BMJ Open

Rate of decline in kidney function with age: a systematic review

Michelle Guppy ,[1,2] Elizabeth Taruna Thomas ,[3] Paul Glasziou ,[1] Justin Clark,[1] Mark Jones,[1] Daniel Vincent O'Hara ,[4,5] Jenny Doust[6]

To cite: Guppy M, Thomas ET, Glasziou P, *et al*. Rate of decline in kidney function with age: a systematic review. *BMJ Open* 2024;**14**:e089783. doi:10.1136/bmjopen-2024-089783

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (https://doi.org/10.1136/bmjopen-2024-089783).

Received 11 June 2024
Accepted 22 October 2024

[1]Institute for Evidence-Based Healthcare, Bond University Faculty of Health Sciences and Medicine, Gold Coast, Queensland, Australia
[2]School of Rural Medicine, University of New England, Armidale, New South Wales, Australia
[3]Nuffield Department of Primary Care Health Services, University of Oxford, Oxford, UK
[4]Kidney Health, NHMRC Clinical Trials Centre, Camperdown, New South Wales, Australia
[5]Department of Renal Medicine, Royal North Shore Hospital, St Leonards, New South Wales, Australia
[6]Australian Women and Girls Health Research (AWaGHR) Centre, School of Public Health, Faculty of Medicine, The University of Queensland, Brisbane, Queensland, Australia

Correspondence to
Professor Michelle Guppy; mguppy2@une.edu.au

ABSTRACT

Objective To determine the distribution of kidney function values as measured by glomerular filtration rate (GFR), and the rate of decline with age in male and female healthy subjects without pre-existing medical conditions.

Design Systematic review and structured synthesis.

Search sources PubMed, Embase, Cochrane Central Register of Controlled Trials and Web of Science, from database inception to 25 October 2023. Unpublished studies were searched from clinical trial registries and the grey literature.

Selection criteria Observational cohort studies, including non-treatment arms of randomised, pseudorandomised and non-randomised controlled trials that assessed the age-related decline in kidney function over time.

Main outcome measures Primary outcomes were rate of change of kidney function over time (absolute and relative change) and rate of change of kidney function with age. Secondary outcomes included rate of change of kidney function compared with baseline GFR, gender, ethnicity and proportion of participants >60 years defined as having chronic kidney disease.

Data collection and analysis Two review authors independently screened studies for inclusion, extracted data and assessed risk of bias. Data could not be pooled because of significant heterogeneity. Instead, a descriptive analysis was used to synthesise results.

Results 12 studies between 1958 and 2021 reported the decline rate of kidney function in healthy individuals: six prospective cohort studies, four retrospective cohort studies and two randomised controlled clinical trials, which included 129 359 healthy participants (range from 15 to 46 682) and ranged from 2 to 23 years duration. Annual decline rates ranged from −0.24 to −3.60 mL/min/1.73 m^2/year (−0.37 to −1.07 in subjects without hypertension). Results were mixed as to whether decline rates sped up or slowed down with age, and whether decline rates differed between women and men, with studies showing conflicting results. This study was unable to determine the decline rates in different ethnicities.

Conclusions This study is the first systematic review to investigate the longitudinal decline in kidney function with age in healthy individuals. The normal decline rate could be considered between −0.37 and −1.07 mL/min/1.73 m^2/year in healthy adults without hypertension. Kidney function decline rates in healthy adults may be helpful to clinicians anticipating patients' kidney trajectory and determining whether chronic kidney disease-specific care is required.

PROSPERO registration number CRD42023096888.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Included studies that reported longitudinal decline of kidney function.
⇒ Excluded studies of people with pre-existing disease (including renal and cardiovascular).
⇒ Excluded studies with fewer than three measures of glomerular filtration rate.

INTRODUCTION

Chronic kidney disease (CKD) is defined as a 'sustained reduction in glomerular filtration rate (GFR) or evidence of structural or functional abnormalities of the kidneys on urinalysis, biopsy or imaging'.[1] The current guidelines define CKD as estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 present for >3 months, or evidence of kidney damage regardless of eGFR that is persistent for >3 months, (ie, proteinuria, haematuria or pathological/structural abnormality).[1] However, an eGFR of <60 mL/min/1.73 m^2 is common in older people, with >40% of people over 70 years of age thereby meeting the definition of CKD.[2] GFR declines with age even in healthy people with no kidney disease.[3] Several cross-sectional studies have charted the normal decline in GFR with age, in order to predict which patients are likely to go on to require kidney replacement therapy.[4–8] End-stage kidney disease is a significant cost to both patients and health services, leading to dialysis, kidney transplantation or death. It is important to identify early those patients in whom screening and strict management are likely to prevent deterioration of their kidney function. However, there have been recommendations against using fixed GFR cutoffs to define disease, irrespective of age, gender or race,[3 9] with other studies recommending including a lower reference range (eg <5th percentile) in the diagnosis of older people.[7 9] A large number of older people with a low GFR will

remain stable and will not go on to develop end-stage kidney disease. In order to target screening and management of those patients at highest risk, it is important to understand the natural rate of decline in kidney function with normal ageing. Therefore, this study aimed to determine the longitudinal decline in GFR with age in healthy adults.

METHODS

The study protocol was registered with PROSPERO CRD42023096888 on 2/10/23.

Criteria for considering studies for this review

Types of studies

Studies that reported the age-related decline of kidney function were eligible for inclusion. Eligible studies included randomised, pseudorandomised and non-randomised controlled trials that had a non-treatment arm, prospective observational cohort studies and retrospective cohort studies. We included studies where three or more measurements of kidney function were undertaken. Cross-sectional studies, or studies where only two measurements of kidney function were taken, were excluded.

Types of participants

We included longitudinal studies in adults that followed some or all of the participants past the age of 60 years. We excluded studies in children. We excluded studies whose primary focus was people on dialysis, people who had a kidney transplant, people with pre-existing kidney disease and people who had diseases on enrolment known to affect kidney function, including diabetes and cardiovascular disease. We included studies that had participants with risk factors for disease (eg, hypertension, hypercholesterolaemia, obesity), but we described studies separately according to how strictly they defined a healthy population.

Types of outcome measures

Our primary outcome measures were rate of change of kidney function over time and rate of change of kidney function with age, irrespective of how this was measured in the studies. Studies of GFR may use measured GFR (mGFR, involving direct measurement of plasma or urinary clearance of exogenous markers of filtration, which is accepted as the gold standard); estimated GFR (eGFR, with a variety of formulae in use to estimate filtration usually based on serum levels of the waste product creatinine, and factoring variables such as age, sex and body weight); levels of serum creatinine; measurement of the endogenous filtration marker cystatin C; estimation of eGFR based on cystatin C ($eGFR_{cys}$) or cystatin C ($eGFR_{cr\text{-}cys}$), or creatinine clearance.[10] Secondary outcomes were rate of change of kidney function compared with baseline GFR, rate of change of kidney function by gender, rate of change of kidney function in different ethnic groups and proportion of participants over 60 years old that were defined as having CKD.

Search methods for identification of studies

We searched the following databases from inception to 25 October 2023: PubMed, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL) and Web of Science. We searched the WHO trials portal (www.who.int/clinical-trials-registry-platform) and ClinicalTrials.gov registry for ongoing studies. The search strategy was conducted by an information specialist (JC) (see online supplemental figure 1). No language restrictions were applied. We checked the reference lists of all primary studies and review articles for additional references. Unpublished studies were also searched for in the grey literature and trial registries.

