Does stage-3 chronic kidney disease matter?

A systematic literature review

Pawana Sharma, Keith McCullough, Graham Scotland, Paul McNamee, Gordon Prescott, Alison MacLeod, Nick Fluck, William Cairns Smith, Corri Black

ABSTRACT

Background

Stage-3 chronic kidney disease (CKD) is the first stage that is identifiable from a blood test alone. In the UK, it accounts for the majority of people on primary care CKD registers. It also represents a group of people who, in the past, would have gone unnoticed clinically. In order to support patients and plan services, the natural history of stage-3 CKD is important.

Aim

To systematically review the natural history of stage-3 CKD in order to describe all cause mortality, cardiovascular morbidity and mortality, and renal outcomes.

Design of study

Systematic review of the literature.

Method

MEDLINE and Embase databases were searched from 1998 to February 2009. Systematic reviews and cohort studies that included adults with stage-3 CKD were considered eligible. Studies were appraised and data extracted by one reviewer and checked by a second.

Results

Thirteen studies were identified including a total of 728 328 people. The all-cause mortality rate varied from 6% in 3 years to 51% in 10 years and was higher in stage-3B CKD (4.8 per 100 person-years) than stage-3A CKD (1.1 per 100 person-years). The relative risk of mortality (all-cause mortality or cardiovascular disease [CVD] mortality) was higher in stage-3 CKD compared with no CKD, but the increase was small for those with stage-3A CKD (hazard ratio [HR] 1.2–1.7) and greater in stage 3B (HR 1.8–3.3). End-stage renal disease was rare (4% in 10 years) and renal progression was evident in <20% of patients after 5 years.

Conclusions

For patients with stage-3 CKD, risk of mortality was higher than for those without CKD, but the risk of progression was low. CKD registers provide an opportunity for GPs to assess the risk of patients developing CVD.

Keywords

chronic kidney disease; natural history; primary care; systematic review.

INTRODUCTION

With prevalence studies currently estimating that around 5% of the adult population will have evidence of stage-3 or 'moderate' chronic kidney disease (CKD),[1–7] the last 5 years has seen CKD become a major healthcare challenge. Commentators have described CKD as a 'major public health problem' and talked of an 'epidemic'.[8–10] Although there is some evidence that the prevalence in CKD is increasing, the change in epidemiology is essentially driven by an increase in detection and awareness.[11]

In 2002, the US Kidney Disease Outcomes Quality Initiative (KDOQI) proposed a definition of CKD with five stages that has been adopted internationally: 'kidney damage or decreased kidney function (glomerular filtration rate [GFR] <60 mL/min/1.73 m^2) for ≥3 months' (Table 1).[12,13] Those with GFR ≥60 mL/min/1.73 m^2 (Stage 1–2) are considered to have CKD if they presented with kidney damage as defined by pathological abnormalities or markers of

P Sharma, *BPharm, MSc, research fellow,* ***G Prescott***, *BSc, MSc, PhD, CStat, senior lecturer in medical statistics,* ***A MacLeod***, *MRCP, MD, professor of medicine and pharmacology,* ***W Cairns Smith***, *PhD, MD, MRCP, FFPH, clinical professor of public health,* ***C Black***, *BSc, MSc, MRCP, FFPH, senior clinical lecturer;* ***G Scotland***, *BSc, MSc, research fellow;* ***P McNamee***, *BA, MSc, PhD, senior research fellow, Health Economics Research Unit, University of Aberdeen, Aberdeen;* ***K McCullough***, *MRCP, specialist registrar in nephrology,* ***N Fluck***, *MRCP, MD, consultant nephrologist, Aberdeen Royal Infirmary Renal Unit, NHS Grampian, Aberdeen.*

Address for correspondence
Mrs Pawana Sharma, University of Aberdeen, Health Service Research Unit, Foresterhill, Health Sciences Building (second floor), Aberdeen, AB25 2ZD.
E-mail: p.sharma@abdn.ac.uk

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damage. In the UK, and elsewhere, this new definition has been accompanied by changes to improve the consistency of laboratory reporting, making it easier for clinicians to recognise impairment in kidney function.[14] The addition of CKD management to the Quality and Outcomes Framework (QOF) in 2006 encouraged GPs who were responsible for the care of the majority of people with CKD to identify those with GFR <60 mL/min/1.73 m^2 (stage-3 CKD or worse) and record them on a practice register. Proactive management of blood pressure and use of angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers is also supported in the QOF and clinical guidelines.[15,16] Internationally, similar opportunistic detection has been implemented and some countries or communities have introduced screening of groups who are at high risk of developing CKD.[17,18]

Stage-3 CKD is the first stage that can be identified from a blood test alone, and accounts for the vast majority of people now being detected and labelled with CKD on general practice disease registers. In every 10 000 adult patients in primary care, an estimated 144 new patients will be detected each year with stage-3 CKD, as compared with three in stage 4 and 0.3 in stage 5.[19] Stage-3 CKD also represents those people who would previously have gone unnoticed clinically, people who reflect a very different population than those diagnosed as having CKD and attending nephrology clinics in the past. In stages 4 and 5, the clinical significance of CKD is well understood, with many individuals experiencing symptoms and complications (hypertension, anaemia, undernutrition, renal bone disease, and metabolic acidosis) as well as an increased risk of cardiovascular disease (CVD), all-cause mortality and end-stage renal disease (ESRD) requiring renal replacement therapy (RRT).[14,15] In stage 3, the clinical implications for the future health of the patient are less clear.[20,21]

In order to support patients, plan services, evaluate cost-effectiveness and develop policies, it is critical that the natural history of stage-3 CKD is understood. This article systematically reviews the natural history of stage-3 CKD in terms of mortality and renal outcomes.

