording of the title of this clinical review by Perviz Asaria and Eithne MacMahon was the result of late changes that we made in the editorial department (*BMJ* 2006;333:890–5, 28 Oct). Owing to pressing deadlines, we made the changes without consulting the authors, who would have pointed out that “eradication” was incorrect in this context. As they explained in their article, eradication relates to worldwide elimination of measles. The error was repeated on the front cover. We apologise for the errors.