Data collection and analysis

Study selection

Two review authors independently screened the titles and abstracts of all potential studies identified as a result of the searches. Full-text study reports of potentially relevant studies were retrieved. Two review authors independently screened the retrieved reports to identify studies for inclusion. Reasons for exclusion of ineligible studies were recorded, and the selection process was delineated in a PRISMA flow chart (figure 1). Disagreements were resolved through discussion and by consultation with a third reviewer. Duplicate reports of the same study were identified and all publications were included and used to extract data. Only the most recent report of each study is used as the Study ID (tables 1 and 2).

Data extraction

A standardised data extraction form was used, which was designed and pilot tested prior to extraction of data. Two review authors extracted data from the included studies. Any disagreements were resolved by consensus or discussion with a third reviewer. The following information was extracted from each study if available:

Study type—randomised controlled trial, observational studies, systematic reviews, cohort studies, longitudinal studies; method—study design, duration of follow-up, number of study centres, location (country), setting (hospital, primary care, community), date of study; participants—age, gender, sample size, method of recruitment, inclusion criteria (including health status), exclusion criteria; outcomes—outcome definition, unit of measurement, time points of collection and reporting, loss to follow-up; other—trial funding, conflicts of interest of authors.

Risk of bias assessment

Two review authors independently assessed risk of bias for each study. For randomised controlled trials, we intended to use the Cochrane risk of bias tool;[11] however, we decided that the Joanna Briggs Institute (JBI) critical appraisal checklist was more appropriate for the type of data we were reviewing. For cohort studies, we used the

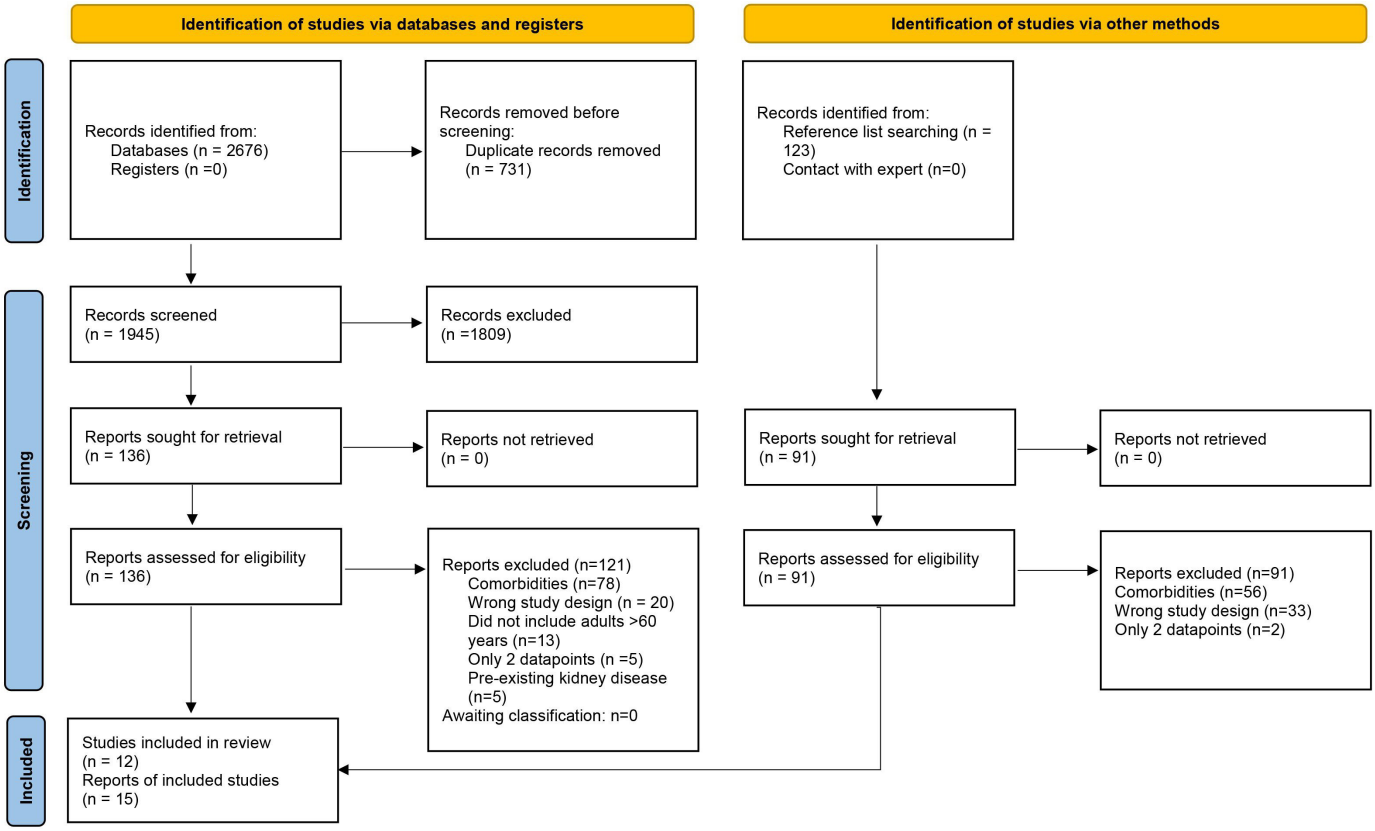

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram displaying the number of studies identified and included from databases, registers and other sources.

JBI critical appraisal checklist for studies reporting prevalence data.[12] Disagreements were resolved by consensus or discussion with a third reviewer. We summarised the risk of bias judgements across different studies for each of the domains in a risk of bias figure (table 3). We graded each potential source of bias as high, low or unclear and provided quotes from the study report with a justification for our judgement in a rationale for risk of bias table (online supplemental table 6). Where information on risk of bias related to unpublished data or correspondence with a trial author, we planned to note this in the rationale for risk of bias judgements table.

Data synthesis

Assessment of heterogeneity

We assessed the studies for heterogeneity across the following characteristics: study design, study duration, age of patients, sample population, unit of measurement. No studies were deemed similar across these domains and so the study results were not pooled. We intended to use a random effects model to synthesise the pooled effects of the studies in a meta-analysis, but due to the substantial heterogeneity between studies, results have instead been presented in a structured summary in tabular form.

Data synthesis

For each study cohort, we extracted the annual decline rates for each kidney function measure. If only summary data was available, data was presented according to analysis type (average rate of decline, rate of change with age, rate of change with baseline) and reported separately. We compared decline rates by gender and ethnicity where available. We also presented age-specific decline rates by decade of age where this data was reported. If this data was not reported, we calculated rates by subtracting the final measures from the initial and dividing by the duration of follow-up. If this data was not available, we attempted to contact the authors to request original data. If outcome data was not able to be extracted from tables or text, then the Plot Digitiser app was used to extract data from figures and graphs. We used the app found here: https://apps.automeris.io/wpd/, accessed: 5/3/2024. For continuous outcomes, the mean difference (MD) (or standardised MD if studies used different measuring scales) and SD were calculated.

Sensitivity analysis

We conducted a sensitivity analysis in the following situations: one or more included studies were dominant in terms of their size, the results of one or more of the included studies differed significantly from the results of other included studies (based on assessing the overlap of 95% CIs) or if quality issues were identified when assessing the risk of bias of included studies.