METHOD

Search strategy

A systematic review of the published literature was conducted, searching the MEDLINE and Embase databases for studies dating from 1998 to February 2009. A combination of medical subject headings and text terms were used for 'chronic kidney disease' and 'natural history' (Table 2). A manual search of reference lists from included studies was carried out.

How this fits in

Chronic kidney disease (CKD) has now been recognised as a major healthcare challenge. The natural history of advanced stages of CKD have been widely reported but less is known about the stage 3 CKD. Stage 3 CKD is the first stage that is identifiable from a blood test alone and accounts for the majority of people on primary care CKD registers. This systematic literature review studied the natural history of stage 3 CKD. It found that mortality was consistently higher and cardiovascular disease was common compared to those without CKD, particularly for those with stage 3B CKD. Risk of progression to ESRD and dialysis was a substantially less frequent outcome.

Searches were restricted to English language.

Inclusion/exclusion criteria

Systematic review, meta-analysis, or follow-up study (prospective or retrospective) of people with CKD that included adults (≥18 years) with stage-3 CKD (GFR 30–59 mL/min/1.73 m^2) were considered eligible. Studies were restricted to non-trial study designs. Where a study also included participants in other stages of CKD, it was required that outcome data were presented separately for stage 3. Studies were required to have a minimum of 2 years' follow-up. Studies with fewer than 100 subjects were excluded. Studies of single specific renal diagnoses or those including only pregnant participants were also excluded.

The primary outcome of interest was all-cause mortality. Secondary outcomes included: cardiovascular morbidity and mortality, and renal outcomes (CKD progression, ESRD or RRT). CKD progression was measured by rate of decline of estimated glomerular filtration rate (eGFR) or creatinine clearance, rise in serum creatinine, or transition through progressive stages of CKD.

Study identification

Two authors independently screened all titles and abstracts to identify potentially relevant studies. Full

Table 1. Kidney Disease Outcomes Quality Initiative definition of chronic kidney disease (modified by the UK Renal Consensus conference to split stage 3 into two subgroups).[12,13]

CKD stage	Definition (chronicity defined by presence of abnormality for ≥3 months)
Stage 1	Kidney damage with normal or raised GFR (≥90 mL/min/1.73 m^2)
Stage 2	Kidney damage with mildly impaired GFR (60–89 mL/min/1.73 m^2)
Stage 3A	Moderately impaired GFR (45–59 mL/min/1.73 m^2)
Stage 3B	Moderately impaired GFR (30–44 mL/min/1.73 m^2)
Stage 4	Severely impaired GFR (15–29 mL/min/1.73 m^2)
Stage 5	End-stage renal failure or GFR <15 mL/min/1.73 m^2

Kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies. CKD = chronic kidney disease. GFR = glomerular filtration rate.

Table 2. Example search strategy for MEDLINE (modified for Embase).

Search	Search term
1	Exp *Kidney Failure, Chronic/
2	(Renal or kidney or nephropath$ or nephrolog$).tw.
3	CKD.tw.
4	Exp *Natural History/
5	Exp Disease Progression/
6	Natural course.tw.
7	Disease course.tw.
8	(Cohort or follow-up or follow-up or longitudinal or prospective or screening or cross sectional or cross-sectional).tw.
9	Population-based stud$.tw.
10	Exp Mass Screening/
11	Exp cohort studies/ or exp cross-sectional studies/
12	Exp “review”/
13	Mass screen$.tw.
14	Review.ti.
15	1 or 2 or 3
16	4 or 5 or 6 or 7
17	8 or 9 or 10 or 11 or 12 or 13 or 14
18	15 and 16 and 17
19	Limit 18 to (English language and humans)

articles were retrieved in cases of disagreement. All the full articles were assessed against the inclusion and exclusion criteria by two authors. All disagreements were resolved by discussion and there was no need to seek the opinion of a third reviewer. Only those studies presenting relevant outcomes by stage-3 CKD were retained for data extraction and quality assessment.

Table 3. Quality and judgement criteria.

Criteria	Details
1. Sample selection	Representativeness of the cohort for that community Study population adequately defined Information recorded prospectively Ascertainment of sample described Assessment of outcome described
2. Follow-up	Losses to follow-up less than 10% Reason for loss to follow-up given Characteristics of patients lost to follow-up described
3. Other biases	Design-specific sources of bias mentioned Design-specific bias corrected
4. Chronicity	CKD defined to be chronic (≥3 months)
5. Measurement of renal impairment	Differences in assays over time or between laboratories accounted for
Quality judgement	
Excellent	Meeting all criteria (1–5) listed above
Good	Meeting any three or four criteria out of the five criteria listed
Moderate	Meeting any two criteria out of the five criteria listed
Poor	Meeting less than two criteria of the five criteria listed

CKD = chronic kidney disease.

Data extraction and quality assessment

One author extracted data and assessed the quality of each study using a specifically designed and piloted data-extraction form. A second researcher checked the extracted data for accuracy and disagreements were resolved by a third reviewer. Quality was assessed as described in Table 3. Studies were not excluded based on quality.

