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Systematic review of the impact of non-alcoholic fatty liver disease on mortality and adverse clinical outcomes for individuals with chronic kidney disease

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Keywords

Chronic renal failure; Hepatology; Myocardial Infarction, End-stage renal failure

Abstract

Objectives: To investigate if non-alcoholic fatty liver disease (NAFLD) impacts mortality and adverse clinical outcomes for individuals with chronic kidney disease (CKD).

Design*:* Systematic review

Data sources: PubMed, EMBASE and Web of Science were searched with no date restrictions.

Eligibility criteria for selecting studies: Observational cohort studies that reported either the risk of all-cause mortality, incidence of non-fatal cardiovascular events (CVE) or progression of kidney disease among adults with established CKD who have NAFLD compared to those without.

Data extraction and synthesis: Two reviewers extracted data and assessed the risk of bias independently.

Results: Of 2,604 records identified three studies were included (UK n=852, South Korea n=1,525, US n=1,413). All were judged to have a low or moderate risk of bias. Data were insufficient for meta-analysis. Two studies examined the influence of NAFLD on all-cause mortality. One reported a significant positive association for NAFLD with all-cause mortality for individuals with CKD ($p<0.05$) (cardiovascular-related mortality p=ns), which was lost following adjustment for metabolic risk factors; the second reported no effect in adjusted and unadjusted models. The latter was the only study to report outcomes for non-fatal CVEs and observed NAFLD to be an independent risk factor for this (propensity matched hazard ratio 2.00, p=0.02). Two studies examined CKD progression; in one adjusted rate of percentage decline in estimated glomerular filtration rate per year was increased in those with NAFLD (p=0.002), whereas the other found no significant difference.

Conclusions: Few studies have examined the influence of NAFLD on prognosis and major clinical outcomes within the CKD population. The studies identified were diverse in design and results were conflicting. This should be a key focus for future research as both conditions continue to rise in prevalence and have end-stage events that are associated with significant health and economic costs.

PROSPERO registration number: CRD42020166508

Article Summary

Strengths and limitations of this study

- This is the only systematic review to date to examine the influence of non-alcoholic fatty liver disease on outcomes for patients with chronic kidney disease
- Only three cohort studies were eligible for inclusion
- A single study showed an association between NAFLD and cardiovascular events in patients with chronic kidney disease; results were conflicting for all-cause mortality and progression of renal disease
- In view of the small number of studies this is an important area for further research

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Introduction

Chronic kidney disease (CKD) is a long-standing condition incorporating impaired renal function and is often associated with a reduced quality of life, increased risk of end-stage renal disease (ESRD), cardiovascular disease (CVD) and premature death.[1,2] CKD is classified according to five stages based on estimated Glomerular Filtration Rate (eGFR), and in practice persistent albuminuria.[3] Around 4-7% of adults living in the United Kingdom (UK) have CKD stages 3-5 (eGFR < 60ml/min/1.73m^2),[4,5] with a higher global prevalence at 11%, although significant variation is recognised due to data availability, measurements used and reliance on coding.[6,7] Global prevalence is estimated to have increased by nearly 30% from 2007-2019[8] and CKD is forecast to move from 16th (2016) to 5th (2040) in the rankings for years of life lost.[9] The disease burden is particularly high in the elderly.[4] Increasing age, hypertension, diabetes and obesity account for the majority of newly diagnosed cases of CKD in the developed world.[10,11] CKD shares these risk factors, many of which are experiencing a significant rise in prevalence, with non-alcoholic fatty liver disease (NAFLD).[12]

NAFLD refers to excessive fat accumulation in the liver affecting more than 5% of hepatocyte and encompasses a spectrum of disease from simple steatosis to non-alcoholic steatohepatitis (NASH), fibrosis and cirrhosis. It is the most common cause of chronic liver disease worldwide, affecting approximately 25% of adults globally and in Europe.[12] It is expected to become the leading indication for liver transplantation in the next decade.[13] NAFLD is referred to as the hepatic manifestation of the metabolic syndrome and recent consensus opinion has proposed a change in nomenclature to 'metabolic associated fatty liver disease, MAFLD'.[14] NAFLD is found in approximately 70% of patients with type 2 diabetes mellitus (T2DM)[15] and 70% of adults with obesity.[16,17] Around 1 in 11 adults worldwide are thought to have diabetes, of which 90% is type 2 and this figure has more than tripled over 20 years.[18] NAFLD is also an independent risk factor for diabetes.[19] In addition, current estimates suggest 65% of adults in England are overweight or obese, with rates having more than doubled since the 1990s.[20,21]

Two meta-analyses have conclusively demonstrated a higher incidence of CKD in individuals with NAFLD (HR 1.37 and HR 1.79).[22,23] Patients with more advanced fatty liver disease, i.e. NASH or fibrosis are at the greatest risk of developing CKD. This association is independent of potential confounders (age, gender, body mass index, diabetes status, lipids, hypertension and smoking).[22,23] CKD is an accelerator of the risk of CVD and an independent risk factor for cardiovascular events (CVEs);[24–26] indeed individuals with CKD are more likely to die from CVD than develop ESRD.[27] NAFLD is also an

independent risk factor for major CVEs,[28–32] although there remains uncertainty regarding its association with an increase in all-cause and cardiac-related mortality, [31,33–35] despite patients with NAFLD being more likely to die from CVD than liver disease.[36,37]

CKD and NAFLD frequently exist together, yet there is a sparsity of data to inform physicians and patients about clinical outcomes in this setting. Understanding if NAFLD plays a role in accelerating progression towards death and adverse clinical outcomes in patients with CKD would help improve risk stratification; permitting more aggressive lifestyle intervention, targeted pharmacological management of shared risk factors and enrolment in clinical trials in this potentially high risk group. We therefore asked what evidence is there for the influence of NAFLD on the risk of mortality, CVEs and progression of kidney disease in patients with established CKD?

Methods

The protocol for this systematic review was registered on PROSPERO a priori (CRD42020166508) (supplementary material 1).

Data sources, searches and study selection

We performed a computerized literature search using PubMed, EMBASE (using Ovid) and Web of Science using the following search terms: *"(chronic kidney disease or CKD or kidney disease or kidney failure or kidney injury or chronic renal disease or renal disease or renal failure or renal injury or renal insufficiency or impaired renal function or glomerular filtration rate or eGFR) and (fatty liver or non-alcoholic fatty liver disease or NAFLD or nonalcoholic steatohepatitis or NASH or liver fat or steatohepatitis or steatosis or hepatic fibrosis)"* (full details in supplementary material 2). We aimed to identify observational (prospective or retrospective) cohort studies that reported either the risk of mortality, CVEs or progression of kidney disease among adults (> 18 years old) with established CKD who have NAFLD compared with those without. We also performed manual searches of reference lists of relevant studies returned by the initial search. No restriction was placed on the earliest search date and searches were performed up to the current date (February 2020). Exclusion criteria included abstracts, case reports, reviews, editorials, practice guidelines, non-cohort design, non-human studies and unpublished studies.

Study participants included adults with established CKD with evidence of the presence or absence of NAFLD. Studies were excluded if they included individuals under 18 years, individuals undergoing renal replacement therapy (RRT) at the start of the study, kidney or liver transplant recipients and individuals with a known other cause of chronic liver disease. CKD was defined as an eGFR ≥ 60 ml/min/1.73m^2 with ACR > 3 mg/mmol (stage G1 and G2), or eGFR < 60 ml/min/1.73m^2 (stages G3a – G5) calculated using the CKD Epidemiology Collaboration (CKD-EPI) or Modified Diet in Renal Disease (MDRD) formula. NAFLD was defined using either biochemistry (elevations in serum aspartate transaminase, alanine transaminase or gamma glutamyl transferase), imaging (ultrasound, computer tomography, magnetic resonance imaging), liver biopsy or non-invasive scores (Fatty Liver Index, Steatotest, NAFLD Liver Fat Score).

Primary outcomes included differences in the risk of all-cause mortality, CVEs and progression of kidney disease in patients with CKD who had NAFLD compared to those without NAFLD. All-cause mortality was defined as any cause of death within the study follow up period. Within this we aimed to look at cardiovascular and non-cardiovascular related deaths. A CVE was defined as any one of the following: acute coronary syndrome, myocardial infarction, non-fatal cardiac arrest, coronary revascularization, new diagnosis of cardiac failure, hospitalisation with an exacerbation of cardiac failure, new diagnosis of peripheral vascular disease, or new diagnosis of cerebrovascular accident (all non-fatal). Progression of CKD was defined as either (1) mean or percentage annual rate of change in the eGFR, or mean or percentage change from baseline, (2) a decline in eGFR category accompanied by a ≥ 25% drop in eGFR from baseline (KDIGO definition), (3) the development of ESRD (eGFR of < 15 ml/min/1.73m^2, or the requirement of some form of RRT), or (4) doubling of creatinine.[3,38] Secondary outcomes included: (1) the risk of CVEs, progression of kidney disease and all-cause mortality in patients with CKD according to the severity of NAFLD, as determined by the presence of NASH or fibrosis (defined using histology, imaging or non-invasive serum biomarkers), and (2) the risk of CVEs, progression of kidney disease and all-cause mortality in patients with CKD according to baseline severity of CKD, as determined by CKD stage. Included and excluded studies were collected following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram (figure 1).

Data extraction and quality assessment

Two investigators (TH and RB) screened all titles and abstracts independently using the Covidence software as recommended by Cochrane. They obtained the full texts of potentially relevant papers to determine if they met the inclusion criteria. Discrepancies were resolved by returning to the original

article to reach a consensus. Data extraction was performed by TH and checked by RB. For all studies data was extracted data on (1) general information (title, authors, journal, country, publication year), (2) study design (population source, demographics, period of follow up, means of defining NAFLD and CKD, inclusion and exclusion criteria, study size, subgroup analysis (including severity of NAFLD and baseline CKD), adjustment for confounding factors) and (3) outcomes examined for NAFLD versus non-NAFLD patients (all-cause mortality, CVE, progression of kidney disease, and definition used, in addition to odds ratio, hazards ratio (HR), relative risk and 95% confidence intervals; or mean or percentage annual rate of change in the eGFR). Where there were multiple publications, we included the most up-to-date or comprehensive information.

The risk of bias was assessed independently by TH and RB. The results were then discussed to reach consensus. We used the Newcastle-Ottawa Score as recommended by Cochrane for the assessment of quality for non-randomised cohort studies.[39] This tool uses a star based system allocating a maximum of 9 points across three domains: (1) selection of study groups (max 4 points), (2) comparability of groups (max 2 points), (3) ascertainment of exposure and outcomes (max 3 points). Studies with an overall score of 9 are judged to be at a low risk of bias, those scoring 7-8 a moderate risk of bias and scores of 6 of less a high risk of bias. Where studies reported more than one primary outcome a separate bias assessment was performed for each.

Patient and public involvement

Patients or the public were not involved in the design, conduct, reporting or dissemination plans of our research.

Results

Details of the study selection process

The process for selecting the studies for inclusion in this systematic review is shown in figure 1. The searches returned 4,339 studies. Overall 1,735 duplicates were removed, leaving 2,604 citations for screening. TH and RB separately reviewed titles and abstracts and identified six potentially relevant studies. After examination of the full texts (supplementary material 3), three were excluded (figure 1). Only three cohort studies remained and were included.[40–42] As a result of the low number of studies

identified, and the fact that primary outcomes reported differed between papers, we did not have sufficient data to perform a meta-analysis.

Characteristics of the included studies

Of the three studies, one recruited patients seen in a renal tertiary referral centre in Salford, UK (Chinnadurai et al, n=852, median follow up 5.4 years),[40] the second recruited individuals attending for comprehensive health screening at a preventive medical centre in South Korea (Jang et al, n=1,525, median follow up 6.5 years),[41] and the third presents results from a retrospective analysis of baseline cross-sectional data collected from the third National Health and Nutrition Examination Survey (NHANES) (United States, US) over time (Paik et al, n=1,413, median follow-up 19.2 years) (**Table 1**).[42]

Liver ultrasound was used to detect NAFLD in all three studies. Prevalence rates of NAFLD were highest in the Korean cohort (41%), compared to the UK (21%) and US (29%) populations, however the US group only included patients with moderate or severe steatosis. CKD was defined using the CKD-EPI equation in all papers; the Salford and US studies only included patients with CKD stage 3 and above (eGFR < 60 mL/min/1.73 m^2), whereas the Korean group also included patients with ≥ 2+ proteinuria, i.e. CKD stage 1 and above. As a result mean baseline eGFR levels were nearly double in the Korean cohort compared to the Salford study (59.1 vs 33.5 mL/min/1.73 m^2). In terms of demographics, the Salford group was slightly older, and the US group included a higher frequency of individuals with metabolic risk factors and was predominantly female in contrast to the other studies.