Dealing with missing data

We described missing data, including dropouts. Reasons for dropout were not reported.

Table 1 Characteristics of included studies (for conditions/risk factors excluded, see online supplemental table 1)

Study ID, dates	Cohort recruitment location, study design	Description of cohort, with conditions/risk factors included
Aurell 1997 Sweden[13]	General practices and primary care clinics, open randomised parallel study	130 clinic attendees with baseline hypertension (81 at end of study), randomised to treatment with metoprolol or enalapril. Mean age 55±8 (enalapril), 54±8 years (metoprolol), 65% male. Hypertension (100%) with diastolic blood pressure between 100 and 120 mm Hg, GFR ≥80 mL/min/1.73 m^2.
Baba 2015 Japan 2004–12[6]	Hospital-based preventative care clinic, retrospective longitudinal	45 586 clinic attendees, >18 years old, healthy, receiving an annual medical check-up. Mean age and SD 43.9±10.2 years, age range 18 to >75, 48% male. Smoking—never 61%, former 20%, current 19%, BMI (mean±SD) 22.0±3.0, 97% had no proteinuria, 3% had trace proteinuria (15 mg/dL).
Cohen 2014 Israel 2000–12[14]	Hospital-based preventative care clinic, retrospective longitudinal	2923 total (2693 healthy, 230 comorbidities) clinic attendees, age 20–80 years, non-pregnant, all with baseline eGFR >90 mL/min/1.73 m^2, and 5 or more clinic visits. Mean age and SD 42.4±8 years, 76.1% male. Total cohort—BMI (mean±SD) males 26.7±4.1, females 24.9±4.6; smoking—males 12.7%, females 12.2%.
Grupper 2019 Israel 2002–16[15]	Medical centre clinic, retrospective longitudinal	211/215 kidney donors, and 211 matched and 2534 healthy control group. Mean age and SD of healthy controls 43.6±8.9 years, age range 21–70.1 years, 66.8% male. Hypertension—12.8%, pre-diabetes 9.1%, metabolic syndrome 3.3%, Mean BMI 25±2.7 kg/m^2, current smokers 20.8%.
Hemmelgarn 2006 Canada 2001–03[16]	Outpatient blood test registry, retrospective cohort	10 184 participants aged 66 or older who had blood tests recorded on an outpatient pathology database. 6573 (64.5%) participants in subgroup with baseline eGFR 60–89 mL/min/1.73 m^2. Mean ±SD age of subgroup 75.1±6.4 years, female 54.9%. Difficult to determine what comorbidities patients might have had, as information only taken from medication data.
Holscher 2019 USA 1985[17]	Multiple renal transplant centres and community volunteers (control), three prospective cohort studies	1295 kidney donors, 8233 healthy non-donor control group. Age range ARIC cohort—45–65 years, CARDIA cohort—18–30 years. Ever smoker 52%, median BMI (IQR) 26 (23–28) kg/m^2.
Kasiske 2015 USA 2006–14[18]	Eight renal transplant centres, prospective controlled observational cohort (with a non-donor control group)	201 (173 follow-up) matched, equally healthy non-donor control group, age range 18–65 years, age (years) 18–34 30.9%, 35–49 35.3%, 50–64 31.3%, 65 2.5%, 32% male. Hypertension—4.5%, hyperlipidaemia—3.5%, CKD 0.5% (1 participant), obesity—normal 41.8%, overweight 35.3%, obese 20.9%, massively obese 1.5%, smoking—never 65.7%, former 22.4%, current 11.9%. One control participant had CKD at baseline. Healthy cohort compared with US population—less medication use, less antihypertensive use, less lipid-lowering medication use, no diabetes medication use.
Larsson 1986 Sweden 1971–81[19]	Community volunteers, longitudinal cohort	1148 initially recruited, systematic subsample of mGFR at age 70 years (n=93), 75 years (n=79), 79 years (n=46). Only 15 still healthy at age 79. 45% male. In the final cohort, 23 cardiac failure, 12 hypertension, 5 diabetes, 6 urinary tract disease, 15 no diseases.
Lengnan 2021 China 2012–14[20]	Hospital clinic, longitudinal cohort	46 682 healthy people attending hospital for routine medical exam, age range 18 to 100 years, mean age 46.79±15.83 years, 4196 participants were >70 years old, 58.33% male.
Lindeman 1984 USA 1958–81[21]	Community volunteers, longitudinal prospective cohort	254 healthy cohort from 446 community-dwelling volunteers, mean (SD) age 56.4±0.8 years, age range 22–97 years. All males. Mean (SEM) systolic blood pressure 128.4±0.95 mm Hg.
Price 2021 UK 2014–19[22]	Hospital based—seven renal transplant centres, longitudinal prospective cohort (with a non-donor control group)	53 healthy non-donor controls, hypercholesterolaemia—7%, hypertension—7%, smoking—current 4%, former 27%.
Vidt 2011 26 countries 2003–08[23]	Participants of clinical trial from 1315 sites in 26 countries, randomised controlled trial of statins 'JUPITER' trial	16 279 study participants, mean age 66 years, 62% male, 72% Caucasian. 58% hypertension.

BMI, Body Mass Index; BP, blood pressure; CKD, chronic kidney disease; GFR, glomerular filtration rate; urine ACR, urine albumin creatinine ratio.

Table 2 Summary of primary reported outcomes (for additional primary reported outcomes, see online supplemental table 2)