Quality assessment included generic quality criteria adapted from various methodological quality assessment tools,[22–26] and CKD-specific quality criteria adapted from a systematic review of the prevalence of CKD.[7] Generic quality issues included sample selection, follow-up, and bias. Specific quality criteria considered the definition of chronicity of CKD and the standardisation of the measure of renal function impairment. It was necessary to establish chronicity in order to exclude acute renal impairment and testing errors and, thus, reduce classification bias. Good-quality studies should use reliable, validated and less-biased assay techniques (modern compensated assays, enzymic assays, assays traceable to gold standard isotope dilution mass spectrometry) to minimise measurement bias.

Synthesis of results

The results were tabulated, grouped by study type, and reported narratively. Relative risk estimates (hazard ratios [HRs] and standardised mortality ratios) were converted to natural logs (ln), and standard deviations estimated to allow graphical presentation using Review Manager software (Version 5). Due to the variability in the reporting of outcomes, data were not pooled in a meta-analysis.

RESULTS

Study selection

Out of 3453 references identified and screened, 118 full papers were retrieved; 17 papers from 13 studies met the inclusion criteria and were critically appraised (Figure 1). Hallan included three papers,[27–29] Keith included two papers,[30,31] and Eriksen included two papers.[32,33] The first study in each is the primary reference and has been quoted throughout. No systematic reviews of the natural history of stage-3 CKD were identified.

Study characteristics

A summary of the characteristics of the included studies is presented in Table 4. There were two methodological groups of studies:

- Clinical populations (n = nine studies): studies based on participants recruited from a clinical population (those from clinical record databases, laboratories, primary care, or clinical settings).[31,32,34–40]

- General populations (*n* = four studies): studies that were based on participants recruited from a general population (representing people in the community and identified through screening programmes).[27,41–43]

All but one study,[32] reported findings for other CKD stages. The results of the participants with stage-3 CKD have been focused on only.

A total of 728 328 people with stage-3 CKD were included; they accounted for between 4.5%[27] and 100%[32] of study cohorts. Follow-up varied from 2 years to 16 years. Most of the studies used the Modification of Diet in Renal Disease equation for GFR estimation, but one used the Cockroft and Gault equation.[35]

Most studies (five) were from the US, with two each from Norway and Taiwan, and one each from the UK, the Netherlands, Canada, and Japan.

Quality of included studies

The quality assessment of included studies is shown in Table 5. None of the studies fulfilled all the quality criteria, however most (nine) were rated as 'good' quality; only one of the studies[35] was graded as 'poor'. Six studies established the chronicity of reduced eGFR.

Evidence of mortality

Studies reported two types of mortality results for stage-3 CKD:

- the rate of mortality (number of deaths in a group per unit of time); and
- the risk of mortality (number of deaths compared with another group).

Among the nine studies reporting all-cause mortality, only one was a general population-based cohort;[43] the other eight included clinical populations.[30,32,34–37,39,40] Two studies reported CVD morbidity[36,41] and three CVD mortality.[27,34,43] Detailed results of all-cause mortality, and CVD morbidity and mortality are given in Table 6 and Figure 2.

Rates of all-cause mortality, and CVD morbidity and mortality. In the six studies reporting mortality rates,[30,32,34–36,39] estimates varied substantially but, where reported, mortality was consistently higher in those who had stage-3 CKD compared with those who did not have CKD. Chiu *et al*[34] reported the lowest cumulative mortality rate of 6% during 3 years' follow-up (2.1 per 100 person-years). The highest was reported by Eriksen and Ingebretsen[32] with a mortality rate of 32% at 5 years and 51% at 10 years. The mortality rate was substantially higher in stage 3B (4.8 deaths per 100 person-years) compared with stage 3A (1.1 deaths per 100 person-years).[36] Stratified annual mortality rates increased with age and eGFR. O'Hare *et al*[39] reported that the mortality rate in the youngest group of patients (aged 18–44 years) with eGFR 50–59 mL/min/1.73 m^2 was as low as 0.8% per year but increased to 14.7% in patients (85–100 years old) with eGFR 30–39 mL/min/1.73 m^2.

CVD mortality and events varied, but again was consistently higher in those who had stage-3 CKD as compared to those with no CKD. In a clinical population study, 2% at 3 years were reported to have CVD deaths.[34] In general population studies, CVD death rates varied from 4% at 13 years[43] to 21% at 10 years.[27] CVD mortality rates were higher in stage 3B (7.4 per 100 person-years,[27] 8% at 13 years[43]) as compared to stage 3A (3.5 per 100 person-years,[27] 3% at 13 years[43]).

CVD event rates also varied from 2.1 per 100 person-years[41] to 11.3 per 100 person-years.[36] CVD event rates more than trebled from 3.7 per 100 person-years at stage 3A to 11.3 per 100 person-years at stage 3B.[36]

Risk of all-cause mortality, and CVD morbidity and mortality versus no CKD. Four studies reported the relative risk of mortality for stage-3 CKD as compared with those without CKD.[32,36,39,43] A small increase in the risk of mortality (HR 1.2–1.8), after adjustment for differences between the comparison groups in age, sex, and comorbidities, was observed for those people with stage-3 CKD compared with those with eGFR ≥60 mL/min/1.73 m^2[36] and eGFR 60–89mL/min/1.73m^2 without proteinuria.[43] Eriksen and Ingebretsen[32] reported an increase in risk of all-cause mortality with an HR of 1.3 (95% CI = 1.1 to