The influence of NAFLD on clinical outcomes in patients with CKD

(1) Mortality

Two publications analysed the impact of NAFLD on mortality within the CKD population. The Salford group concluded that CKD patients with NAFLD were not at higher risk of all-cause (NAFLD 27.3% vs no NAFLD 33.0%, p=0.14; unadjusted HR 0.79 [0.58-1.08]) or cardiovascular-related mortality (NAFLD 31.3% vs no NAFLD 40.5%, p=0.36), despite experiencing more non-fatal CVEs (**Table 2**). Significance outcomes were unchanged in the propensity matched sample. The US based study reported an increase in overall mortality for CKD patients with NAFLD compared to those without (54.7% vs 46.5%, p<0.05). Statistical significance was lost however when adjusted for age and following multivariate analysis (p=ns when comparing adjusted HRs), and no significant impact was seen for NAFLD on

cardiovascular-related mortality (16.0% NAFLD vs 16.2% no NAFLD). No significant association between advanced fibrosis and all-cause or cardiovascular-related mortality was seen for patients with NAFLD and CKD within the US cohort.

(2) Non-fatal cardiovascular events

The Salford group published the only study to analyse the incidence of non-fatal CVEs. A higher frequency of non-fatal CVEs was seen in patients with NAFLD vs those without NAFLD (25.1% vs 12.3%; p<0.001) over an average of 5 years (**Table 2**). Cox regression analysis revealed NAFLD to be strongly associated with the incidence of non-fatal CVEs in CKD patients (HR 2.07 [1.39-3.09], p<0.001). This remained the case following multivariate analysis for all confounders in the propensity-matched cohort (HR 2.00 [1.10-3.66], p=0.02). Significant differences were also reported between groups according to the type of CVE (cardiac events p=0.02, cerebrovascular events p=0.04, cardiac failure p=0.005), although individually significance values were lost following adjustment for confounders.

(3) Progression of CKD

The Salford and Korean groups analysed the impact of NAFLD on CKD progression. Both examined decline in eGFR; the Salford group presented this as rate of change of eGFR from baseline to the study end-point, whereas the Korean study examined the average percentage change in eGFR from baseline per year (**Table 2**). The Salford group reported a decline in the eGFR slope for patients with and without NAFLD (-2.54 vs -2.09 mL/min/1.73 m^2) over the course of the study, however no statistically significant differences were detected between groups (p=0.09). Conversely a greater rate of decline in the eGFR slope in patients with NAFLD vs those without, was seen in the Korean study (−0.79% vs 0.30% per year, p=0.002). This relationship remained significant after adjustment for all confounders (average difference in percentage decline of eGFR per year for NAFLD vs no NAFLD: -1.06%, p=0.002). The Salford group also reported no correlation between the presence of NAFLD and the development of ESRD (commencement of RRT or eGFR <10 mL/min/1.73 m^2). In terms of our secondary outcomes, the Korean group reported that patients with a NAFLD fibrosis score ≥ −1.455 and more advanced renal disease at baseline (eGFR < 45 ml/min/1.73 m^2) experienced the greatest average difference in annual percent changes in eGFR compared to individuals without NAFLD, although the significance of a low baseline eGFR was lost following adjustment for all metabolic confounders (**Table 2**).

Discussion

Summary of findings

The key finding of this systematic review is the identification of a significant gap in the literature within this field. Only three studies examining the clinical impact or prognostic implications of NAFLD within the CKD population were identified preventing further meta-analysis and results were conflicting. Data from the US showed a significant association for NAFLD with all-cause (but not cardiovascular) mortality for individuals with CKD, although this relationship was lost following adjustment for age and metabolic risk factors.[42] No effect on all-cause or cardiovascular-related mortality was observed within the Salford CKD cohort despite the authors identifying NAFLD to be a strong independent risk factor for non-fatal CVEs and a high percentage of patients having significant co-morbidities.[40] Possible explanations include a significantly longer follow-up period for the US group. In addition the US study only included patients with moderate or severe steatosis, suggesting that perhaps the association between NAFLD and mortality is related to the degree of fat, and subsequent inflammation in the liver. The same group found no association between advanced fibrosis and mortality in this cohort however.[42]

Data was also conflicting for the progression of kidney disease. The Korean group reported a significantly greater adjusted rate of percentage decline in eGFR per year for patients with CKD and NAFLD, compared to individuals with CKD without NAFLD,[41] whereas the Salford study reported a non-significant trend in CKD progression for individuals with NAFLD versus those without, and no differences were seen for the incidence of ESRD.[40] The cause of these discrepancies is unclear, particularly given that participants in the Salford cohort had a lower baseline eGFR,[40] which was found to be associated with a greater rate of decline in renal function in the Korean study.[41] The incidence of ESRD was low in the Salford cohort, and the study may have been under-powered for this outcome. Of note the authors of the Salford study published a related paper examining the impact of NAFLD on mortality rates, incidence of non-fatal CVEs and progression of CKD in patients with diabetic kidney disease and reported similar findings.[43] This represented a subgroup of the main Salford cohort and therefore was excluded from this review.

Possible pathophysiological mechanisms linking NAFLD and clinical outcomes for CKD

Broadly the findings from this review mirror findings in the general population where NAFLD is an accepted risk factor for CVEs,[28–32] with debate over whether it is associated with all-cause and cardiovascular mortality. These are summarised in figure 2.[31,33–35] Several mechanisms may explain the influence of NAFLD on CKD incidence and progression, and the development of CVEs within this cohort beyond their shared cardiometabolic risk factors. NAFLD can exacerbate insulin resistance leading to the release of multiple pro-inflammatory, pro-oxidant and pro-fibrogenic mediators important in the pathogenesis of both CKD and CVD.[44,45] Insulin resistance can lead to activation of the renin-angiotensin system and atherogenic dyslipidaemia, key drivers of renal and vascular damage. Steatohepatitis can potentiate the production of inflammatory mediators including reactive oxygen species, cytokines and lipopolysaccharides, exacerbating insulin resistance, tissue inflammation and endothelial damage. None of the studies included in this review reported the prevalence rates of NASH in their cohorts, and this could be a significant factor accounting for the variation observed between study outcomes. Other emerging mechanistic links between NAFLD and CKD include impaired antioxidant defences, abnormal metabolism of lipoproteins, altered intestinal barrier integrity, dysbiosis of intestinal microbiota and dietary factors.[10]

Study strengths and limitations

This is the only systematic review to date to examine the influence of NAFLD on serious adverse clinical outcomes for patients with CKD. Our study benefits from a broad definition of NAFLD and CKD with a number of primary outcomes and no restriction on publication date, with the purpose of maximising the number of papers retrieved. All studies were judged to be of a low or moderate risk of bias (supplementary material 4) and recruited over 800 participants; they spanned three continents and were matched in terms of using ultrasound as their means of diagnosing NAFLD, which is recommended for first line screening.[46] Only cohort studies were chosen to allow us to make inferences about cause and effect.

There are significant limitations associated with this review. Only three studies met our inclusion criteria, recruiting under 4000 individuals with CKD between them. Significant variability was encountered in terms of method of recruitment for participants with CKD, definitions of CKD and NAFLD employed, outcomes assessed and method of adjustment for co-variates. The use of ultrasound for the detection of NAFLD introduced bias, as patients with CKD without an indication for

a liver ultrasound scan were excluded. Patients with a pre-existing background of CVD were also included in both studies which examined the influence of NAFLD on mortality. None of the studies looked at the incidence of non-fatal and fatal CVEs in combination which is highly clinically relevant should represent an important end-point for future prospective studies. Finally this review did not address the influence of CKD within the NAFLD population. In this setting data observational studies shows consensus that CKD is associated with increased all-cause and cardiovascular-related mortality in patients with NAFLD, however there is disagreement regarding whether this effect is independent of metabolic confounders and mediators.[42,47,48]

Supporting evidence from the literature and clinical relevance

In addition to the three cohort studies described in this review, a small cross-sectional study reported a negative correlation between the severity of hepatic steatosis, determined by controlled attenuation parameter, and eGFR in 62 patients with CKD stages 3 and 4 ($r=-0.413$; $p<0.01$).[49] No such association was found for liver stiffness however. Furthermore individuals receiving RRT are more likely to have CVD and experience non-fatal CVEs in the presence of NAFLD.[50–52]

Our findings highlight a potential interplay between NAFLD and CKD and clinical outcomes. This represents an extremely important topic for future research for a number of reasons. Firstly the incidence of both CKD and NAFLD is rising.[10–12] The prevalence risk of CKD among individuals with NAFLD is estimated to be two fold higher compared to individuals without NAFLD[22] and reported prevalence rates of NAFLD within CKD cohorts vary from 21%-86%.[40,41,49] The number of individuals in the US with both NAFLD and renal insufficiency was estimated to be 18.7 million persons in 2016 (prevalence rates 7.7% up from 5.7% in 1999).[47] CKD and NAFLD are profoundly linked to health inequalities globally. This is particularly apparent in advanced disease as a result of disparities in access to treatment, increased burden of lifestyle-related risk factors and the influence of socio-economic status and ethnicity on disease progression.[53–55] The development of end-stage disease also accounts for the overwhelming majority of healthcare costs for patients with kidney disease, with more than half of the CKD budget in England being spent on RRT, and the cost of excess strokes and myocardial infarctions in this population estimated to be £178 million.[56] Avoiding progression towards ESRD and cardiovascular complications associated with CKD via the recognition and management of NAFLD as a potential high risk co-morbidity could therefore be important to reduce these burdens.

Future research and implications for clinical practice

These findings emphasise a need for large prospective collaborative studies to better understand the clinical and prognostic implications for patients who have both CKD and NAFLD. Outcomes should include mortality, CVEs and CKD progression. Patients with NAFLD should also be assessed for NASH and advanced fibrosis. Large routinely collected datasets linked to clinical outcomes maybe less useful in this setting as NAFLD screening is likely to lack robust assessment of inflammation or markers of fibrosis (serum biomarkers, transient elastography and histology), instead being reliant on liver enzymes or simple ultrasound scan. It would also be beneficial to examine is there is an association with NAFLD and acute kidney injury outside the setting of cirrhosis. Other potential research opportunities include understanding the implications of having both CKD and NAFLD-related fibrosis or cirrhosis on drug metabolism. Furthermore shared pathophysiological pathways involving pro-inflammatory mediators, oxidative stress and the gut microbiome present promising therapeutic targets for both NAFLD, CKD and CVD within a co-morbid setting.[44,57]

Approximately 40,000–45,000 individuals with CKD die prematurely each year in England, primarily due to CVD.[58,59] There are currently no recommendations to screen for NAFLD in patients with CKD due to a lack of supportive evidence in terms of prevalence, outcomes and cost-effectiveness. However patients with CKD undergo annual health checks in primary care. Identification of the metabolic syndrome, T2DM and obesity should prompt ultrasound screening for NAFLD in accordance with current guidelines.[46,60] Awareness of these guidelines may be low within this setting currently. Liver enzymes are frequently normal in patients with NAFLD, especially those with CKD and should not be used to rule out liver disease.[40,41,49] Few specific treatments delay the clinical course of CKD, so the identification of NAFLD as a potential risk factor for future adverse events will hopefully provide a further modifiable target for lifestyle (physical activity, Mediterranean diet) or pharmacological intervention (vitamin E, pioglitazone and newer agents).[46,60] Current UK guidelines suggest all patients with NAFLD should be assessed for advanced fibrosis using the Enhanced Liver Fibrosis score,[46] and this should also be the case for CKD patients where liver fibrosis has implications for CKD progression and mortality.[41,47] Patients with NAFLD will nearly certainly have an eGFR performed as part of their routine care, however it is vital that the clinical implications of an abnormal value are appreciated.[42,47,48] Encouragingly weight loss, currently the only proven effective intervention for patients with NAFLD,[61] can reduce the incidence of CKD in this cohort,[62] and improve renal function in individuals with biopsy-proven NASH.[63]

Summary

This systematic review has identified a significant gap in the literature regarding the clinical outcomes and prognostic implications of NAFLD within the CKD population. Studies are conflicting regarding an association between NAFLD and CKD progression and mortality in this cohort. While data suggests a positive correlation with non-fatal CVEs only one study has examined this outcome to date. The prevalence of NAFLD and CKD are rising and are frequently found together. It is therefore vital to understand if there is any synergism in terms of CVD risk, progression towards ESRD and death which would inform the need for aggressive intervention in this potentially high risk group.