Study	Measurement method	Mean (SD) absolute decline per year (mL/min/1.73 m^2/year)	Age-related decline
Aurell 1997[13]	mGFR^{51}Cr-EDTA	−1.4±2.6 mL/min/year (enalapril group n=40), −1.1±2.4 mL/min/year (metoprolol group n=41), overall=−1.25 Year 1 of study GFR decline of −3.1 (enalapril) and −4.1 (metoprolol), thereafter <1 mL/min/year decline	Not reported
Baba 2015[6]	eGFR 3 variable Japanese equation	Overall −1.07±0.42	Slope (mL/min/1.73 m^2/year) Males age 18 to 29 years −1.22, 30 to 39 years −1.12, 40 to 49 years −1.02, 50 to 59 years −0.93, 60 to 69 years −0.85, 70 to >75 years −0.84. Females age 18 to 29 years −1.27, 30 to 39 years −1.21, 40 to 49 years −1.10, 50 to 59 years −1.00, 60 to 69 years −0.93, 70 to >75 years −0.87
Cohen 2014[14]	eGFR CKD- Epi	Healthy cohort −0.97±0.02	Decline in healthy subjects (mL/min/1.73 m^2/year) Age 20 to 30 years −0.82±0.22, 31 to 40 years −0.84±0.08, 41 to 50 years −1.07±0.08, ≥50 years −1.15±0.12. In 15.4% of subjects, there was no decline in eGFR with age
Grupper 2019[15]	eGFR CKD-Epi	−0.24 (control group)	Not reported
Hemmelgarn 2006[16]	eGFR- MDRD	Subgroup of participants without diabetes, and eGFR 60–89 mL/min/1.73 m^2. Males −2.3 (95% CI −1.8 to 2.9) n=2964, females −1.1 (95% CI −0.6 to −1.6) n=3609 Overall decline −1.64	Did not report but stated they adjusted for age
Holscher 2019[17]	eGFR- CKD-Epi	White, no hypertension −0.38 (CI −0.41 to −0.35) n=6741, hypertension −0.76 (−0.90 to −0.62) n=586 Black, no hypertension −0.32 (−0.38 to −0.25) n=825 Hypertension −0.91 (−1.20 to −0.62) n=81 Overall decline (no hypertension) −0.37	Not reported
Kasiske 2015[18]	mGFR using Iohexol, eGFR CKD-Epi	Healthy control group 12–36-month follow-up: mGFR −0.44±7.35, $eGFR_{cr}$ −1.04±6.16, $eGFR_{cys}$ −0.33±7.36, $eGFR_{cr\text{-}cys}$ −0.73±6.38 36-month follow-up (n=173): mGFR −0.39±4.81, $eGFR_{cr}$ −0.46±3.68, $eGFR_{cys}$ −0.16±4.68, $eGFR_{cr\text{-}cys}$ −0.07±3.85	mGFR (mL/min/year) <45 years −0.08±9.46 ≥45 years −0.75±5.34
Larsson 1986[19]	S-creatinine clearance, ^{51}Cr-EDTA clearance	All: n=46 75 years=67±14.4, 79 years=70±11.8 Without disease: n=15, 75 years=69±10.5, 79 years=71±12.1, decline rate+0.4	Cohort was aged between 75 and 79 years. No change in GFR during the study period
Lengnan 2021[20]	S-creatinine, eGFR: CKD-Epi, MDRD, MDRDc, and FAS equations	Not reported	eGFR (CKD-Epi) mL/min/year: Males, age: 20–24 0.48, 25–29 0.46, 30–34 0.36, 35–39 0.40, 40–44 0.39, 45–49 0.30, 50–54 0.17, 55–59 0.07, 60–64 0.09, 65–69 0.04, 70–74 0.03, 75–79 −0.01, ≥80 00.14. Females, age: 20–24 −0.11, 25–29 −0.08, 30–34 −0.02, 35–39 −0.03, 40–44 −0.07, 45–49 −0.06, 50–54 −0.06, 55–59 0.00, 60–64 0.10, 65–69 −0.02, 70–74 0.11, 75–79 0.09, ≥80 00.06

Continued

Table 2 Continued

Study	Measurement method	Mean (SD) absolute decline per year (mL/min/1.73 m^2/year)	Age-related decline
Lindeman 1984[21]	S-creatinine clearance	Bcr (±SEM) −0.75±0.12, n=254, SD=1.9	Mean (SEM) GFR (mL/min/year) Age 30–39.9 years+0.67±0.36, 40–49.9 years −0.32±0.19, 50–59.9 years −0.57±0.20, 60–69.9 years −1.24±0.28, 70–79.9 years −1.49±0.30, 80–89.9 years −3.25±0.70
Price 2021[22]	eGFR CKD-Epi	Healthy controls −1.0±2	Age range 18–80, mean age at 5-year follow-up 50.3±12.91, age-specific decline not reported
Vidt 2011[23]	S-creatinine, eGFR: CKD-Epi, MDRD	MDRD statin group −3.43, placebo group −3.6 CKD-Epi statin group −2.95, placebo group −3.2	Not reported

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, Body Mass Index; BP, blood pressure; CKD, chronic kidney disease; GFR, glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; NSAID, non-steroidal anti-inflammatory; urine ACR, urine albumin creatinine ratio.

Patient and public involvement

Patients were not involved in the design, data extraction nor analysis of this review.

RESULTS

Description of studies

Search results

After exclusion of duplicates, we identified 1945 studies. From these, 136 full-text reports were assessed for eligibility (figure 1). 121 studies were excluded: 78 studies included participants with pre-existing comorbidities, 20 studies were not designed to longitudinally assess kidney function decline rates, 13 studies did not include adults >60 years old, 5 studies had fewer than 3 data points, and 5 studies included participants with pre-existing kidney disease. Additionally, 91 full texts were identified and reviewed from reference lists, with none of these being eligible for inclusion (figure 1).

12 studies in total met inclusion criteria.[6 13–23] Six were prospective cohort studies, four were retrospective cohort studies and two were randomised controlled clinical trials (table 1). Three studies assessed particpants in the USA, two each in Israel and Sweden and one each in Canada, China, Japan and the UK. One clinical trial was conducted across 26 countries. The studies included 129 359 healthy participants and ranged in size from 15 to 46 682 participants. The studies were conducted between 1958 and 2021 and ranged from 2 to 23 years duration (table 1). Five studies were performed in hospital outpatient or screening clinics. Two studies were performed at kidney transplant centres, and three studies consisted of community volunteers. One study was performed in 15 general practices, and one study recruited clinical trial participants from 1315 sites. All studies reported a healthy cohort but differed in the way they defined this. Studies that were performed at kidney transplant centres included non-donor control groups, and the healthy non-donors are the participants included in this systematic review. Exclusion and inclusion criteria for participants in each study are reported in table 1 and online supplemental table 1. Measurement method of GFR varied with each study, with some reporting measured GFR and others reporting estimated GFR with different equations (tables 1 and 2, online supplemental table 1).

Outcome measures

A meta-analysis was not performed due to substantial heterogeneity between the included studies, and instead, a structured synthesis was undertaken. 10 studies demonstrated a decline in GFR over time, with mean annual rates of decline in the studies that reported overall cohort results ranging from −0.24[15] to −3.60[23] mL/min/1.73 m^2/year (table 2, figure 2). One longitudinal study reported no decline between age 75 and 79, but only had 15 healthy participants in the final analysis,[19] and one study did not report mean GFR change over time.[20] Four studies were considered to have the strictest exclusion criteria, reporting cohorts without hypertension,[6 14 17 21] and reported a mean annual decline rate of −0.37 to −1.07 mL/min/1.73 m^2 (figure 2). Decline rates differed according to method of measurement, with the study that reported a decline in mGFR of −0.39 mL/min/1.73 m^2/year recording only a −0.07 mL/min/1.73 m^2/year decline for $eGFR_{cr\text{-}cys}$[18] (table 2). The study that reported the largest decline rate had the shortest follow-up and was only measured over an average 2.3-year period.[23] Only one study reported overall relative decline rate per year, with a result of −1.29 %/year[6] (online supplemental table 2).

Five studies reported age-specific decline rates during each decade of age and one study dichotomised age into <45 and ≥45 years[6 14 18 20 21] (table 2, online supplemental figure 2). One of these studies reported that the slope of decline with age decreased;[6] whereas, three studies[14 18 21] reported an increase in decline rate with age (table 2,

Table 3 Risk of bias summary (full detail in supplementary files, online supplemental table 6)

Study ID	Representativeness of the exposed cohort	Ascertainment of exposure	Confounders accounted for	Outcome of interest not present at start of study	Assessment of outcome	Duration of follow-up	Adequacy of follow-up	Appropriate analysis
Aurell 1997[13]	+	+	−	+	+	+	−	+
Baba 2015[6]	+	+	+	+	−	+	−	+
Cohen 2014[14]	+	+	−	+	−	+	+	+
Grupper 2019[15]	+	+	+	+	−	+	+	+
Hemmelgarn 2006[16]	+	+	−	−	−	−	−	+
Holscher 2019[17]	+	+	+	−	−	+	−	+
Kasiske 2015[18]	+	+	+	+	+	+	+	+
Larsson 1986[19]	−	+	−	−	+	+	−	+
Lengnan 2021[20]	+	+	+	+	−	−	−	+
Lindemann 1984[21]	+	+	−	+	−	+	−	+
Price 2021[22]	+	+	−	+	−	+	−	+
Vidt 2011[23]	+	+	−	−	−	−	+	+