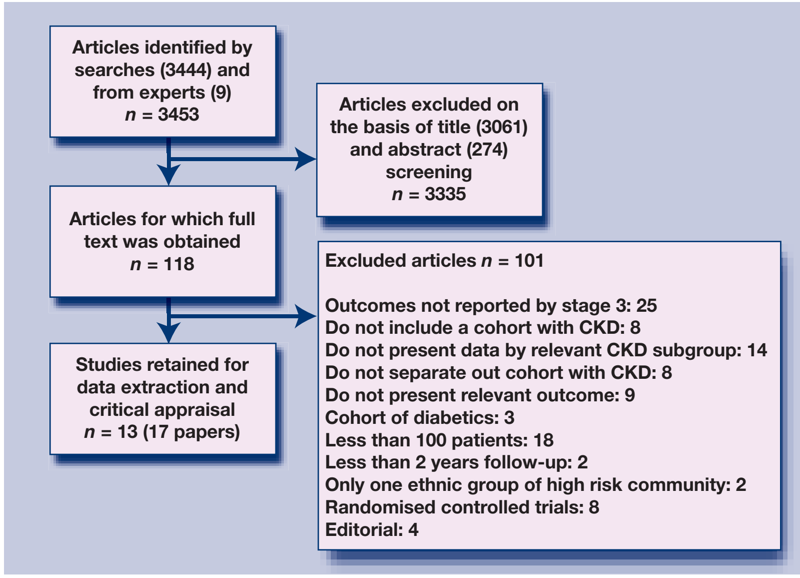


Figure 1. Summary of study selection.

Table 4. Characteristics of included studies.

Study	Cohort ascertainment	Minimum follow-up, years	Participants, *n*: All	Participants, *n*: Stage 3 CKD (% of total)	Mean age of participants, years: All	Mean age of participants, years: Stage 3 CKD	Male participants (%): All	Male participants (%): Stage 3 CKD	Comorbidities, stage 3 CKD only (%)
Clinical population-based cohort									
Chiu *et al*[34] Taiwan, 2008	Referrals to nephrology outpatient clinic	3	433	184 (42.5)	65.6	65.7	61.7	74.5	DM: 30.4 HBP: 6.0 CVD: 27.2 P: 70.6
Djamali *et al*[35] US, 2003	Hospital inpatients and outpatients with creatinine >1.3 mg/dL	16	1762	403 (46.0)	54	56	60	54	DM: 43
Eriksen and Ingebretsen[32] Norway, 2006 Additional publication[33]	Hospital laboratory database	10	3047	3047 (100)	75[a]	75	30	30	NR
Go *et al*[36] US, 2004	Hospital laboratory database and renal registry	4	1 120 295	3: 187 701 (16.8) 3A: 153 426 (13.7) 3B: 34 275 (3.0)	52.2	3A: 65.4 3B: 71.2	45.4	3A: 39.3 3B: 38.4	DM 3A: 12.3 3B: 19.6 CVD 3A: 13.2 3B: 20.6 P 3A:8.9 3B: 17.7
Hemmelgarn *et al*[37] Canada, 2006	Regional laboratory database	Median 2 (IQR 1.9–2.2)	10 184	3 191 (31.0)	range: 75–78	77.8	45.1–37.5	37.5	DM: 19.8
Keith *et al*[30] US, 2004 Additional publication[31]	Health insurance claims database	5.5	27 998	1 741 (6.2)	range: 61–74	71.6	NR	37.8	[b]DM:15.8 [b]CVD: 13.1 [b]HBP: 37.4
Khatami *et al*[38] UK, 2007	Hospital database	4	8160	520 (6.4)	Male: 63.5[a] Female: 67[a]	NR	58.7	NR	[b]DM: 1.3 [b]CVD: 0.4
O'Hare *et al*[39] US, 2006	Veterans' health insurance database (128 centres) and National ESRD registry	Mean 3.17 (SD 0.62)	2 583 911	476 337 (18.4)	63.6	NR	95	NR	[b]DM: 10-36 [b]CVD: 6-58
Orlando *et al*,[40] US, 2007	Veterans' health insurance (single centre)	Approx. 5 (mean 3.5)	1553	416 (26.8)	70	NR	100	100	[b]DM: 52 [b]HBP: 92 [b]P: 89
General population-based cohort									
Brantsma *et al*[41] the Netherlands, 2008	Health screening: sample enriched for those with albuminuria	Median 7.5 (IQR: 6.9–7.8)	8495	491 (31.0)	49.2	63.2	50	53.4	DM: 5.9 HBP: 46.3
Hallan *et al*[27] Norway, 2006 Additional publications[28,29]	Health screening	10.3	65 604	3: 2973 (4.5) 3A: 2389 (3.6) 3B: 548 (0.8)	49	NR	46.8	NR[b]	DM: 3 [b]HBP: 11.1 [b]CVD: 7.9
Imai *et al*[42] Japan, 2008	Health screening	10	120 727	3: 25 715 (21.4)	range 40–79	NR	32.7	NR	[b]HBP: 13.9 [b]P: 1.7
Wen *et al*[43] Taiwan, 2008	Health screening	13	462 293	3: 25 609 (5.5) 3A: 22 597 (4.9) 3B: 3 012 (0.7)	41.8	61.9	49.8	53.4	DM: 14.5 HBP: 56.6 P: 20.4

CKD = chronic kidney disease. CVD = cardiovascular disease. DM = diabetes mellitus. ESRD = end-stage renal disease. HBP = high blood pressure. IQR = interquartile range. NR = not reported. P = proteinuria. [a]Median age in years. [b]Comorbidities in total CKD participants.