Contributorship statement

TH, JP, PR, SF and OK were responsible for the study concept and design; TH and RB performed the searches and screened the papers; TH performed the data extraction which was checked by RB and drafted the manuscript; JP, PR, SF, OK and RB edited the revised manuscript.

Competing interests statement

None of authors have any competing interests

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Data sharing statement

Data was obtained from previously published cohort studies which are accessible to the public via the journals cited in this review.

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Figure legends

Figure 1. A schematic showing the selection of relevant studies for inclusion in the systematic review

Figure 2. A summary of the evidence linking the clinical outcomes for chronic kidney disease and non-alcoholic fatty liver disease.

Acknowledgements

None

Table 1. Summary of study characteristics (n=3)

Study	Chinnadurai et al. *Nephrol Dial Transplant* (2019)[40]	Jang et al. *Scientific report* (2018)[41]	Paik et al. *Liver International* (2019)[42]
Country	United Kingdom	South Korea	United States
Median follow up	5.4 years	6.5 years	19.2 years
Years	Liver USS (01/01/2000 - 31/12/2014), end of analysis period 31/12/2015	January 2003 - December 2013	NHANES III 1988 – 1994 Linked mortality files up to 2011 or date of death
Population source	Salford Kidney Study	Individuals who had health screening at the Samsung Medical Centre, South Korea	Third National Health and Nutrition Examination Survey (NHANES) & linked mortality database
Study size	852 CKD patients	1,525 CKD patients	1,413 CKD patients (11,695 adults overall: (i) CKD+NAFLD+ 2.6%, (ii) CKD+NAFLD- 6.8%, (iii) CKD-NAFLD+ 16.1%, (iv) CKD-NAFLD- 74.6%)
Demographics	Mean age 66 years, males 60.7%, mean BMI 28, DM 34%, HTN 78%, hyperlipidaemia 49%, median eGFR 33.5 mL/min/1.73 m^2	Mean age 61 years, males 69.8%, mean BMI 25, DM 24%, HTN 60%, hyperlipidaemia 41%, median eGFR 59.1 mL/min/1.73 m^2	*CKD with NAFLD:* Mean age 54 years, males 45.6%, obesity 52.2%, DM 43.2%, HTN 77.4%, hyperlipidaemia 86.9% *CKD without NAFLD*: Mean age 53 years, males 36.1%, obesity 30.0%, DM 16.8%, HTN 66.4%, hyperlipidaemia 81.7%
NAFLD prevalence	21% (183/852)	41% (902/1,525)	29% (413/1,413)
NAFLD definition	Liver ultrasound scan	Liver ultrasound scan	Liver ultrasound (moderate / severe steatosis only)
CKD definition	eGFR <60 ml/min/1.73m^2	eGFR <60 ml/min/1.73m^2 or proteinuria ≥ 2+	eGFR <60 ml/min/1.73m^2 +/- albuminuria
Co-variate adjustments	Propensity matching (n=276) for: age, gender, BMI, SBP, DBP, baseline HTN, DM, hypercholesterolaemia, IHD, MI, CCF, CVA, PVD, malignancy, use of statin & renin–angiotensin blocking agents, eGFR	Stratified analyses according to pre-defined subgroups: age (<60 vs ≥ 60 yrs), gender, smoking (never/former vs current), alcohol (none vs moderate), BMI ≥ 25, HTN (SBP ≥ 140 mmHg / DBP ≥ 90 mmHg / use antihypertensives), DM (fasting glucose ≥ 126 mg/dl / HbA1c ≥ 6.5% / use antidiabetic drugs), hyperlipidaemia (HDL < 40 mg/dl men, < 50 mg/dl women / TG ≥ 150 mg/dl / use lipid-lowering drugs) & baseline eGFR (<45 vs ≥ 45 ml/min/1.73 m^2)	Age-adjustment based on the direct method to the Census 2000 population using the age groups 20-39, 40-59 & 60-74. Groups adjusted for the following in multivariable analysis: age category, gender, race, current smoker & the metabolic syndrome.

CKD: chronic kidney disease, NAFLD: non-alcoholic fatty liver disease, BMI: body mass index, DM: diabetes, HTN: hypertension, eGFR: estimated glomerular filtration rate, SBP: systolic blood pressure, DBP: diastolic blood pressure, IHD: ischaemic heart disease, MI: myocardial infarction, CCF: congestive cardiac failure, CVA: cerebrovascular accident, PVD: peripheral vascular disease, HDL: high density lipoprotein, TG: triglycerides, USS: Ultrasound scan

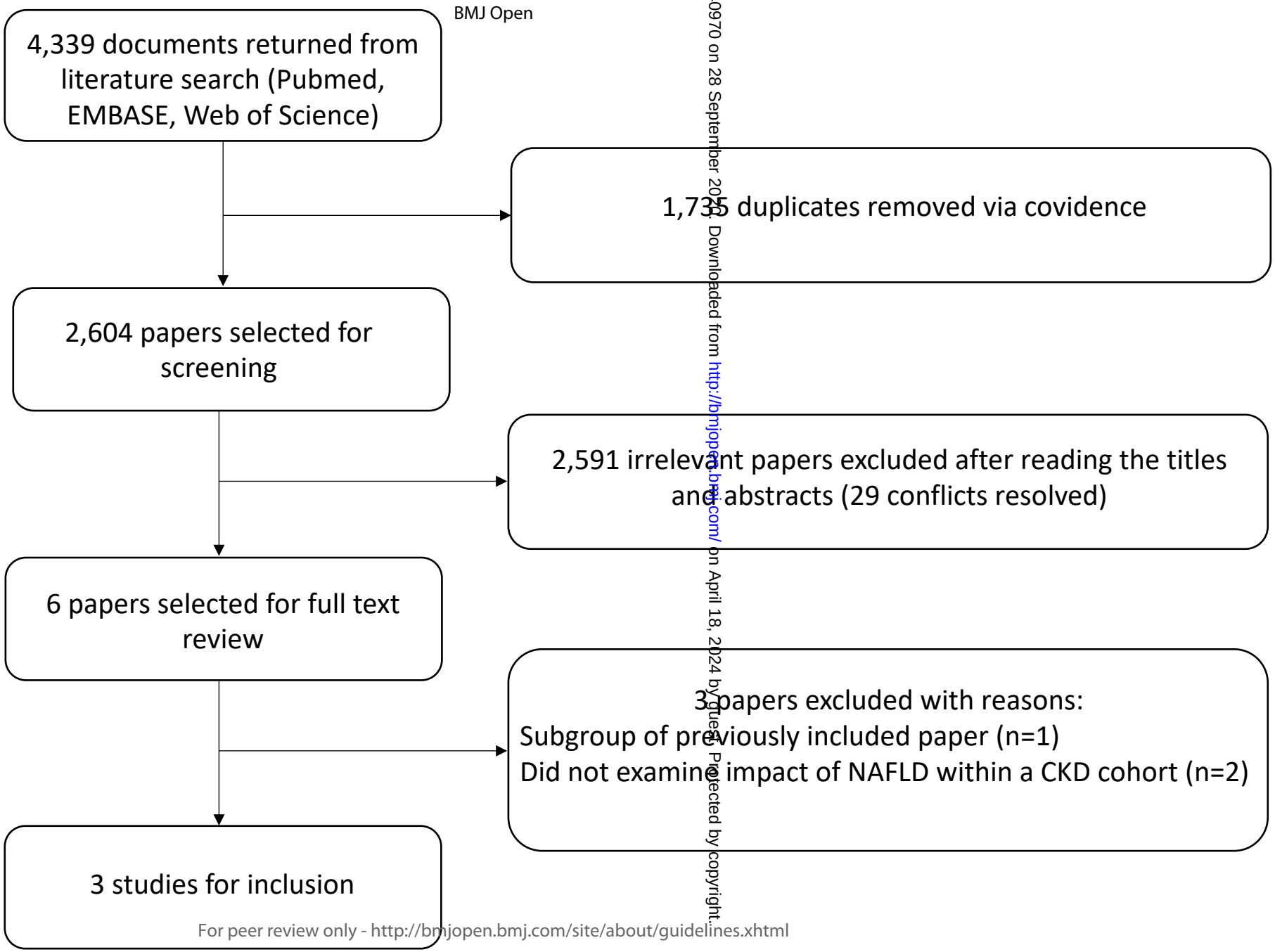
Table 2. Summary of study outcomes (n=3)