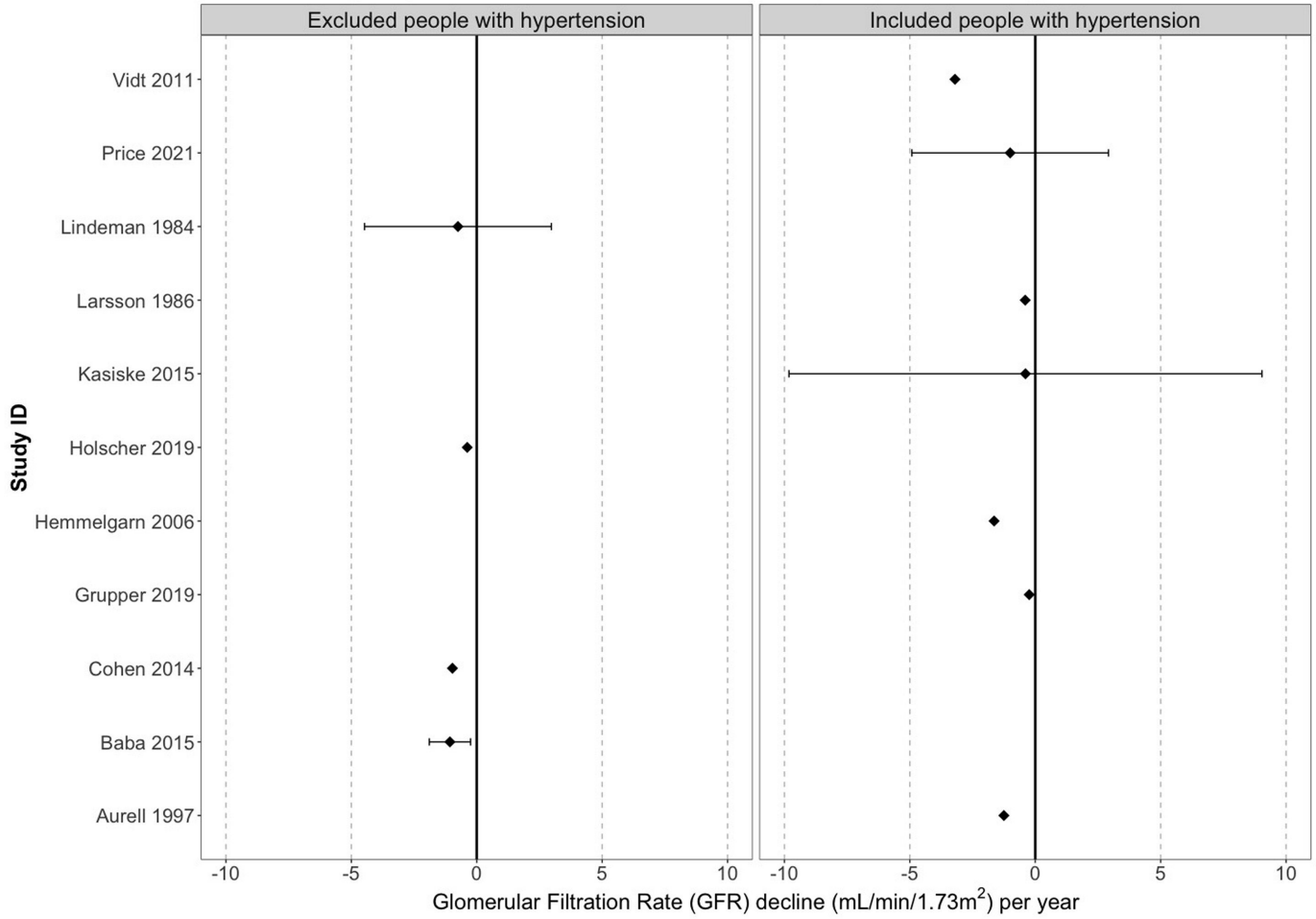

Figure 2 Annual rate of age-related GFR decline in adults with no history of renal disease in 11 studies, grouped by studies which either excluded or included participants based on hypertension status.

online supplemental figure 2). One study reported a stable eGFR with age[20] and one study reported no age-related decline in eGFR between age 75 and 79.[19]

Three studies reported the decline in GFR according to baseline GFR[6 16 23] (online supplemental table 2). They showed opposite results, with two reporting a steeper slope with higher baseline GFR and a shallower slope with lower baseline GFR.[6 23] The other study reported that the rate of decline in GFR increased as GFR decreased.[16] This study excluded participants with a GFR >90 mL/min/1.73 m^2 (online supplemental table 1).

Four studies reported rate of decline with gender,[6 14 16 19] and in one study, participants were only male[21] (online supplemental table 3 and figure 3). One of these studies reported a faster decline in males than females at −1.4 mL/min/1.73 m^2/year (95% CI 1.2 to 1.6) for men and −0.8 mL/min/1.73 m^2/year (95% CI 0.6 to 1.0) for women in Canada;[16] whereas, a larger study with longer-term follow-up of Japanese participants reported the opposite—a slower decline in males compared with females at −1.0±0.4 mL/min/1.73 m^2/year in men and −1.1±0.4 mL/min/1.73 m^2/year in women.[6] The other two studies reported no difference between genders[14 19] (online supplemental table 3). Decline rates compared with ethnicity were not specifically reported; however, one study was done in Japanese people,[6] one in Chinese people,[20] seven in majority Caucasian populations,[13 16 18 19 21 23] two in Israeli populations[14 15] and one study specified and reported on a small proportion of African American participants[17] (online supplemental table 3).

The proportion of participants that met the definition of CKD is described in Supplementary table 3 and ranges from 0% to 10% with one study reporting a separate subgroup of eGFR <60 mL/min/1.73 m^2.[16]

Risk of bias of included studies

Risk of bias assessment of the included studies is reported in table 3 with further detail in online supplemental table 6. We made several assumptions when considering risk of bias, which are described below. Only one study was judged to be at low risk of bias overall across every 'risk of bias' item.[18] The remainder were judged to be at unclear or high risk of bias for one or more items. 11 studies were considered representative of a healthy community or outpatient cohort. All studies were low risk of bias for measurement of exposure, with age being the exposure of interest. Five studies were deemed at low risk of bias for

possible confounders, but three studies were unclear and four studies were at high risk of bias from confounding factors. Proteinuria is a significant risk factor for declining kidney function and therefore, a potential confounder. We considered the two studies that did not exclude participants with proteinuria at baseline to be high risk of bias for confounders,[16 19] and one study[23] an unclear risk of bias for this parameter. Eight studies excluded participants with reduced kidney function at baseline and hence, had a low risk that the outcome of interest (kidney function decline) was present at the start of the study (mean baseline eGFR 81.5–129.9 mL/min/1.73 m^2), but two were unclear, and two were considered high risk of bias. Given that mGFR is the gold standard of validity for the outcome measurements, and that eGFR has various measurement issues, we considered studies that only used eGFR to be unclear risk of bias for outcome measurements. Only three studies used mGFR, and the remainder used various eGFR equations. We considered that 3 years was the minimum study length to be sufficiently long for the outcomes of interest to occur. Nine studies had adequate duration of follow-up. Four studies had complete or adequate follow-up, but it was unclear how follow-up was measured in five of the studies, and two studies had inadequate follow-up. All 12 studies had appropriate statistical analysis.