1.4) for each 10 mL/min/1.73 m^2 decrease in eGFR. Go *et al*[36] and Wen *et al*[43] reported that the relative risk of mortality for stage 3B was almost double that of stage 3A (Figure 2).

Table 5. Quality assessment of included studies.

Quality criteria	Study reference number 41	34	35	32	36	27	37	42	30	38	39	40	43
Sample selection													
Representative of the community	Y	Y	U	Y	Y	Y	Y	Y	Y	U	Y	Y	Y
Study population adequately defined	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	Y
Information recorded prospectively	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Ascertainment of sample described	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Assessment of outcome described	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Follow-up													
Loss to follow-up <10%	N	Y	N	C	N	C	C	C	C	C	U	Y	C
Reason for loss to follow-up given	N	N	Y	n/a	Y	n/a	n/a	n/a	n/a	n/a	–	N	n/a
Characteristics of patient loss to follow-up described	Y	N	N	n/a	Y	n/a	n/a	n/a	n/a	n/a	–	N	n/a
Other biases													
Design-specific sources of bias mentioned	Y	Y	Y	N	N	Y	Y	Y	Y	N	Y	Y	Y
Design-specific bias corrected	Y	Y	N	Y	N	Y	Y	Y	Y	N	Y	Y	Y
Chronicity													
CKD defined to be chronic (≥3 months)	N	Y	Y	Y	Y	N	N	N	Y	U	N	Y	N
Measurement of renal impairment													
Difference in assays over time or between labs accounted for	N	N	N	U	Y	Y	Y	Y	U	Y	N	N	Y
Overall quality	M	G	P	G	G	G	G	G	G	M	M	G	G

C = complete. CKD = chronic kidney disease. G = good. M = moderate. N = no. n/a = not applicable. P = poor. U = unclear. Y = yes.

O'Hare *et al*[39] estimated the relative risk of mortality stratified by age and level of renal function across stage 3 (eGFR only reported by following categories: 50–59, 40–49 and 30–39 mL/min/1.73 m^2), as compared with eGFR ≥60 mL/min/1.73 m^2. For those with eGFR 50–59 mL/min/1.73 m^2, older age groups (65–74 years) were found to be at no increased risk of all-cause mortality (HR 1.02, 95% CI = 1.0 to 1.1), whereas in younger patients (aged 18–44 years) the HR was 1.6 (95% CI = 1.3 to 1.9). For those with a lower level of renal function (eGFR 40–49 and 30–39 mL/min/1.73 m^2), associated relative risk decreased with increasing age. For example, risk of all-cause mortality for those with eGFR 40–49 mL/min/1.73 m^2 decreased from HR 1.9 (95% CI = 1.4 to 2.7 in those aged 18–44 years) to HR 1.4 (95% CI = 1.3 to 1.4 in those aged 65–74 years). Similarly, for those with eGFR 30–39 mL/min/1.73 m^2, risk decreased from HR 3.6 (95% CI = 2.5 to 5.1 in those aged 18–44 years) to HR 1.8 (95% CI = 1.8 to 1.9 in those aged 65–74 years).

Two studies reported risk of CVD events,[36,41] while only one[43] reported risk of CVD mortality. The risk of CVD events was increased in stage-3 CKD, as compared with no CKD (stage-3 HR 1.3 [95% CI = 1.0 to 1.7][41] and stage-3A HR 1.4 [95% CI = 1.4 to 1.5]).[36] Stage 3B had a 60% greater risk of CVD events than stage 3A.[36] Wen *et al*[43] reported an adjusted HR of 1.7 (95% CI = 1.5 to 2.0) for CVD deaths for those with stage-3A CKD (as compared with those with eGFR 60–89 mL/min/1.73 m^2 without proteinurea), again with a higher risk in those with stage 3B (HR 3.3; 95% CI = 2.7 to 4.1)[43] (Figure 2).

Evidence of renal outcomes

Renal outcomes were reported by eight studies and included ESRD, RRT, and CKD progression (Table 7).

End-stage renal disease or renal replacement therapy. Four studies reported rates of ESRD or RRT for specified time periods.[27,30,32,34] Cumulative incidence of renal failure at 5 years was 1.3–2% and 4% at 10 years for those with stage-3 CKD.[30,32] Chiu *et al*,[34] studying patients referred to a nephrologist, reported an ESRD (defined as initiation of RRT) rate of 1.4 per 100 person-years. Hallan *et al*,[27] in their general population study, reported a lower rate of ESRD for stage-3A CKD (0.04 per 100 person-years) than stage-3B CKD (0.2 per 100 person-years).

One study reported the risk of renal failure[32] and one reported the risk of ESRD[27] for those with stage-3 CKD, as compared with no CKD. Eriksen and Ingebretsen[32] reported an HR of 2.5 (95% CI = 1.9 to 3.3) for each eGFR decrease of 10 mL/min/1.73 m^2; a risk 5.3 times greater than the general population (standardised for age and sex). Hallan *et al*[27] estimated that the risk of progression to ESRD was 11.5 (95% CI = 6.6 to 20.2) for those with stage-3A

Table 6. Summary of all-cause mortality, and CVD morbidity and mortality in stage-3 CKD.