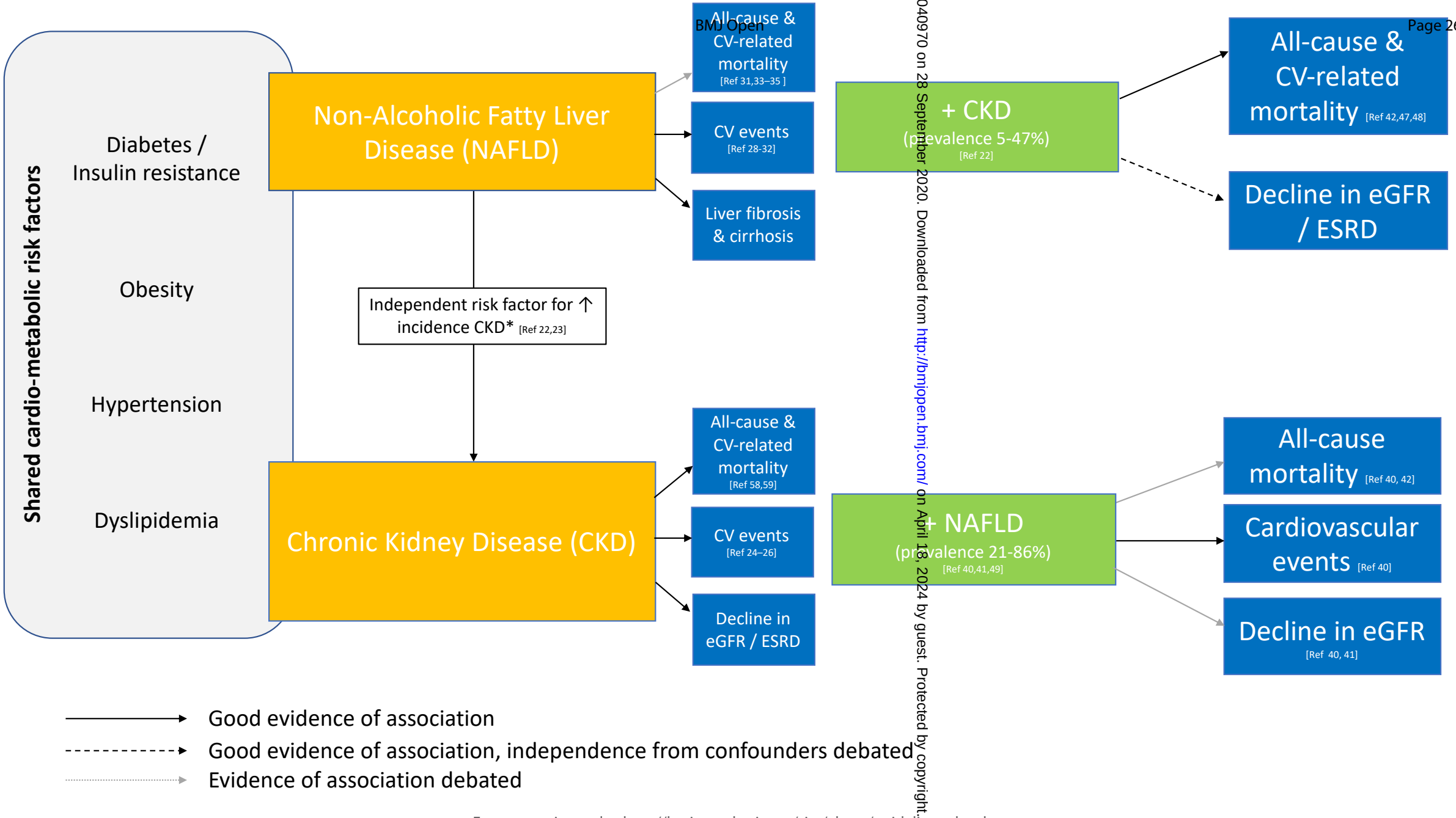
Study	Chinnadurai et al. *Nephrol Dial Transplant* (2019)[40]	Jang et al. *Scientific reports* (2018)[41]	Paik et al. *Liver International* (2019)[42]
Primary outcomes & definition	*(1) ESRD:* commencement of RRT or eGFR <10 mL/min/1.73 m^2 *(2) CKD progression*: rate of change of eGFR from baseline to study end-point (3) *NFCVE:* composite of ACS, non-fatal MIs, non-fatal cardiac arrest, coronary revascularization, new diagnosis CCF / admission with exacerbation of CCF, new diagnosis of PVD, CVAs (4) *All-cause mortality* *(5) Cardiovascular-related mortality:* Ia cause of death was due to cardiac event, CVA, CCF or PVD	(1) *CKD progression*: average annual percent change in eGFR from baseline	(1) *All-cause mortality* (2) *Cardiovascular-related mortality:* death due to heart diseases (ICD-10: I00-I09, I11, I13, I20-I51) & cerebrovascular diseases (ICD-10: I60-I69)
Secondary outcomes & definition	None	(1) *NAFLD severity according to NFS*: high-intermediate (NFS ≥ −1.455) & low probability (NFS < −1.455) of advanced fibrosis (2) *Severity of CKD at baseline*: eGFR ≥45 ml/min/1.73 m^2 vs <45 ml/min/1.73 m^2 (dividing stages 3a & 3b)	(1) *Presence of advanced liver fibrosis:* ≥ 1 of the following fibrosis markers – APRI > 1, FIB-4 score > 2.67 or NFS > 0.676
Cases	(1) *ESRD*: NAFLD n=26 (14.2%), no NAFLD n=134 (19.1%), p=0.07 (2) *CKD progression*: NAFLD -2.54 [-7.61 - 0.31] mL/min/1.73 m^2, no NAFLD -2.09 [-6.14 - 1.06] mL/min/1.73 m^2 (3) *NFCVE:* NAFLD n=46 (25.1%), no NAFLD n=82 (12.3%), p<0.001 (4) *All-cause mortality*: NAFLD n=50 (27.3%), no NAFLD n=221 (33.0%), p=0.14	(1) *Average annual percent change in eGFR from baseline:* NAFLD -0.79% [-1.31 - -0.27], no NAFLD 0.30% [-0.14 - 0.76] (2) *Average difference in % decline of eGFR per year NAFLD vs no NAFLD:* (i) Adjusted for age, sex, year of visit: -1.09% [-1.77 - -0.41] (ii) Adjusted for all confounders: -1.06% [-1.73 - -0.38]	(1) *All-cause mortality:* NAFLD 54.7% (SE 3.6), no NAFLD 46.5% (SE 2.4), p<0.05 (age adjusted: NAFLD 31.0% [25.0-37.0], no NAFLD 25.9% [22.0-29.7], p=ns) (2) *Cardiovascular-related mortality:* NAFLD 16.0% (SE 2.5), no NAFLD 16.2% (SE 1.7), p=ns (age adjusted: NAFLD 7.8% [3.7-11.9], no NAFLD 8.2% [5.6-10.9], p=ns)

	(5) *Cardiovascular-related mortality:* NAFLD n=10 (31.3%), no NAFLD n=67 (40.5%), p=0.36		
Risk of bias Newcastle Ottawa Score (NOS)	Mortality NOS = 8, non-fatal CVE NOS = 8, CKD progression NOS = 9	NOS = 9	NOS = 7
Primary outcome results	(1) *ESRD:* total sample HR 0.99 [0.65–1.52], p=0.90; matched HR 0.64 [0.35-1.16], p=0.145 (2) *CKD progression*: total sample p=0.09; matched p=0.58 (3) *NFCVE:* total sample HR 2.07 [1.39-3.09], p<0.001; matched HR 1.85 [1.04-3.30], p=0.04 (multivariate: total sample HR 2.03 [1.33-3.13], p<0.001; matched HR 2.00 [1.10-3.66], p=0.02) (4) *All-cause mortality*: total sample HR 0.79 [0.58-1.08], p=0.14; matched HR 0.88 [0.57–1.34], p=0.54 (5) *Cardiovascular-related mortality:* HR not published	*Average difference in % decline of eGFR per year NAFLD vs no NAFLD:* (i) Adjusted for age, sex, year of visit: p=0.002 (ii) Adjusted for all confounders: p=0.002	(1) *All-cause mortality:* CKD+NAFLD+ vs no CKD/NAFLD adjusted HR 2.34 [1.91-2.87], CKD+NAFLD- HR vs no CKD/NAFLD adjusted HR 2.08 [1.80-2.40], p=ns (2) *Cardiovascular-related mortality:* CKD+NAFLD+ vs no CKD/NAFLD adjusted HR 2.12 [1.44-3.13], CKD+NAFLD- HR vs no CKD/NAFLD adjusted HR 2.43 [1.8-3.28], p=ns
Secondary outcome results	None	(1) *Adjusted average difference in annual % change in eGFR:* low NFS vs no NAFLD 0.01% [−0.74 - 0.99]; high-intermediate NFS vs no NAFLD −2.12% [−2.93 - −1.31], p<0.0001 (2) *Adjusted average difference in annual % change in eGFR among patients with eGFR < 45 ml/min/1.73 m² at baseline for patients with NAFLD vs those without*: -5.61% [-11.43 – 0.59], p=0.075.	(1) *CKD + NAFLD + advanced fibrosis (n=60)* All-cause mortality: 73.1% [50.7-95.5], p=ns vs no advanced fibrosis; adjusted HR 3.49 [2.25-5.43], p=ns vs no advanced fibrosis Cardiovascular-related mortality: 14.6% [1.6-27.7], p=ns vs no advanced fibrosis; adjusted HR 2.83 [0.69-11.51], p=ns vs no advanced fibrosis (2) *CKD + NAFLD + no advanced fibrosis (n=97)* All-cause mortality: 52.1% [44.8-59.3]; adjusted HR 2.51 [1.98-3.18] Cardiovascular-related mortality: 16.5% [11.1-21.9]; adjusted HR 2.45 [1.61-3.73]

CKD: chronic kidney disease, ESRD: End-stage renal disease, RRT: renal replacement therapy, NFCVE: non-fatal cardiovascular event, ACS: acute coronary syndrome, MI: myocardial infarction, CCF: congestive cardiac failure, PVD: peripheral vascular disease, CVA: cerebrovascular accident, NAFLD: non-alcoholic fatty liver disease, HR: hazard ratio, NFS: NAFLD fibrosis score, APRI: AST to platelet ratio index, FIB-4, fibrosis-4, SE: standard error

95% confidence intervals are shown in square brackets.





* Predictors: hepatic fibrosis, age, male, obesity, hypertension, diabetes, dyslipidaemia, cardiovascular disease

Study Protocol

Background

Chronic kidney disease (CKD) is a long-standing condition resulting in impaired renal function associated with a reduced quality of life, increased risk of end-stage renal disease (ESRD), cardiovascular disease and premature death.(1) CKD is classified according to five stages largely based on estimated Glomerular Filtration Rate (eGFR), although persistent albuminuria also determines prognosis.(2) Moderate-severe CKD (stage 3-5) is defined as an eGFR of less than 60ml/min/1.73m^2 for more than 3 months. According to the Quality Outcomes Framework and Health Survey for England 2016 around 4-7% of UK adults have CKD stages 3-5.(3,4) The disease burden is particularly high in the elderly.(3) The global prevalence of CKD is higher at 11% for stages 3-5,(5) and it is estimated that the absolute global prevalence increased by 27% from 2007-2019.(6) CKD is forecasted to move from 16th (2016) to 5th (2040) in the rankings for years of life lost, predominantly as a result of aging, but also due to an increase in the prevalence of metabolic risk factors.(7) In addition to increasing age, hypertension, diabetes and obesity are major disease risk factors accounting for the majority of newly diagnosed cases of CKD in the developed world.(8,9) In terms of prognosis, it is estimated that 40,000–45,000 individuals with CKD die prematurely each year in England, with cardiovascular disease being the primary cause of morbidity and mortality.(10) The rate for individuals over 65 with CKD to progress to ESRD is reported to be 0.5 per 100 person-years and 6.8 per 100 person-years for all-cause mortality (3.0 for cardiovascular and 3.8 for non-cardiovascular mortality), i.e. patients with CKD are more likely to die from cardiovascular disease than develop ESRD.(11) CKD is both an accelerator of the risk of cardiovascular disease and an independent risk factor for cardiovascular events,(12–14) and is thought to account for 7000 extra strokes and 12,000 extra myocardial infarctions (MI) per year.(15)

Non-alcoholic fatty liver disease (NAFLD) refers to excessive fat accumulation in the liver affecting more than 5% of hepatocytes or liver volume. NAFLD is the most common cause of chronic liver disease worldwide, affecting approximately 25% of the adult population globally and in Europe.(16) It is expected to become the leading indication for liver transplantation in the next decade. It is estimated 90% of patients with type 2 diabetes mellitus (T2DM) have NAFLD, along with 70% of adults with obesity (17) and 90% of individuals who qualify for bariatric surgery.(18) While there is a lack of large prospective data in this field, paired liver biopsy studies from tertiary care suggest that around 23% of patients with simple steatosis are likely to develop non-alcoholic steatohepatitis (NASH) (hepatocytes injury (ballooning) and necro-inflammation) over a 3 year period, (19) and 44% over an average 8 year period.(20) Overall up to 30% of individuals with NAFLD are thought to have NASH,(21) and this is associated with a 25% risk of progression to cirrhosis over a 10 year period.(22) There is also evidence that NASH can lead to an elevated risk of hepatocellular carcinoma (HCC) even in the absence of cirrhosis.(23)

NAFLD and CKD share several cardiometabolic risk factors, many of which have now reached epidemic levels in the UK.(24) Current estimates suggest that 35.6% of adults in England are overweight and a further 28.7% are obese, with rates having more than doubled since 1991.(25,26) Around 1 in 11 adults worldwide (463 million) are thought to have diabetes, of which 90% is type 2.(27) This figure has more than tripled over the past 20 years, making diabetes one of the fastest growing health challenges of the 21st century.(27) Approximately 9% of men and 7% of women have diabetes in England,(28) however prevalence rates are as high as 25-30% in Pacific nations, followed by the Middle East and North Africa.(29) The International Diabetes Federation project the number of adults with diabetes worldwide will rise to 700 million by 2045, with the largest increases coming from regions experiencing economic transitions from low-income to middle-income levels.(27) While the prevalence of hypertension remains static it affects 30% of men and 26% of women.(28) Of huge concern is the fact that 22% and 34% of children starting primary school and secondary school

respectively are either overweight or obese.(30) While the incidence of T2DM for those under 17 years old in the UK remains low at 0.72 per 100,000 / year (2015/16), the number of cases diagnosed per year continues to rise,(31) and prevalence rates are significantly higher in the United States.(32)

It is well established that individuals with NAFLD are at increased risk of mortality from liver disease, cardiovascular disease and cancer (HCC and extra-hepatic) (33,34) however its association with kidney disease and its outcomes are less well understood. Two systematic reviews have now conclusively demonstrated a higher risk of incident CKD in individuals with NAFLD (hazard ratio (HR) 1.37 [95% CI 1.20-1.53] and 1.79 [95% CI 1.65-1.95].(35,36) Both reviews report that patients with more advanced fatty liver disease, i.e. NASH or hepatic fibrosis are at the greatest risk. Surprisingly this association has been consistently found to be independent of common risk factors and potential confounders, for example age, gender, body mass index, diabetes status, lipids, hypertension and smoking.(35,36) Of note NAFLD is also thought to be an independent risk factor for cardiovascular disease.(37) It has therefore been proposed that shared proinflammatory, prothrombotic and profibrotic molecular pathways may play a mediating role, in addition to the fact that NAFLD itself exacerbates insulin resistance, leading to atherogenic dyslipidaemia.(24) No causal link has been definitively demonstrated, however lifestyle modification has been shown not only to improve NAFLD histology but also kidney function in patients with biopsy proven NASH.(38). It is important to note that this association may manifest itself at an early stage, as children with NAFLD have been found to be at increased risk of developing renal dysfunction.(39) NAFLD is estimated to affect 3-10% of children worldwide.(40) It is possible that children and young adults with NAFLD may be at risk of an accelerated disease course in terms of cardiovascular complications, liver disease and kidney disease, especially given the increasing prevalence of shared cardiometabolic risk factors experienced by this age group.