Sensitivity analysis

We explored the heterogeneity in study duration. We compared the mean annual decline rate of all studies with mean study duration. After excluding the two studies with <3-year follow-up,[16 23] the highest rate of decline reduced from −3.60 to −1.07 mL/min/1.73 m^2 (online supplemental figure 4). The study of 10 years duration only had 15 healthy participants in its final cohort (out of an initial 1148); therefore, even though they reported no change in GFR (annual decline rate+0.4 mL/min/1.73 m^2 between ages 75 and 79), we have excluded this study from our overall estimate of results due to concerns about survival bias.[19]

DISCUSSION

Statement of principal findings

This systematic review of 12 longitudinal cohort studies conducted in six countries (in addition to 26 countries from one study) provides a summary of the evidence for the change in kidney function (as measured by GFR) with age in healthy adults. Kidney function declines with age in normal, healthy adults. Mean decline rates range from −0.24 to −3.60 mL/min/1.73 m^2/year across all participants and from −0.37 to −1.07 mL/min/1.73 m^2/year in people without hypertension. Results are mixed as to whether the decline rate speeds up or slows down with age. The relative rates of decline between men and women vary—with two studies reporting no difference, one study reporting a faster decline rate in men than women and one study reporting the opposite (faster decline in women). We were unable to compare differences in decline rates with ethnicity.

Strengths and limitations of this study

This systematic review assessed all the available primary studies to determine the decline of kidney function with age in healthy adults and included a large number of participants (n=129 359). The review was limited to studies with three or more measurements of kidney function due to inherent inaccuracies with only two measurements, thereby improving the accuracy of the findings. However, this may introduce a survival bias into the results. Studies in this review ranged from 2 years to 23 years. The shorter duration of studies may not fully indicate the change in kidney function over time; whereas, the longer studies may have a survival bias. Rowe 1976 reports that annual testing for 18 years would be the minimally acceptable time to accurately assess an individual's kidney function trajectory.[24] We excluded studies that contained participants with pre-existing disease in order to determine the decline rate in healthy adults. This limits the generalisability of these results to the general population, as the study population was by design a healthier one. Another limitation is that the studies did not record which participants went on to develop hypertension, diabetes or proteinuria, which are risk factors for worsening kidney function. With one study, we were unclear about whether the study team excluded all possible comorbidities, particularly heart disease[16]; therefore, the results may not be consistent with the rest of the studies in the review. One study had a higher proportion of participants with hypertension (58%),[23] and one study had 100% hypertensive participants,[13] which may have skewed their results to show a faster rate of decline in kidney function compared with the other studies which had only small proportions of participants with hypertension. One study only had a very small final cohort of healthy participants (n=15/1148),[19] raising concerns about survival bias; therefore, we excluded this study from our overall summation of results. Our studies ranged in time from 1958 to 2021. While all studies standardised their GFR measurements to body surface area, there may be differences in body composition in cohorts across that period of time.[25] Additionally, there were changes in the methods of measurement of creatinine and GFR across this period, and in calculation of eGFR, which may limit the comparison of the results.[10] Three of the studies in this review used mGFR,[13 18 19] and the remainder used eGFR with different equations. There is still debate over the accuracy of eGFR equations across the lifespan.[10] Only one of the studies in this review assessed both mGFR and eGFR, with slightly slower decline in mGFR than eGFR but without a statistical comparison being performed.[18]

We were unable to pool the results due to heterogeneity between the studies. The findings are also limited by the quality of the studies, with only one study judged to be at low risk of bias in all domains.[18] The studies were mainly performed in populations of Japanese, Chinese

and Caucasian ethnicities, and only a small number of African American participants, with other participants' ethnicity not specified, so this limits the generalisability of results to other populations.

Comparison with previous research

There is physiological evidence that kidney function declines in healthy ageing. As kidneys age, there is gradual senescence of the nephron and interstitium, with increasing numbers of sclerotic glomeruli and tubulointerstitial fibrosis.[26 27] Various mechanisms of sclerosis and fibrosis have been suggested. Renal fibrosis in ageing may be caused by the tissue repair response to injury, which may be normal or pathological.[28 29] Additionally, there is a 10% decline per decade (from the age of 30) in renal plasma flow.[26 27 30] This occurs in healthy adults, and a greater change is seen in men compared with women.[31] These mechanisms are accelerated by comorbidities such as hypertension, glucose intolerance and diabetes, atherosclerosis and lipid abnormalities.[32 33] However, they also reflect the normal ageing process and are found in healthy persons of advanced age.[26]

Previous cross-sectional studies have shown the decline in kidney function with age in healthy adults in different populations[4 6–8 31 34–50] (see online supplemental table 4). These 22 studies represented a wide population range from Europe, Asia and Africa to the Americas. They included from 52 to 106 366 participants, all of whom were healthy, with an age range from 18 to 110 years. Annual decline rates for both sexes ranged from −0.40 to −1.49±0.61 mL/min/1.73 m^2/year in these studies. A seminal paper on this topic reported that this decline commenced after the age of 40 years, based on the independence of age as a variable for participants aged 19–40 years according to cross-sectional data.[41] However, data from five longitudinal studies in our systematic review, which included participants above and below the age of 40 years, show a mixed relationship with increasing age. Three of the longitudinal studies reported an increase in decline with increasing age consistent with the cross-sectional data,[14 18 21] but one reported no change,[20] and one reported a slower decline with increasing age compared with participants under the age of 40 years.[6] Most of the cross-sectional studies reported a similar decline rate in males and females, with a cross-sectional meta-analysis also supporting no difference in rates of decline between the sexes.[8] However, selective mortality, cohort differences and individual variability of GFR may limit the interpretation of this cross-sectional data. Longitudinal data from cohort studies was required to evaluate incidence and individual risk with ageing.

We excluded studies with only two data points from this review due to reproducibility issues inherent in GFR calculation—the technical and clinical variability in measurement of GFR and biological variability of GFR in an individual.[10] Decline rates from these excluded studies can be found in Supplementary Tables 4 and 5.[51–57] They show a mean decline rate of between −0.36 and −1.83 mL/min/1.73 m^2/year, which is consistent with the data seen in this systematic review. We also excluded studies that included participants with comorbidities. There are several large longitudinal cohort studies with millions of individuals with data on GFR decline.[2 58] However, the purpose of these studies was to investigate the relative risk of various comorbidities on the decline in GFR, and so, conclusions cannot be made about the normal decline with healthy ageing from these studies. The cross-sectional studies, studies with only two data points and studies in this systematic review all have a broad concordance regarding the rate of decline of GFR with age.

Implications for clinicians and policymakers

This systematic review shows that there is a decline in kidney function over time in healthy adults with no comorbidities or chronic disease. The decline in kidney function could be considered a normal part of healthy ageing. The normal decline rate could be considered between −0.37 and −1.07 mL/min/year in healthy adults without hypertension. With hypertension, this decline rate could be as high as −3.60 mL/min/1.73 m^2/year at higher GFRs, although it may steady out and become less as the GFR drops below 60 mL/min/1.73 m^2. This has implications for the diagnosis of chronic kidney disease, which currently has an absolute cut-off value of eGFR <60 mL/min/1.73 m^2, and does not take age into account. It also has implications for the monitoring of GFR in the elderly.