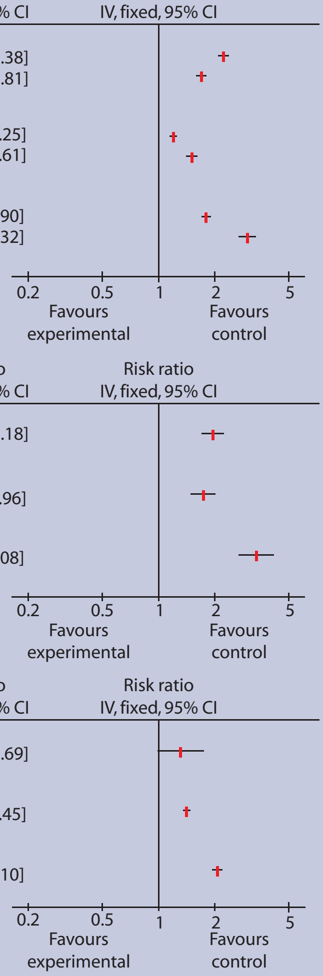
Study	Measures	All-cause mortality	CVD morbidity and mortality	Comments
Clinical population-based cohort				
Chiu *et al*[34]			CVD deaths	
	n/N:	11/184	3/184	
	Rates:	2.1 deaths/100py		
		6% at 3 years	2% at 3 years	
Djamali *et al*[35]	n/N:	85/403 (21%)	NR	
	Rates:	21% at 12.6 years	NR	Adjusted for age and sex
Eriksen and Ingebretsen[32]	n/N:	959/3047 (31.5%)	NR	
	Rates:	32% at 5 years (95% CI = 30 to 34)		
		51% at 10 years (95% CI = 48 to 55)		NR
Go *et al*[36]			CVD events[a]	
	n/N:	Stage 3: 19371/187701 (10.3%)	Stage 3: 53270/187701 (28.4%)	
		Stage 3A: 11569/153426 (7.5%)	Stage 3A: 34690/153426 (22.6%)	
		Stage 3B: 7802/34275 (22.8%)	Stage 3B: 18580/34275 (54.2%)	
	Rates:	Stage 3A: 1.1 deaths/100py[b]	Stage 3A: 3.7/100py[c]	Compared with those with eGFR ≥60:
		Stage 3B: 4.8 deaths/100py[b]	Stage 3B: 11.3/100py[c]	
Hemmelgarn *et al*[37]	n/N :	Stage 3B: 192/3191(6.0%)	NR	Proportions not reported for stage 3 or 3A
	Rates:	Not calculable[d]	NR	
Keith *et al*[30]	n/N:	423/1741	NR	
	Rates:	24% at 5 years	NR	
O'Hare[39]	n/N :	NR	NR	
	Rates:	Stratified by age group	NR	
Orlando *et al*[40]	n/N:	205/416	NR	
	Rates:	49% at ~5 years[e]	NR	
General population-based cohort				
Brantsma *et al*[41]			CVD events	
	n/N:	NR	NR	
	Rates:	NR	2.1/100py	Compared with those without CKD = 0.7/100py
Hallan *et al*[27]			CVD deaths	
	n/N:	NR	Stage 3: 641/2973 (21.6%)	
			Stage 3A: 456/2389 (19.1%)	
			Stage 3B: 185/548 (33.8%)	
	Rates:	NR	Stage 3A: 3.5/100py	Compared with eGFR ≥60 = 0.4/100py
			Stage 3B: 7.4/100py	
Wen *et al*[43]			CVD deaths	
	n/N:	Stage 3: 3856/25609 (15.1%)	Stage 3: 1032/25609 (4.0%)	
		Stage 3A: 2975/22597 (13.2%)	Stage 3A: 778/22597 (3.4%)	
		Stage 3B: 881/3012 (29.2%)	Stage 3B: 254/3012 (8.4%)	
	Rates:	Stage 3: 15% at 13 years	Stage 3: 4% at 13 years	
		Stage 3A: 14% at 13 years	Stage 3A: 3% at 13 years	
		Stage 3B: 29% at 13 years	Stage 3B: 8% at 13 years	

[a]An individual can experience more than one event. [b]0.76/100py. [c]2.11/100py; standardised for age. [d]Only median follow-up time reported. [e]Proportions who died while in stage 3. CKD = chronic kidney disease. CVD = cardiovascular disease. eGFR = estimated glomerular filtration rate expressed as mL/min/1.73 m^2. n = number of events. N = total number of patients with stage-3 CKD. NR = not reported. py = person-years.

CKD and 52.6 (95% CI = 29.6 to 93.4) for those with stage-3B CKD, as compared with those without CKD (eGFR ≥60 mL/min/1.73 m^2).

CKD progression. Rate of progression, as mean GFR or creatinine clearance decline, was reported by four studies[32,34,35,42] and ranged from 1.03 to 5.4 mL/min/1.73 m^2/year. Hemmelgarn *et al*[37] reported greater decline in eGFR per year (adjusted for age) for male participants (1.9 mL/min/1.73 m^2/year; 95% CI = 1.5 to 2.3) versus females (1.1 mL/min/1.73 m^2; 95% CI = 0.8 to 1.4).