We are interested in whether the presence of NAFLD predisposes individuals with CKD to be at increased risk of cardiovascular events, progression of kidney disease and all-cause mortality (figure 1). A brief review of the literature has revealed two cohort studies from the same group which used data from the Salford Kidney Study database.(41,42) The first follows 1,148 patients with CKD who also had a liver ultrasound to look for hepatic steatosis, for a median of 5.4 years.(41) They concluded that NAFLD was a strong independent risk factor for cardiovascular events (HR 2.03) (even in advanced CKD associated with high levels of comorbidity), but was not associated with all-cause mortality (HR 0.79) or CKD progression (p=0.09 for the rate of decline of the eGFR slope). The second study was confined to diabetic patients with CKD (n=149) and demonstrated comparable findings.(42) A third study from South Korea reported a greater rate of decline in eGFR in patients with NAFLD vs those without (−0.79% [−1.31% - −0.27%] vs 0.30% [−0.14% - 0.76%], p=0.002) in a cohort of 1,525 individuals with CKD.(43) Differences persisted in a multivariable adjusted model demonstrating that NAFLD is independently associated with CKD progression. Similarly in the haemo- and peritoneal dialysis population, patients with NAFLD have been found to have significantly worse cardiovascular outcomes.(44–46) Within NAFLD cohorts, CKD is associated with increased overall mortality, however there is disagreement regarding whether this is independent or due to the greater prevalence of metabolic comorbidities.(47,48)

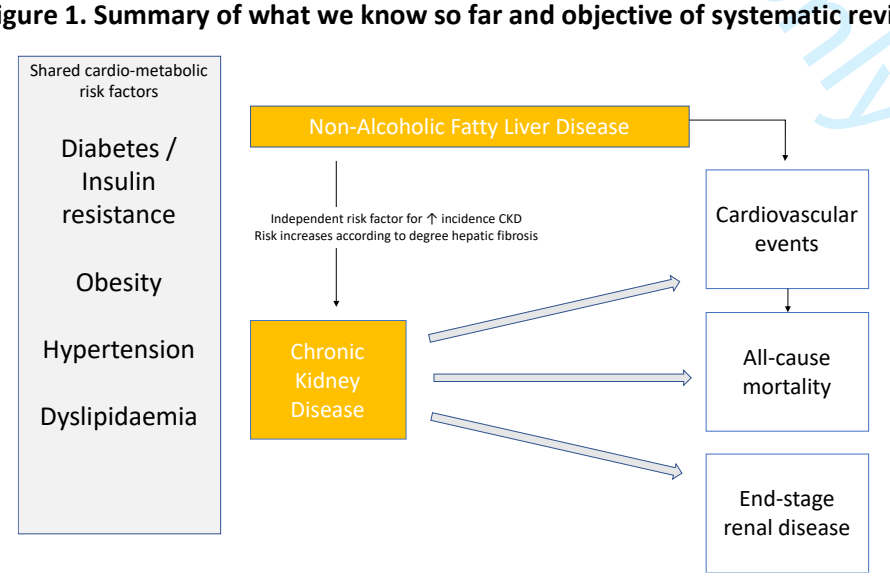
Importance of this review

Both CKD, NAFLD and their cardiometabolic risk factors (obesity and T2DM in particular) present huge challenges for both UK and global health providers.(16,49) In addition to the rising prevalence rates described above, both these conditions are profoundly linked to health inequalities. The incidence rates of CKD are estimated to be four times higher in low and middle income countries (LMIC), with Oceania, South East Asia, the Caribbean, Latin America, North Africa and the Middle East experiencing significant increases in disease burden.(6,50) Furthermore individuals of African descent experience

an accelerated course towards ESRD once they develop CKD.(51,52) With scarce resources for renal replacement therapy (RRT) in such countries, patients with ESRD are often faced with a death sentence. Similarly the burden of NAFLD is felt most heavily by low and middle income regions, including India (nearly 50%), South America and parts of the Middle East (approximately 30%).(53,54) Such inequalities nearly certainly result from a disparity in the prevalence of metabolic risk factors across economies. Nearly 80% of individuals with diabetes live in LMICs.(27) While obesity continues to predominantly affect higher income populations rates are levelling off, and instead are increasing in emerging economies.(55) Within England there is a large depravity gap in obesity prevalence for both adults and children which is increasing.(30) There is therefore a pressing need to address both the risk factor burden and predictors of clinical outcomes for both CKD in NAFLD, as LMIC and ethnic minorities are set to become disproportionately affected by these two conditions. Furthermore the financial costs associated with CKD are considerable. CKD was estimated to cost the English NHS £1.45 billion 2009-2010 (1.3% of all NHS spending).(15) More than half of this was spent on RRT serving 2% of the CKD population.(15) The cost of excess strokes and MIs was estimated to be up to £178 million.(15) Avoiding progression towards ESRD and the cardiovascular complications associated with CKD is therefore essential to reduce this huge cost burden.

CKD and NAFLD frequently exist together and independently contribute towards an increased risk of cardiovascular events and mortality. There is strong evidence that NAFLD is associated with an increased incidence of CKD, however research into the influence of NAFLD on the development of cardiovascular events, ESRD and premature death in the CKD population is at a much earlier stage. Understanding if there is a role for NAFLD in accelerating progression towards these adverse events could lead to improve health outcomes, reduced health inequalities and significant cost savings. This is a highly clinically relevant topic as individuals presenting to both primary and secondary care are increasingly likely to have both conditions. It is vital for their quality of care that clinicians are not only able to recognise the importance of looking for each of these diseases as a comorbidity, but also to identify patients who may be at the greatest risk for future cardiovascular events, rapid progression of kidney disease or early death. This would allow more aggressive lifestyle intervention, strict control of shared risk factors and enrolment in clinical trials. These findings are also likely to inform the need for improved cross-talk between diabetologists, cardiologists, hepatologists and renal physicians to help manage these patients optimally and lead to reductions in health care spending if end-stage events can be prevented. The findings of this review will be used to design an observational study which will further explore this question in an independent cohort.

Figure 1. Summary of what we know so far and objective of systematic review



HR: Hazard ratio, NAFLD: non-alcoholic fatty liver disease, CKD: Chronic kidney disease

Objective

To determine the influence of NAFLD on the risk of cardiovascular events, progression of kidney disease and all-cause mortality in patients with established CKD, and identify if this is independent of confounding factors

Methods

Types of studies

- Inclusion criteria: Observational (prospective or retrospective) cohort studies that report either the risk of cardiovascular events, progression of kidney disease or all-cause mortality among adults (> 18 year old) with established CKD who have NAFLD compared with those without NAFLD. Only studies that include meta-analysable outcomes will be included (mean difference, standardised difference, odds ratio (OR), HR or relative risk (RR)).
- Exclusion criteria: Abstracts, case reports, reviews, editorials, practice guidelines, non-cohort design, non-human studies, unpublished studies
- Search dates: No restriction on earliest publication date to present day
- Searches will be re-run just before the final analyses and any further studies identified, retrieved for inclusion
- We will register the protocol on PROSPERO a priori (https://www.crd.york.ac.uk/PROSPERO/)

Types of participants

- Inclusion criteria: Adults with established CKD with evidence of the presence or absence of NAFLD
- Exclusion criteria: Individuals under 18 years of age, individuals undergoing renal replacement therapy, eg haemodialysis, individuals who have had either a kidney or liver transplant, and individuals with a known other cause of chronic liver disease
- Definition of chronic kidney disease (CKD): eGFR ≥ 60 ml/min/1.73m^2 with albumin to creatinine ratio (ACR) > 3 mg/mmol (stage G1 and G2) or eGFR < 60 ml/min/1.73m^2 (stages G3a – G5) calculated using the CKD Epidemiology Collaboration (CKD-EPI) or Modified Diet in Renal Disease (MDRD) formula
- Definition of non-alcoholic fatty liver disease (NAFLD): biochemistry (elevations in serum AST, ALT, or GGT), imaging (ultrasound, computer tomography, magnetic resonance imaging), liver biopsy, non-invasive scores (Fatty Liver Index, Steatotest, NAFLD Liver Fat Score)

Primary outcome

- This review will aim to establish if there are any differences in the risk of cardiovascular events, progression of kidney disease and all-cause mortality in patients with CKD who have NAFLD compared to those without.
- Definition of cardiovascular events: Any one of the following - acute coronary syndrome, myocardial infarction, non-fatal cardiac arrest, coronary revascularization, new diagnosis of cardiac failure, hospitalisation with an exacerbation of cardiac failure, new diagnosis of peripheral vascular disease, new diagnosis of cerebrovascular accident (stroke / transient ischemic event) (all non-fatal).
- Definition of the progression of chronic kidney disease:
  1. Mean or percentage annual rate of change in the eGFR, or
  2. A decline in eGFR category accompanied by a ≥ 25% drop in eGFR from baseline, or
  3. The development of ESRD: eGFR of < 15 ml/min/1.73m^2, or the requirement of some form of renal replacement therapy, or

4. Doubling of creatinine

- Definition of all-cause mortality: Any cause of death within the study follow up period as determined by electronic patient records or the office of national statistics. Where possible we will break this down according to deaths due to a cardiovascular event, cancer or progression of kidney disease.

Secondary outcome

- The risk of cardiovascular events, progression of kidney disease and all-cause mortality in patients with CKD according to the severity of NAFLD, as determined by the presence of NASH or fibrosis.
- The risk of cardiovascular events, progression of kidney disease and all-cause mortality in patients with CKD according to the baseline severity of CKD, as determined by CKD stage.