Implications for research

It is unclear what the normal rate of decline in kidney function is in other ethnicities, and further research should be performed in ethnicities not included in this systematic review. There is still lack of clarity around which eGFR equations are best for which age groups, with an ideal eGFR equation not yet available.[25] In the meantime, consideration should be given to the use of several biomarkers (eg, creatinine+cystatin C) to get an accurate picture in older patients with lower muscle mass. The relationship between kidney volume and healthy ageing is another parameter for further research and what role it might play in predicting adverse outcomes.[59]

CONCLUSION

This study is the first systematic review to investigate the longitudinal decline in kidney function with age in healthy individuals. The normal decline rate could be considered between −0.37 and −1.07 mL/min/year in healthy adults without hypertension. Kidney function decline rates in healthy adults may be helpful to clinicians anticipating patients' kidney trajectory and determining whether CKD-specific care is required.

X Daniel Vincent O'Hara @Daniel_V_OHara

Contributors MG is responsible for the overall content as the guarantor. MG, PG and JD conceived of the original study plan. MG, PG, ETT, MJ, JC, DVO and JD had input into the study protocol. MJ advised on the study design and analysis of results. JC developed and implemented the search strategy. MG and ETT conducted

the title and abstract screening, full-text screening and data extraction. MG and ETT did the risk of bias analysis with input from the other authors. MG drafted the paper; all authors had input into writing and editing the final version of the paper.

Funding The Royal Australian College of General Practitioners Foundation-Therapeutic Guidelines research grant funded the original proposal. The funders did not play any role in the research processes.

Competing interests PG and JD report grants from the Australian National Health and Medical Research Council (NHMRC) during the period of this study. MG, PG and JD received a grant from the Royal Australian College of General Practitioners Foundation to undertake this research. DVO receives support through an Australian Government Research Training Program Scholarship, the Royal Australian Society of Nephrology Jacquot Research Entry Scholarship and the NHMRC Clinical Trials Centre Postgraduate Research Scholarship. ETT, JC and MJ report no competing interests.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Data extracted from the individual studies is available on request by emailing researchdata@bond.edu.au.

ORCID iDs
Michelle Guppy http://orcid.org/0000-0001-7256-4938
Elizabeth Taruna Thomas http://orcid.org/0000-0001-7008-8763
Paul Glasziou http://orcid.org/0000-0001-7564-073X
Daniel Vincent O'Hara http://orcid.org/0000-0001-6066-8860

REFERENCES

1 Kidney Disease Improving Global Ooutcomes. KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Int* 2024;105:S117–s314.
2 Levey AS, de Jong PE, Coresh J, *et al*. The definition, classification, and prognosis of chronic kidney disease: a KDIGO Controversies Conference report. *Kidney Int* 2011;80:17–28.
3 Poggio ED, Rule AD. A critical evaluation of chronic kidney disease--should isolated reduced estimated glomerular filtration rate be considered a "disease"? *Nephrol Dial Transplant* 2009;24:698–700.
4 Poggio ED, Rule AD, Tanchanco R, *et al*. Demographic and clinical characteristics associated with glomerular filtration rates in living kidney donors. *Kidney Int* 2009;75:1079–87.
5 Benghanem Gharbi M, Elseviers M, Zamd M, *et al*. Chronic kidney disease, hypertension, diabetes, and obesity in the adult population of Morocco: how to avoid "over"- and "under"-diagnosis of CKD. *Kidney Int* 2016;89:1363–71.
6 Baba M, Shimbo T, Horio M, *et al*. Longitudinal Study of the Decline in Renal Function in Healthy Subjects. *PLoS ONE* 2015;10:e0129036.
7 Wetzels JFM, Kiemeney LALM, Swinkels DW, *et al*. Age- and gender-specific reference values of estimated GFR in Caucasians: the Nijmegen Biomedical Study. *Kidney Int* 2007;72:632–7.
8 Pottel H, Hoste L, Yayo E, *et al*. Glomerular Filtration Rate in Healthy Living Potential Kidney Donors: A Meta-Analysis Supporting the Construction of the Full Age Spectrum Equation. *Nephron* 2017;135:105–19.
9 Delanaye P, Jager KJ, Bökenkamp A, *et al*. CKD: A Call for an Age-Adapted Definition. *J Am Soc Nephrol* 2019;30:1785–805.
10 Porrini E, Ruggenenti P, Luis-Lima S, *et al*. Estimated GFR: time for a critical appraisal. *Nat Rev Nephrol* 2019;15:177–90.
11 Higgins JPT, Altman DG, Gøtzsche PC, *et al*. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;343:d5928.
12 Munn Z, Moola S, Riitano D, *et al*. The development of a critical appraisal tool for use in systematic reviews addressing questions of prevalence. *Int J Health Policy Manag* 2014;3:123–8.
13 Aurell M, Bengtsson C, Björck S. Enalapril versus metoprolol in primary hypertension--effects on the glomerular filtration rate. *Nephrol Dial Transplant* 1997;12:2289–94.
14 Cohen E, Nardi Y, Krause I, *et al*. A longitudinal assessment of the natural rate of decline in renal function with age. *J Nephrol* 2014;27:635–41.
15 Grupper A, Angel Y, Baruch A, *et al*. Long term metabolic and renal outcomes of kidney donors compared to controls with excellent kidney function. *BMC Nephrol* 2019;20:30.
16 Hemmelgarn BR, Zhang J, Manns BJ, *et al*. Progression of kidney dysfunction in the community-dwelling elderly. *Kidney Int* 2006;69:2155–61.
17 Holscher CM, Haugen CE, Jackson KR, *et al*. Self-Reported Incident Hypertension and Long-Term Kidney Function in Living Kidney Donors Compared with Healthy Nondonors. *Clin J Am Soc Nephrol* 2019;14:1493–9.
18 Kasiske BL, Anderson-Haag T, Israni AK, *et al*. A prospective controlled study of living kidney donors: three-year follow-up. *Am J Kidney Dis* 2015;66:114–24.
19 Larsson M, Jagenburg R, Landahl S. Renal function in an elderly population. A study of S-creatinine, 51Cr-EDTA clearance, endogenous creatinine clearance and maximal tubular water reabsorption. *Scand J Clin Lab Invest* 1986;46:593–8.
20 Lengnan X, Aiqun C, Ying S, *et al*. The effects of aging on the renal function of a healthy population in Beijing and an evaluation of a range of estimation equations for glomerular filtration rate. *Aging (Albany NY)* 2021;13:6904–17.
21 Lindeman RD, Tobin JD, Shock NW. Association between blood pressure and the rate of decline in renal function with age. *Kidney Int* 1984;26:861–8.
22 Price AM, Moody WE, Stoll VM, *et al*. Cardiovascular Effects of Unilateral Nephrectomy in Living Kidney Donors at 5 Years. *Hypertension* 2021;77:1273–84.
23 Vidt DG, Ridker PM, Monyak JT, *et al*. Longitudinal assessment of estimated glomerular filtration rate in apparently healthy adults: a post hoc analysis from the JUPITER study (justification for the use of statins in prevention: an intervention trial evaluating rosuvastatin). *Clin Ther* 2011;33:717–25.
24 Rowe JW, Andres R, Tobin JD, *et al*. The effect of age on creatinine clearance in men: a cross-sectional and longitudinal study. *J Gerontol* 1976;31:155–63.
25 Zsom L, Zsom M, Salim SA, *et al*. Estimated Glomerular Filtration Rate in Chronic Kidney Disease: A Critical Review of Estimate-Based Predictions of Individual Outcomes in Kidney Disease. *Toxins (Basel)* 2022;14:127.
26 Bolignano D, Mattace-Raso F, Sijbrands EJG, *et al*. The aging kidney revisited: a systematic review. *Ageing Res Rev* 2014;14:65–80.
27 Chou YH, Chen YM. Aging and Renal Disease: Old Questions for New Challenges. *Aging Dis* 2021;12:515–28.
28 Roberts AB, McCune BK, Sporn MB. TGF-beta: regulation of extracellular matrix. *Kidney Int* 1992;41:557–9.
29 Peters H, Noble NA, Border WA. Transforming growth factor-beta in human glomerular injury. *Curr Opin Nephrol Hypertens* 1997;6:389–93.
30 Gourtsoyiannis N, Prassopoulos P, Cavouras D, *et al*. The thickness of the renal parenchyma decreases with age: a CT study of 360 patients. *Am J Roentgenol* 1990;155:541–4.
31 Berg UB. Differences in decline in GFR with age between males and females. Reference data on clearances of inulin and PAH in potential kidney donors. *Nephrol Dial Transplant* 2006;21:2577–82.
32 Ribstein J, Du Cailar G, Mimran A. Glucose tolerance and age-associated decline in renal function of hypertensive patients. *J Hypertens* 2001;19:2257–64.
33 Fliser D, Franek E, Joest M, *et al*. Renal function in the elderly: impact of hypertension and cardiac function. *Kidney Int* 1997;51:1196–204.
34 Araumi A, Ichikawa K, Konta T, *et al*. The distribution of eGFR by age in a community-based healthy population: the Japan specific health checkups study (J-SHC study). *Clin Exp Nephrol* 2021;25:1303–10.