Imai *et al*[42] graphically presented the annual rate of eGFR decline stratified by different age groups (40–49, 50–59, 60–69 and 70–79 years), sex and baseline eGFR (50–59, 40–49 and 30–39 mL/min/1.73 m^2). In general, it was observed that the rate of decline increased as the level of



All-cause mortality

Study or subgroup	log[risk ratio]	SE	CKD stage 3 Total	No CKD Total	Risk ratio IV, fixed, 95% CI
1.1.1 CKD stage 3					
Eriksen 2006 clinical[a]	0.799	0.035	3047	0	2.22 [2.08, 2.38]
Wen 2008 general	0.531	0.032	25609	405316	1.70 [1.60, 1.81]
1.1.2 CKD stage 3a					
Go 2004 clinical	0.182	0.022	153426	924136	1.20 [1.15, 1.25]
Wen 2008 general	0.412	0.034	22597	405316	1.51 [1.41, 1.61]
1.1.3 CKD stage 3b					
Go 2004 clinical	0.588	0.028	34275	924136	1.80 [1.70, 1.90]
Wen 2008 general	1.095	0.054	3012	405316	2.99 [2.69, 3.32]

Cardiovascular mortality

Study or subgroup	log[risk ratio]	SE	CKD stage 3 Total	No CKD Total	Risk ratio IV, fixed, 95% CI
1.2.1 CKD stage 3					
Wen 2008 general	0.652	0.066	25609	405316	1.92 [1.69, 2.18]
1.2.2 CKD stage 3a					
Wen 2008 general	0.531	0.072	22597	405316	1.70 [1.48, 1.96]
1.2.3 CKD stage 3b					
Wen 2008 general	1.194	0.108	3012	405316	3.30 [2.67, 4.08]

Cardiovascular events

Study or subgroup	log[risk ratio]	SE	CKD stage 3 Total	No CKD Total	Risk ratio IV, fixed, 95% CI
1.3.1 CKD stage 3					
Brantsma 2008 general	0.262	0.135	491	6095	1.30 [1.00, 1.69]
1.3.2 CKD stage 3a					
Go 2004 clinical	0.336	0.018	153426	924136	1.40 [1.35, 1.45]
1.3.3 CKD stage 3b					
Go 2004 clinical	0.693	0.026	34275	924136	2.00 [1.90, 2.10]

[a]Risk reported as standardised mortality ratio. CKD = chronic kidney disease.

Figure 2. Relative risk of all-cause mortality, cardiovascular disease mortality, and cardiovascular disease events.

kidney function decreased in both males and females and across all age groups (except in males aged 50–59 years). The highest rate of decline (mean 3.3; standard error of mean 0.7 mL/min/1.73 m^2/year) was observed in the youngest male group (aged 40–49 years) with an eGFR of 30–39 mL/min/1.73 m^2.

Eriksen and Ingebretsen's study,[32] which included only patients with stage-3 CKD, reported that only 6% had a mean eGFR decline greater than 5 mL/min/1.73 m^2 and 27% experienced no decline in function. Khatami *et al*[38] followed people with eGFR <60 mL/min for 4 years and reported that approximately 4% progressed to stage-4 or stage-5 CKD, 20% regressed to stage-2 CKD and 76% were stable. Orlando *et al*[40] reported that only 17% of those patients at stage 3 progressed to the next stage during at least 5 years follow-up.

DISCUSSION

Summary of evidence

Despite the substantial focus clinically, and at a policy level, on the management of mild to moderate or 'early' CKD, this is, to the best of our knowledge, the first systematic review of the natural history of stage-3 CKD.

The absolute rate of death among those with stage-3 CKD varied between studies but was as high as 51% at 10 years and was markedly higher in stage 3B compared with stage 3A. Compared with those with no CKD, mortality was consistently higher after adjustment of age, sex, and comorbidities. However, the increase was small for those with stage-3A disease and greater in stage 3B. As age increased, the additional risk of death attributable to low eGFR decreased. This has two important implications in general practice: in older age groups, a large number of deaths may occur in patients with CKD; however, because risk of death from other causes is also increased, for the individual patient, the additional diagnosis of CKD has little impact on risk of death.

ESRD was a rare outcome (4% after 10 years follow-up, 0.04 per 100 person-years) but was greater in those with stage-3B CKD compared with

Table 7. Summary of renal outcomes in stage-3 CKD.

Study	Measures	ESRD or RRT	CKD progression	Comments
Clinical population-based study				
Chiu *et al*[34]		ESRD		ESRD defined as initiation of RRT
	n/N:	7/184 (3.8%)	NR	
	Rates:	1.4/100py 4% at 3 years	Mean GFR decline: 2.2 (SE 0.3) mL/min/1.73 m^2/year	
Djamali *et al*[35]	n/N:	NR	NR	
	Rates:	NR	Mean CrCl decline: 5.4 (SD 7.4) mL/min/year	Progression defined as mean rate of CrCl decline in mL/min/year
Eriksen and Ingebretsen[32]		ESRD		ESRD defined as stage 5 CKD or initiation of RRT
	n/N:	62/3047 (2.0%)	Proportion with eGFR decline >0 mL/min/1.73 m^2/year: 73% >5 mL/min/1.73 m^2/year: 6%	
	Rates:	2% at 5 years 4% at 10 years	mean eGFR decline: 1.03 mL/min/1.73 m^2/year	
Hemmelgarn *et al*[37]	n/N:	NR	NR	
	Rates:	NR	eGFR decline (mL/min/1.73 m^2/year) M: 1.9 (95% CI = 1.5 to 2.3) F: 1.1 (95% CI = 0.8 to 1.4)	Rates adjusted for age, sex, diabetes mellitus, and comorbidity score; the rates were for participants without diabetes mellitus
Keith *et al*[31]		RRT		
	n/N :	23/1741 (1.3%)	NR	
	Rates:	1.3% at 5 years (transplant: 0.2%; dialysis: 1.1%)	NR	
Khatami *et al*[38]	n/N :	NR	Progression to stage 4/5: 22/520	Approximate proportions reported for regression and no progression
	Rates:	NR	Progression to stage 4/5: 4% at 4 years Regression to stage 2: ~20% at 4 years No progression: ~76% at 4 years	
Orlando *et al*[40]	n/N:	NR	70/416	CKD progression defined as progression to next stage
	Rates:	NR	17% at ~5 years	
General population-based study				
Hallan *et al*[27] Hallan *et al*[29]		ESRD		
	n/N:	Stage 3: 16/2973 (0.5%) Stage 3A: 9/2389 (0.3%) Stage 3B: 7/548 (1.3%)	NR	
	Rates:	Stage 3A: 0.04/100py Stage 3B: 0.2/100py	NR	
Imai *et al*[42]	n/N :	NR	NR	
	Rates:	NR	Annual progression rate stratified by age, sex and baseline eGFR	