Search methods for the identification of studies

- We will perform a computerized literature search in: PubMed, Embase (using Ovid) and Web of Science

Example of literature search strategy

"chronic kidney disease" [Title/Abstract] OR "CKD" [Title/Abstract] OR "kidney disease" [Title/Abstract] OR "kidney failure" [Title/Abstract] OR "kidney injury" [Title/Abstract] OR "chronic renal disease" [Title/Abstract] OR "renal disease" [Title/Abstract] OR "renal failure" [Title/Abstract] OR "renal injury" [Title/Abstract] OR "renal insufficiency" [Title/Abstract] OR "impaired renal function" [Title/Abstract] OR "glomerular filtration rate" [Title/Abstract] OR "eGFR" [Title/Abstract]
AND
"fatty liver" [Title/Abstract] OR "nonalcoholic fatty liver disease" [Title/Abstract] OR "NAFLD" [Title/Abstract] OR "nonalcoholic steatohepatitis" [Title/Abstract] OR "NASH" [Title/Abstract] OR "liver fat" [Title/Abstract] OR "steatohepatitis" [Title/Abstract] OR "steatosis" [Title/Abstract] OR "hepatic fibrosis" [Title/Abstract])

Study selection

- Relevant studies will be identified by systematically searching PubMed, Embase and Web of Science up to the present date using the free text terms described above
- Reference lists of relevant papers and previous review articles will be hand searched for other studies.
- Two investigators will examine all titles and abstracts, and obtain the full texts of potentially relevant papers. We will read the papers and determine if they met inclusion criteria.
- Discrepancies will be resolved by returning to the original article along with a third author in order to reach a consensus
- Inclusion criteria: Observational (prospective or retrospective) cohort studies that report either the risk of cardiovascular events, progression of kidney disease or all-cause mortality among adults (> 18 year old) with established CKD who have NAFLD compared with those without NAFLD. Only studies that include meta-analysable outcomes will be included (mean difference, standardised difference, OR, HR or RR).
- Exclusion criteria: Abstracts, case reports, reviews, editorials, practice guidelines, non-cohort design, non-human studies, unpublished studies

Data extraction

- Data will be extracted from each study independently by two authors and recorded on a standardised data extraction sheet
- We will use the Covidence software as recommended by Cochrane to upload search results, screen abstracts and full text, complete data collection, conduct risk of bias assessment, resolve disagreements and export data into Excel
- The following details will be extracted from all studies:
    - General information: title, authors, journal, funding, year of publication
    - Study design: population source and demographics, period of follow up and years, means of defining NAFLD, quality of study defined by the ACROBAT-NSRI tool, inclusion and exclusion criteria, study size, subgroups analysis (including severity of NAFLD and baseline CKD), confounding factors
    - Outcomes for NAFLD vs non-NAFLD patients: Outcome of interest (cardiovascular event / progression of kidney disease / all-cause mortality and definition used); OR, HR, RR and 95% confidence intervals; or mean/percentage annual rate of change in the eGFR
- In the event of missing data the researchers will attempt to contact the study investigators for unreported data or additional details. Contact information for study authors will be identified from PubMed or from the Internet and corresponding authors will be e-mailed or contacted by phone to ask if they are willing to share their study data. Up to 3 contact attempts will be made within a month. Manuscripts for which we are unable to obtain missing data will not be included in our analyses.
- Data will be reported according to the PRISMA guidelines

Assessment of bias (quality assessment)

- Two authors will independently be involved in the quality assessment
- Any discrepancies will be addressed by a revaluation of the original article by a third author
- We will use the Newcastle-Ottawa Score as recommended by Cochrane for the assessment of quality for non-randomised cohort studies.(56)
- This tool uses a star based system allocating a maximum of 9 points across three domains: (1) selection of study groups (max 4 points), (2) comparability of groups (max 2 points), (3) ascertainment of exposure and outcomes (max 3 points)
- Studies with an overall score of 9 are judged to be at a low risk of bias, those scoring 7-8 a moderate risk of bias and scores of 6 of less a high risk of bias.
- Where studies report more than one primary outcome a separate bias assessment will be performed for each.

Data synthesis

- Data will be synthesised if this review is able to identify 5 of more studies which meet the inclusion criteria described above, and that report the same outcome (either risk of a cardiovascular event, progression of kidney disease, or all-cause mortality)
- In the case of binary outcomes (risk of a cardiovascular event, ESRD, a decline in eGFR category accompanied by a ≥ 25% drop in eGFR from baseline, doubling of creatinine and all-cause mortality), adjusted and unadjusted HR/OR/RRs will be pooled with their 95% confidence intervals as a measure of effect size.
- In the case of continuous outcomes (mean/percentage annual rate of change in the eGFR) we will pool the adjusted and unadjusted mean or percentage differences

- Random-effects model: An overall estimate of effect size will be calculated using a random-effects model, as this takes into account any differences between studies even if there is no statistically significant heterogeneity.
- Statistical heterogeneity: The I^2 statistic will be used to investigate statistical heterogeneity. This estimates the percentage of variability in effect across studies resulting from heterogeneity rather than chance, to ensure that the effects found in the individual studies are similar enough that a combined estimate will be a meaningful. If heterogeneity between the effects found in single studies is too large ($I^2 > 0.5$) we will explore the source.
- Publication (small study bias): If the number of included studies is sufficient, publication bias will be examined using funnel plots and the Egger's regression test. We will use the trim and fill method to calculate adjusted estimates if publication bias is detected.
- Sensitivity analysis: For all outcomes we will use a meta-analysis influence test (involves repeating the meta-analysis after one study at a time is removed) to investigate any excessive influence of individual studies
- Meta-regression analysis: When 8 or more studies are available and report the same outcome, the effect of continuous variables (age, body mass index, waist circumference, insulin resistance estimated by homeostasis model assessment of insulin resistance index, and duration of follow-up) on the association between NAFLD and the reported outcome will be evaluated by meta-regression analysis

Analysis of subgroups or subsets

- If we are able to identify at least 5 cohort studies reporting the same outcome as described above, we will perform a sub-group analysis in order to address potential heterogeneity between studies
- Individuals may be stratified using any of the following criteria at the level of the study:
    - Quality of study as identified by the ACROBAT-NSRI tool
    - Follow-up duration
    - Age
    - Ethnicity
    - Means of defining NAFLD (biochemistry, imaging, liver biopsy, non-invasive scores)
    - Severity of NAFLD (NASH vs no NASH; fibrosis vs no fibrosis)
    - Severity of CKD according to disease stage at baseline
    - Patients with diabetes vs those without diabetes
    - Patients with cirrhosis vs those without cirrhosis
    - Patients with a history of excessive alcohol consumption vs those without
    - Whether the study has fully adjusted for covariates (age, gender, body mass index, hypertension, smoking, baseline eGFR, diabetes, dyslipidaemia, previous cardiovascular event)

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Supplementary material

Methods

Exact search criteria for online databases

1. PUBMED – 1,020 results (1,012 uploaded to Covidence). Save file .xml & open with textedit

("chronic kidney disease" [Title/Abstract] OR "CKD" [Title/Abstract] OR "kidney disease" [Title/Abstract] OR "kidney failure" [Title/Abstract] OR "kidney injury" [Title/Abstract] OR "chronic renal disease" [Title/Abstract] OR "renal disease" [Title/Abstract] OR "renal failure" [Title/Abstract] OR "renal injury" [Title/Abstract] OR "renal insufficiency" [Title/Abstract] OR "impaired renal function" [Title/Abstract] OR "glomerular filtration rate" [Title/Abstract] OR "eGFR" [Title/Abstract]) AND ("fatty liver" [Title/Abstract] OR "nonalcoholic fatty liver disease" [Title/Abstract] OR "NAFLD" [Title/Abstract] OR "nonalcoholic steatohepatitis" [Title/Abstract] OR "NASH" [Title/Abstract] OR "liver fat" [Title/Abstract] OR "steatohepatitis" [Title/Abstract] OR "steatosis" [Title/Abstract] OR "hepatic fibrosis" [Title/Abstract])

2. EMBASE (includes all Medline content; use Ovid for search) 'Embase 1974 to yesterday's date, http://ovidsp.dc1.ovid.com/sp-4.04.0a/ovidweb.cgi – 1,851 results. Export as .ris files. (1,968 to screen when added to pubmed)

((chronic kidney disease or CKD or kidney disease or kidney failure or kidney injury or chronic renal disease or renal disease or renal failure or renal injury or renal insufficiency or impaired renal function or glomerular filtration rate or eGFR) and (fatty liver or non-alcoholic fatty liver disease or NAFLD or nonalcoholic steatohepatitis or NASH or liver fat or steatohepatitis or steatosis or hepatic fibrosis)).ti,ab

3. Web of Science core collection, '1970-2020'. Topic (TS): title, abstract, keywords. 1,476 results. Import to Mendeley, then save as .ris. (2,604 to screen when added to pubmed & EMBASE)

TS=(("chronic kidney disease" OR CKD OR "kidney disease" OR "kidney failure" OR "kidney injury" OR "chronic renal disease" OR "renal disease" OR "renal failure" OR "renal injury" OR "renal insufficiency" OR "impaired renal function" OR "glomerular filtration rate" OR eGFR) AND ("fatty liver" OR "nonalcoholic fatty liver disease" OR NAFLD OR "nonalcoholic steatohepatitis" OR NASH OR "liver fat" OR steatohepatitis OR steatosis OR "hepatic fibrosis"))

Title
Authors
Journal
Year publication
Country
Funding
Population source
Demographics
Period follow up
Years of study
Study size
Intervention'
NAFLD definition
CKD definition
Quality (Newcastle-Ottawa Score)
Inclusion criteria
Exclusion criteria
Study design
Subgroup analysis
Adjustments for confounding factors
Longitudinal f/u
Outcome examined & definition
Statistical analysis
NAFLD prevalence
Cases
Primary outcome results
Secondary outcome results
OUTCOME

Non-alcoholic fatty liver disease and clinical outcomes in chronic kidney disease	
Rajkumar Chinnadurai, James Ritchie, Darren Green and Philip A. Kalra	
Nephrol Dial Transplant	
2019	
UK	
?	
Salford Kidney Study (SKS) - extension of the Chronic Renal Insufficiency Standards Implementations Study (CRISIS)	
Mean age 66 years, males 60.7%, mean BMI 28, DM 34%, HTN 78%, hyperlipidaemia 49%, median eGFR 33.5 mL/min/1.73 m ^{2}	
Median 65 months	
Liver USS (01/01/2000 - 31/12/2014), end of analysis period 31/12/2015	
1148 CKD patients (205 NAFLD, 752 normal liver, 191 had other hepatic abnormalities on USS) 852 CKD patients (183 NAFLD, 669 normal liver) after excluding patients with incomplete follow-up data sets 276 CKD patients (138 NAFLD, 138 normal liver) with 1:1 propensity score matching	
NAFLD vs no NAFLD	
Liver USS (hyperechogenicity or echobright liver consistent with fatty infiltration)	
eGFR <60 mL/min/ 1.73 m^2 using CKD-EPI formula	
(1) Mortality NOS = 8, (2) non-fatal CVE NOS = 8, (3) CKD progression NOS = 9	
Patients ≥ 18 years old referred to Salford renal service (tertiary centre); eGFR <60 mL/min/ 1.73 m ^{2}, not needing immediate RRT	
Maintenance RRT at time of liver USS , drinking above 21 units men / 14 units women, history of chronic hepatitis B & C or other chronic liver diseases	
Retrospective observational longitudinal cohort study	
NFCVE outcomes subgroup analysis: cardiac event, cerebrovascular event, PVD CCF Deaths analysed according to: cardiac, non-cardiac No subgroup analysis according to severity of NAFLD / severity CKD at baseline	
Propensity matching for: age, gender, BMI, SBP, DBP, baseline hypertension, diabetes, hypercholesterolaemia, IHD, MI, CCF, CVA, PVD, malignancy, use of statin and renin–angiotensin blocking agents, eGFR (NB age difference, NAFLD 66 yrs, normal liver 68 yrs p=0.04)	
Annual review: comorbidities, hospital admissions, cardiovascular events, medications, blood results	
(1) ESRD: commencement of RRT or eGFR of <10 mL/min/1.73 m^2 (2) Rate of change of eGFR (eGFR slope) from baseline to study end-point (3) NFCVE: composite of ACS, non-fatal MIs, non-fatal cardiac arrest, coronary revascularizations, new diagnosis cardiac failure / admissions with exacerbations of cardiac failure, new diagnosis of PVD, CVAs (4) All-cause mortality	
Univariate & multivariate Cox proportional hazards models to determine HRs & 95% CI (outcomes 1,3,4) Linear regression slope generated using serial serum creatinine measurements (outcome 2)	
17.9% (205 / 1148)	
(1) ESRD: NAFLD 26 (14.2%), normal 134 (19.1%), p=0.07 (2) CKD progression (rate of decline of eGFR slope): NAFLD -2.54 [-7.61 - 0.31] mL/min/1.73 m^2, normal -2.09 [-6.14 - 1.06] mL/min/1.73 m^2 (3) NFCVE: NAFLD 46 (25.1%), normal 82 (12.3%), p<0.001 (4) All cause mortality: NAFLD 50 (27.3%), normal 22 (33.0%), p=0.14	
(1) ESRD: total sample HR 0.99 [0.65–1.52], p=0.90; matched HR 0.64 [0.35-1.16], p=0.145 (2) CKD progression (rate of decline of eGFR slope): total sample p<0.09; matched p=0.58 (3) NFCVE: total sample HR 2.07 [1.39-3.09], p<0.001; matched HR 1.85 [1.04-3.30], p<0.04 (multivariate: total sample HR 2.03 [1.33-3.13], p<0.001; matched HR 2.00 [1.10-3.66], p=0.02) (4) All-cause mortality: total sample HR 0.79 [0.58-1.08], p=0.14; matched HR 0.88 [0.57–1.34], p=0.54	
N/A	
INCLUDE	