35 Barai S, Bandopadhayaya GP, Patel CD, *et al*. Do healthy potential kidney donors in india have an average glomerular filtration rate of 81.4 ml/min? *Nephron Physiol* 2005;101:p21–6.
36 Blake GM, Sibley-Allen C, Hilton R, *et al*. Glomerular filtration rate in prospective living kidney donors. *Int Urol Nephrol* 2013;45:1445–52.
37 Dutra MC, Uliano EJM, Machado DFG de P, *et al*. Assessment of kidney function in the elderly: a population-based study. *J Bras Nefrol* 2014;36:297–303.
38 Eriksen BO, Palsson R, Ebert N, *et al*. GFR in Healthy Aging: an Individual Participant Data Meta-Analysis of Iohexol Clearance in European Population-Based Cohorts. *J Am Soc Nephrol* 2020;31:1602–15.
39 Fastbom J, Wills P, Cornelius C, *et al*. Levels of serum creatinine and estimated creatinine clearance over the age of 75: a study of an elderly Swedish population. *Arch Gerontol Geriatr* 1996;23:179–88.
40 Fehrman-Ekholm I, Skeppholm L. Renal function in the elderly (>70 years old) measured by means of iohexol clearance, serum creatinine, serum urea and estimated clearance. *Scand J Urol Nephrol* 2004;38:73–7.
41 Grewal GS, Blake GM. Reference data for 51Cr-EDTA measurements of the glomerular filtration rate derived from live kidney donors. *Nucl Med Commun* 2005;26:61–5.
42 Hamilton D, Riley P, Miola U, *et al*. Total plasma clearance of 51Cr-EDTA: variation with age and sex in normal adults. *Nucl Med Commun* 2000;21:187–92.
43 Hoang K, Tan JC, Derby G, *et al*. Determinants of glomerular hypofiltration in aging humans. *Kidney Int* 2003;64:1417–24.
44 Holness JL, Fleming JS, Malaroda AL, *et al*. (99m)Tc-DTPA volume of distribution, half-life and glomerular filtration rate in normal adults. *Nucl Med Commun* 2013;34:1005–14.
45 Ma Y-C, Zuo L, Chen L, *et al*. Distribution of measured GFR in apparently healthy Chinese adults. *Am J Kidney Dis* 2010;56:420–1.
46 Peters AM, Perry L, Hooker CA, *et al*. Extracellular fluid volume and glomerular filtration rate in 1878 healthy potential renal transplant donors: effects of age, gender, obesity and scaling. *Nephrol Dial Transplant* 2012;27:1429–37.
47 Rule AD, Gussak HM, Pond GR, *et al*. Measured and estimated GFR in healthy potential kidney donors. *Am J Kidney Dis* 2004;43:112–9.
48 Raymond NT, Zehnder D, Smith SCH, *et al*. Elevated relative mortality risk with mild-to-moderate chronic kidney disease decreases with age. *Nephrol Dial Transplant* 2007;22:3214–20.
49 Soares AA, Prates AB, Weinert LS, *et al*. Reference values for glomerular filtration rate in healthy Brazilian adults. *BMC Nephrol* 2013;14:54:54–60:.
50 Sun X, Chen Y, Chen X, *et al*. Change of glomerular filtration rate in healthy adults with aging. *Nephrology (Carlton)* 2009;14:506–13.
51 Eriksen BO, Stefansson VTN, Jenssen TG, *et al*. Elevated blood pressure is not associated with accelerated glomerular filtration rate decline in the general non-diabetic middle-aged population. *Kidney Int* 2016;90:404–10.
52 Eriksen BO, Småbrekke S, Jenssen TG, *et al*. Office and Ambulatory Heart Rate as Predictors of Age-Related Kidney Function Decline. *Hypertension* 2018;72:594–601.
53 Melsom T, Nair V, Schei J, *et al*. Correlation Between Baseline GFR and Subsequent Change in GFR in Norwegian Adults Without Diabetes and in Pima Indians. *Am J Kidney Dis* 2019;73:777–85.
54 Imai E, Horio M, Yamagata K, *et al*. Slower decline of glomerular filtration rate in the Japanese general population: a longitudinal 10-year follow-up study. *Hypertens Res* 2008;31:433–41.
55 Jiang S, Sun X, Gu H, *et al*. Age-related change in kidney function, its influencing factors, and association with asymptomatic carotid atherosclerosis in healthy individuals--a 5-year follow-up study. *Maturitas* 2012;73:230–8.
56 Qin X, Wang Y, Li Y, *et al*. Risk factors for renal function decline in adults with normal kidney function: a 7-year cohort study. *J Epidemiol Community Health* 2015;69:782–8.
57 Li Y, Qin X, Xie D, *et al*. Body mass index and annual estimated GFR decline in Chinese adults with normal renal function. *Eur J Clin Nutr* 2015;69:922–6.
58 Matsushita K, Coresh J, Sang Y, *et al*. Estimated glomerular filtration rate and albuminuria for prediction of cardiovascular outcomes: a collaborative meta-analysis of individual participant data. *Lancet Diabetes Endocrinol* 2015;3:514–25.
59 Hommos MS, Glassock RJ, Rule AD. Structural and Functional Changes in Human Kidneys with Healthy Aging. *J Am Soc Nephrol* 2017;28:2838–44.