CKD = chronic kidney disease. CrCl = creatinine clearance. (e)GFR = (estimated) glomerular filtration rate. ESRD = end-stage renal disease; F = female. M = male. n = number of events. N = total number of patient with stage-3 CKD. NR = not reported. py = person-years. RRT = renal replacement therapy. SD = standard deviation. SE = standard error.

those with stage-3A CKD. Where a cohort was selected from a nephrology clinic, the ESRD rate was higher than in general population studies (1.4 per 100 person-years), perhaps reflecting the clinical selection of patients at high risk of developing CKD. This could also highlight why extrapolating the experience from nephrology clinics to community practice and to patients identified through opportunistic or population screening may not be appropriate.

Policy-makers have focused on 'early' CKD and 'early' detection based on a model of progressive renal-function decline.[12] From three studies, it was possible to estimate the proportion of people who did not demonstrate evidence of progressive renal-function decline: Eriksen and Ingebretsen[32] reported that 27% showed no fall in eGFR during up to 10 years' follow-up; two further studies reported that ≥80% did not show any worsening of CKD stage after up to 5 years' follow-up.[38,40] In practice, therefore, the number of patients with stage-3 CKD progressing to ESRD is likely to be low.

Looking for other indicators of underlying pathology and markers of kidney damage will be important in helping to identify which patients are at risk of a progressive course. The number of patients with CKD experiencing cardiovascular events and mortality will be much greater; as such, assessing for cardiovascular risk factors should be an important aspect of CKD patient care. As more experience is gained of the natural history of stage-3 CKD in people identified through opportunistic and population screening, it may become possible to identify those who could benefit most from more intensive management and referral to a nephrology specialist.

Strengths and limitations of the study

This review was undertaken systematically, with pre-specified inclusion and exclusion criteria in order to minimise bias when selecting studies for inclusion. Thirteen studies were identified, nine of which were considered to be of good quality, but all had methodological weaknesses. Six studies used validated methods to establish the chronic nature of eGFR impairment. Although having a clear definition of chronic kidney impairment is of clinical importance and is relevant in identifying those at greater risk of progressive disease, it is important to note that population screening studies, relying on the much less specific marker of a single reduced estimated GFR, still reported the increased risks of mortality.

It has not been possible to produce a pooled estimate of the risk of death or renal disease progression for people with stage-3 CKD. There were inconsistencies in the way studies reported their findings which, along with the clinical heterogeneity in the study populations, meant that a pooled estimate would be uninterpretable. However, the risks are influenced by a range of factors — including age, sex, and comorbidities — and varied with geography (a marker for different ethnic groups and healthcare systems). Adjusted analyses suggest that stage-3 CKD is an independent risk factor for increased mortality and renal progression — a risk that increases as eGFR falls and is substantially greater for those with stage-3B disease than those with stage-3A disease.

A decision was made to exclude data from the control arms of randomised controlled trials (RCTs). Although such studies do provide a view of the natural history of the condition, the strict selection of patients to participate in them means that their outcomes are very different and difficult to generalise. For example, Jafar *et al*[44] reported a meta-analysis of RCTs for ACE inhibitors in non-diabetic renal disease. From pooled RCT data for CKD stages 3–5, they reported a low all-cause mortality (1.2% in a mean follow-up of 2.2 years) and a relatively high progression to ESRD (11.6%); this reflected the selection of trial participants and the difficulty in generalising such findings. In addition, very few of the intervention trials have reported their findings for stage-3 CKD separately.

Conclusion

In the UK, and internationally, there has been a major drive to detect people with 'early' CKD. The QOF supports the identification of people with stage-3 CKD in primary care, and management of their blood pressure in particular. The findings of this review highlight that, for patients identified through opportunistic detection methods where testing was undertaken for a variety of clinical indications, all-cause mortality was higher than for those with no CKD and CVD was common. The risk of progression to ESRD and dialysis was substantially less.

CKD registers provide an opportunity for GPs to assess risk of CVD, and optimise care for individuals at high risk of developing CVD. For many, CKD occurs as part of a complex comorbidity cluster, with hypertension, diabetes mellitus, and CVD; as such, care should not be considered in isolation.

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Competing interests

The authors have stated that there are none.

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