Nonalcoholic fatty liver disease accelerates kidney function decline in patients with chronic kidney disease: a cohort study
Hye Ryoun Jang, Danbee Kang, Dong Hyun Sinn, Seonhye Gu, Soo Jin Cho, Jung Eun Lee, Wooseong Huh, Seung Woon Paik, Seungho Ryu, Yoosoo Chang, Tariq Shafi, Mariana Lazo, Eliseo Guallar, Juhee Cho, Geum-Youn Gwak
Scientific reports
2018
South Korea
?
Individuals who underwent a comprehensive health screening examination at the Samsung Medical Centre Health Promotion Centre, Seoul, South Korea
Mean age 60.8 years, males 70%, mean BMI 24.8, DM 24%, HTN 60%, hyperlipidaemia 41%, median eGFR 59.1 mL/min/1.73 m^2
Average 6.5 years
January 2003 through December 2013
1,525 CKD patients
NAFLD vs no NAFLD
USS based on standard criteria, including parenchymal brightness, liver-to-kidney contrast, deep beam attenuation and bright vessel walls
eGFR < 60 ml/min/1.73 m^2 using CKD-EPI formula, or proteinuria ≥2+ on urinalysis
NOS = 7
Patients ≥ 18 years old who underwent a comprehensive health screening examination at the Samsung Medical Centre Health Promotion Centre and were found to have CKD with at least 1 additional follow up serum creatinine
History of cancer, liver cirrhosis, positive hepatitis B surface antigen, or hepatitis C virus antibodies, alcohol intake ≥ 30 g/day in men or ≥20 g/day in women, previous kidney transplant or started dialysis within 1 year after baseline examination, missing information on alcohol intake, NFS, or less than 6 months follow up
Retrospective observational longitudinal cohort study
(1) Severity NAFLD assessed via NFS: −1.675 + 0.037 × age (years) + 0.094 × BMI + 1.13 × impaired fasting glucose/diabetes (yes = 1, no = 0) + 0.99 × AST/ALT ratio − 0.013 × platelet count (×10^9/l) − 0.66 × albumin (g/dl). Based on NFS, patients were classified as high-intermediate (NFS ≥ −1.455) and low probability (NFS < −1.455) of advanced fibrosis. (2) Severity of CKD at baseline: cut-off value eGFR ≥45 ml/min/1.73 m^2 vs. <45 ml/min/1.73 m^2 (dividing G3a and G3b)
Stratified analyses to evaluate if association of NAFLD with CKD progression differed in pre-specified subgroups: age (<60 vs. ≥ 60 years), sex, smoking (never or former vs. current), alcohol drinking (none vs. moderate), BMI ≥ 25 kg/m2, hypertension (SBP ≥ 140 mmHg, DBP ≥ 90 mmHg, or use of antihypertensives), diabetes (fasting serum glucose ≥ 126 mg/dl, HbA1c ≥ 6.5%, or use of antidiabetic medication), hyperlipidaemia (HDL < 40 mg/dl in men or < 50 mg/dl in women, TG ≥ 150 mg/dl, or use of lipid-lowering medication), or baseline eGFR (<45 vs. ≥ 45 ml/min/1.73 m^2).
At each visit demographic characteristics, smoking status, alcohol consumption, medical history and medication use were collected through standardized, self-administered questionnaires along with blood results
CKD progression: average annual percent change in eGFR from baseline eGFR
Compared serial changes in eGFR among CKD patients with or without NAFLD at baseline using linear mixed models for longitudinal data with random intercepts and random slopes. Used loge-transformed eGFR as outcome and estimated the average difference in annual % change in eGFR (with 95% CI).
40.9% (902/1525)
Average annual percent change in eGFR from baseline: NAFLD -0.79% [-1.31 - -0.27], no NAFLD 0.30% [-0.14 - 0.76]
Average difference in % decline of eGFR per year NAFLD vs no NAFLD: (i) Adjusted for age, sex, year of visit: -1.09% [-1.77 - -0.41] (ii) Adjusted for all confounders: -1.06% [-1.73 - -0.38]
Average difference in % decline of eGFR per year NAFLD vs no NAFLD: (i) Adjusted for age, sex, year of visit: p=0.002 (ii) Adjusted for all confounders: p=0.002
(1) Multivariable adjusted average difference in annual % changes in eGFR for low NFS (≤ 1.455) or intermediate to high NFS (≥ −1.455) & those without NAFLD: 0.01% [−0.74 - 0.99) & −2.12% (−2.93 - −1.31) respectively (2) Multivariable adjusted average difference in annual % changes in eGFR among patients with eGFR < 45 ml/min/1.73 m^2 at baseline -6.27% [-12.08 - - 0.08] (n=168) vs -0.76 [-1.32 - -0.19] (n=1357) for baseline eGFR ≥ 45
INCLUDE

Chronic kidney disease is independently associated with increased mortality in patients with nonalcoholic fatty liver disease.
James Paik, Pegah Golabi, Zahra Younoszai, Alita Mishra, Gregory Trimble, Zobair M. Younossi
Liver International
2019
USA
None
NHANES-III & linked mortality files
Mean age 43.3 years, males 48.4%, DM 6.5%, HTN 40.7% (total cohort)
Average 19.2 years
NHANES-III 1988 - 1994; linked mortality files up to 2011 or date of death
11,695 adult participants 'NAFLD- CKD-' 74.6%, 'NAFLD+ CKD-' 16.1%, 'NAFLD- CKD+' 6.8%, 'NAFLD+ CKD+' 2.5%
CKD vs no CKD in NAFLD cohort (main results reported in paper) NAFLD in CKD cohort (some data)
Liver USS (moderate/severe hepatic steatosis in absence of any other possible cause CLD)
eGFR < 60 ml/min/1.73 m2 using CKD-EPI formula +/- albuminuria
NOS = 9
Persons aged 20-74 at time of examination with complete data on ultrasound video images for hepatic steatosis assessment and serum creatinine measurements
Patients with other causes of chronic liver disease were excluded
Retrospective analysis of data collected from cross-sectional study
Presence of fat within hepatic parenchyma graded as normal, mild, moderate, or severe hepatic steatosis. NAFLD-associated advanced fibrosis was defined with ultrasound diagnosed NAFLD and at least one of the following fibrosis markers: APRI> 1, FIB-4 index >2.67, or NFS>0.676. Cardiovascular mortality was defined as death due to heart diseases (ICD-10: I00-I09, I11, I13, and I20-I51) and cerebrovascular diseases (ICD-10: I60-I69).
Age, gender, race, smoker, metabolic syndrome
Data linked with mortality files
(1) All-cause mortality (2) Cardiovascular-related mortality: death due to heart diseases (ICD-10: I00-I09, I11, I13, I20-I51) & cerebrovascular diseases (ICD-10: I60-I69)
Logistic regression & cox proportional hazards model
29% (410/1,413)
(1) All-cause mortality: NAFLD 54.7% (SE 3.6), no NAFLD 46.5% (SE 2.4), p<0.05 (age adjusted: NAFLD 31.0% [25.0-37.0], no NAFLD 25.9% [22.0-29.7], p=ns) (2) Cardiovascular-related mortality: NAFLD 16.0% (SE 2.5), no NAFLD 16.2% (SE 1.7), p=ns (age adjusted: NAFLD 7.8% [3.7-11.9], no NAFLD 8.2% [5.6-10.9], p=ns)
(1) All-cause mortality: adjusted HR NAFLD 2.34 [1.91-2.87], no NAFLD 2.08 [1.80-2.40], p=ns (2) Cardiovascular-related mortality: adjusted HR NAFLD 2.12 [1.44-3.13], no NAFLD 2.43 [1.8-3.2], p=ns
(1) CKD + NAFLD + advanced fibrosis (n=60) All-cause mortality: 73.1% [50.7-95.5], p=ns vs no advanced fibrosis; adjusted HR 3.49 [2.25-5.43], p=ns vs no advanced fibrosis Cardiovascular-related mortality: 14.6% [1.6-27.7], p=ns vs no advanced fibrosis; adjusted HR 2.83 [0.69-11.51], p=ns vs no advanced fibrosis (2) CKD + NAFLD + no advanced fibrosis (n=97) All-cause mortality: 52.1% [44.8-59.3]; adjusted HR 2.51 [1.98-3.18] Cardiovascular-related mortality: 16.5% [11.1-21.9]; adjusted HR 2.45 [1.61-3.73]
INCLUDE

Increased Risk for Cardiovascular Events in Patients with Diabetic Kidney Disease and Non-Alcoholic Fatty Liver Disease.
Rajkumar Chinnadurai, Constantina Chrysochou, Philip A. Kalra
Nephron
2018
UK
?
Salford Kidney Study (SKS) - extension of the Chronic Renal Insufficiency Standards Implementations Study (CRISIS)
Mean age 65 years, males 66%, mean BMI 30, DM 100%, HTN 87%, median eGFR 31.6 mL/min/1.73 m^2, hyperlipidaemia 79%
Median 69 months
Liver USS (01/01/2000 - 31/12/2014), end of analysis period 31/12/2015
192 patients with DKD (55 NAFLD, 113 normal liver, 24 had other hepatic abnormalities on USS) 149 patients with DKD (183 NAFLD, 669 normal liver) after excluding patients with incomplete follow-up data sets
NAFLD vs no NAFLD
Liver USS (hyperechogenicity or echobright liver consistent with fatty infiltration)
eGFR <60 mL/min/ 1.73 m^2 using CKD-EPI formula
Patients ≥ 18 years old referred to Salford renal service (tertiary centre); eGFR <60 mL/min/ 1.73 m^2, not needing immediate RRT
Maintenance RRT at time of liver USS , drinking above 21 units men / 14 units women, history of chronic hepatitis B & C or other chronic liver diseases
Retrospective observational longitudinal cohort study
NFCVE outcomes subgroup analysis: cardiac event, cerebrovascular event, PVD CCF Deaths analysed according to: cardiac, non-cardiac No subgroup analysis according to severity of NAFLD / severity CKD at baseline
Propensity matching for: age, gender, BMI, SBP, DBP, baseline hypertension, diabetes, hypercholesterolaemia, IHD, MI, CCF, CVA, PVD, malignancy, use of statin and renin–angiotensin blocking agents, eGFR (NB age difference, p=0.04)
Annual review: comorbidities, hospital admissions, cardiovascular events, medications, blood results
(1) ESRD: commencement of RRT or eGFR of <10 mL/min/1.73 m^2 (2) Rate of change of eGFR (eGFR slope) from baseline to study end-point (3) NFCVE: composite of ACS, non-fatal MIs, non-fatal cardiac arrest, coronary revascularizations, new diagnosis cardiac failure / admissions with exacerbations of cardiac failure, new diagnosis of PVD, CVAs (4) All-cause mortality
Univariate & multivariate Cox proportional hazards models to determine HRs & 95% CI (outcomes 1,3,4) Linear regression slope generated using serial serum creatinine measurements (outcome 2)
28.6% (55/192)
(1) ESRD: NAFLD 7 (14.6%), normal 17 (16.8%), p=0.73 (2) CKD progression (rate of decline of eGFR slope): NAFLD -3.97 [-7.2 - 0.12] mL/min/1.73 m^2, -2.95 [-9.07 - 0.407] normal mL/min/1.73 m^2 (3) NFCVE: NAFLD 20 (41.7%), normal 14 (13.9%), p<0.001 (4) All cause mortality: NAFLD 16 (33.3%), normal 36 (35.6%), p=0.78
(1) ESRD: not reported (2) CKD progression (rate of decline of eGFR slope): p=0.65 (3) NFCVE: HR 3.48 [1.59-7.6], p=0.002 (multivariate: HR 2.95 [1.31-6.60], p=0.01) (4) All-cause mortality: HR 0.72 [0.40-1.31], p=0.28
N/A
Sub group of previous paper by Chinnadurai

Nonalcoholic Fatty Liver Disease and Renal Function Impairment: A Cross-Sectional Population-Based Study on Its Relationship From 1999 to 2016
Michael H. Le, Yee Hui Yeo, Linda Henry, and Mindie H. Nguyen
Hepatology Communications
2019
USA
?
National Health and Nutrition Examination Survey (NHANES): cross-sectional survey conducted in US by the National Centre for Health Statistics of the Centres for Disease Control and Prevention (CDC)
Mean age 53 years, males 56%, mean BMI 34, DM 24%, HTN 52.3%, median eGFR 90.5 mL/min/1.73 m^2, dyslipidaemia 61%
1999 - 31 Dec 2015
14,255 adults (not all had renal insufficiency); 4680 NAFLD patients (population of interest for this study)
Renal insufficiency vs no renal insufficiency
U.S. Fatty Liver Index (USFLI) ≥30 to rule in fatty liver
eGFR determined CKD-EPI & ACR. Unable to determine if renal insufficiency was acute or chronic. Renal insufficiency divided into 4 stages: no RI, mild, moderate & severe
People aged 18 years and older, who participated in a medical examination at a mobile centre, and underwent fasting blood work during their examination.
Participants <18 years old, missing laboratory data needed to calculate the non-invasive indices (age, race/ethnicity, waist circumference, GGT, fasting insulin, fasting glucose, serum creatinine, urine creatinine, and urine albumin), those who had a diagnosis of viral hepatitis, and those with heavy alcohol use.
Cross-sectional study
Severity of liver fibrosis assessed using NAFLD Fibrosis Score (NFS). NFS >0.676 rule in stage 3-4 fibrosis, NFS <–1.455 rule out stage 3-4 fibrosis.
2 yearly cross-sectional interviews, examinations and laboratory data
(1) Trends in NAFLD +/- renal insufficiency prevalence over time in US (2) Predictors of RI in NAFLD patients (3) Health literacy levels for kidney & liver disease (4) Mortality (national death index): all-cause mortality, cause-specific mortality from diseases of heart and malignant neoplasms: compared NAFLD + renal insufficiency vs NAFLD without renal insufficiency (5) Risk factors predicting mortality in NAFLD cohort with & without renal insufficiency
Univariate & multivariate logistic regression; Kaplein Meier curves; cox regression
31.2% (not all patients had renal insufficiency)
(1) Prevalence 1999-2000: NAFLD without RI 23.5% [20.2-27.1], NAFLD-RI 5.7% [4.3-7.6]; prevalence 2015- 2016, NAFLD without RI 27.3% [23.7-31.1], NAFLD-RI 7.7% [6.2-9.5]. Trend analysis 1999-2016: prevalence of overall NAFLD, NAFLD without RI & NAFLD-RI all significantly increased over time (p=0.007, p=0.048, p=0.006 respectively). Among those with NAFLD, RI prevalence did not increase significantly 1999-2016 (p=0.221). No significant increases were observed in mild, moderate, or severe RI in those with NAFLD (p=0.448, p=0.222, p=0.478 respectively) (2) Significant independent predictors of RI in NAFLD: age > 65, HTN, DM, dyslipidaemia, CVD, high probability of fibrosis stage 3 and 4 (multivariate analysis) (3) Among those with NAFLD-RI, awareness of kidney disease was 8.56% [6.69-10.89], awareness of liver disease among all NAFLD was 4.49% [3.17-6.33] (4) 5 yr cumulative mortality incidence: NAFLD alone 4.5%; mild RI 14.2%, moderate 21.2%, and severe 36.0% RI (p<0.001). 15 yr cumulative mortality incidence: NAFLD alone 19.9%, mild RI 42.4%, moderate RI 80.6%, and severe RI 85.5% (p<0.001). 5 yr cumulative incidence CV-related mortality highest in NAFLD + severe RI at 10.5% (36.7% at 15 years). Independent risk factors for all-cause mortality in NAFLD: age, mild/mod/sever RI, high probability of fibrosis; former/current smoker; history of CVD. Independent risk factors for CV mortality in NAFLD: older age, moderate & severe RI, history of CVD.
Intervention is CKD in NAFLD cohort rather than NAFLD in CKD cohort.

Predicting timing of clinical outcomes in patients with chronic kidney disease and severely decreased glomerular filtration rate.
Grams ME1, Sang Y2, Ballew SH2, Carrero JJ3, Djurdjev O4, Heerspink HJL5, Ho K6, Ito S7, Marks A8, Naimark D9, Nash DM10, Navaneethan SD11, Sarnak M12, Stengel B13, Visseren FLJ14, Wang AY15, Köttgen A16, Levey AS12, Woodward M17, Eckardt KU18, Hemmelgarn B19, Coresh J20
Kidney Int.
2018
30 countries
Participants in International Chronic Kidney Disease Prognosis Consortium
Median eGFR 24 mL/min/1.73 m2
264,296 individuals
Age, sex, race, eGFR, ACR, SBP, smoking status, DM, history of CVD.
eGFR < 30 ml/min/1.73m2
Aim to develop 2 & 4 year models of the probability & timing of kidney failure requiring RRT, a non-fatal CVD event & death
Competing-risk regression, random-effect meta-analysis, and Markov processes with Monte Carlo simulations
NAFLD was not examined in this study

Newcastle-Ottawa Scale (NOS)	Questions	Chinnadurai R et al. Nep Mortality
1) Selection of study groups (max 4)	1) Representativeness of the exposed cohort a) truly representative of the average patient with CKD in the community * b) somewhat representative of the average patient with CKD in the community * c) selected group of users eg nurses, volunteers d) no description of the derivation of the cohort	* Only those who had an USS included
	2) Selection of the non exposed cohort a) drawn from the same community as the exposed cohort * b) drawn from a different source c) no description of the derivation of the non exposed cohort	*
	3) Ascertainment of exposure a) secure record (eg surgical records) * b) structured interview * c) written self report d) no description	*
	4) Demonstration that outcome of interest was not present at start of study a) yes * b) no	Some patients had disease, eg IHD at baseline
	TOTAL SCORE	3
2) Comparability of groups (max 2)	1) Comparability of cohorts on the basis of the design or analysis a) study controls for components of themetabolic syndrome * b) study controls for any additional factor (mortality: underlying CVD, baseline eGFR; CVE: underlying CVD; CKD progression: baseline eGFR)*	 * *
	TOTAL SCORE	2
3) Ascertainment of exposure and outcomes (max 3)	1) Assessment of outcome a) independent blind assessment* b) record linkage * c) self report d) no description	*
	2) Was follow-up long enough for outcomes to occur a) yes (select an adequate follow up period for outcome of interest) * b) no	*
	3) Adequacy of follow up of cohorts a) complete follow up - all subjects accounted for* b) subjects lost to follow up unlikely to introduce bias - small number lost (< 20%), or description provided of those lost* c) follow up rate < 80% and no description of those lost d) no statement	*
	TOTAL SCORE	3
	OVERALL SCORE	8

hrol Dial Transplant. 2019;34(3):449-457		Jang HR, et al. Sci Rep. 2018;8(1):4718.		Paik J et al. *Liver Int* . 2019;39(2):342-352.			
CVE	**CKD progression**	**Mortality**	**CVE**	**CKD progression**	**Mortality**	**CVE**	**CKD progression**
* Only those who had an USS included	* Only those who had an USS included			* Only those who had an USS included	* Only those who had an USS included & under 75s		
*	*			*	*		
*	*			*	*		
Some patients had disease, eg IHD at baseline	*			*	Some patients had disease, eg CVD at baseline		
3	4			4	3		
*	*			*	*		
*	*			*	No		
2	2			2	1		
*	*			*	*		
*	*			*	*		
*	*			* Included only participants with at least 1 f/u eGFR	* Participants with no death records were presumed alive through f/u		
3	3			3	3		
8	9			9	7		

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5-6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6-7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	N/A

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	N/A
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7-8, figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8 & table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	11 & table 2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	8-9 & table 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	N/A
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	11-12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	12-13
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	3

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

BMJ Open

Systematic review of the impact of non-alcoholic fatty liver disease on mortality and adverse clinical outcomes for individuals with chronic kidney disease

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Primary Subject Heading:	Renal medicine
Secondary Subject Heading:	Gastroenterology and hepatology, Cardiovascular medicine, Epidemiology, General practice / Family practice
Keywords:	Chronic renal failure < NEPHROLOGY, Hepatology < INTERNAL MEDICINE, Myocardial infarction < CARDIOLOGY, End stage renal failure < NEPHROLOGY

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Systematic review of the impact of non-alcoholic fatty liver disease on mortality and adverse clinical outcomes for individuals with chronic kidney disease

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Keywords

Chronic renal failure; Hepatology; Myocardial Infarction, End-stage renal failure

Abstract

Objectives: To investigate if non-alcoholic fatty liver disease (NAFLD) impacts mortality and adverse outcomes for individuals with chronic kidney disease (CKD).

Design*:* Systematic review

Data sources: PubMed, EMBASE and Web of Science were searched up to 1/2/2020 with no restriction on the earliest date.

Eligibility criteria for selecting studies: Observational cohort studies that reported either the risk of all-cause mortality, incidence of non-fatal cardiovascular events (CVE) or progression of kidney disease among adults with established CKD who have NAFLD compared to those without.

Data extraction and synthesis: Two reviewers extracted data and assessed bias independently.

Results: Of 2,604 records identified three studies were included (UK n=852, South Korea n=1,525, US n=1,413). All were judged to have a low or moderate risk of bias. Data were insufficient for meta-analysis. Two studies examined the influence of NAFLD on all-cause mortality. One reported a significant positive association for NAFLD with all-cause mortality for individuals with CKD ($p<0.05$) (cardiovascular-related mortality p=ns), which was lost following adjustment for metabolic risk factors; the second reported no effect in adjusted and unadjusted models. The latter was the only study to report outcomes for non-fatal CVEs and observed NAFLD to be an independent risk factor for this (propensity matched hazard ratio 2.00, p=0.02). Two studies examined CKD progression; in one adjusted rate of percentage decline in estimated glomerular filtration rate per year was increased in those with NAFLD (p=0.002), whereas the other found no significant difference.

Conclusions: Few studies have examined the influence of NAFLD on prognosis and major adverse clinical outcomes within the CKD population. The studies identified were diverse in design and results were conflicting. This should be a focus for future research as both conditions continue to rise in prevalence and have end-stage events associated with significant health and economic costs.

PROSPERO registration number: CRD42020166508

Article Summary

Strengths and limitations of this study

- This is the only systematic review to date to examine the influence of non-alcoholic fatty liver disease on outcomes for patients with chronic kidney disease
- Only three cohort studies were eligible for inclusion
- A single study showed an association between NAFLD and cardiovascular events in patients with chronic kidney disease; results were conflicting for all-cause mortality and progression of renal disease
- In view of the small number of studies this is an important area for further research

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Introduction

Chronic kidney disease (CKD) is a long-standing condition incorporating impaired renal function and is often associated with a reduced quality of life, increased risk of end-stage renal disease (ESRD), cardiovascular disease (CVD) and premature death.[1,2] CKD is classified according to five stages based on estimated Glomerular Filtration Rate (eGFR), and in practice persistent albuminuria.[3] Around 4-7% of adults living in the United Kingdom (UK) have CKD stages 3-5 (eGFR < 60ml/min/1.73m^2),[4,5] with a higher global prevalence at 11%, although significant variation is recognised due to data availability, measurements used and reliance on coding.[6,7] Global prevalence is estimated to have increased by nearly 30% from 2007-2019[8] and CKD is forecast to move from 16th (2016) to 5th (2040) in the rankings for years of life lost.[9] The disease burden is particularly high in the elderly.[4] Increasing age, hypertension, diabetes and obesity account for the majority of newly diagnosed cases of CKD in the developed world.[10,11] CKD shares these risk factors, many of which are experiencing a significant rise in prevalence, with non-alcoholic fatty liver disease (NAFLD).[12]

NAFLD refers to excessive fat accumulation in the liver affecting more than 5% of hepatocyte and encompasses a spectrum of disease from simple steatosis to non-alcoholic steatohepatitis (NASH), fibrosis and cirrhosis. It is the most common cause of chronic liver disease worldwide, affecting approximately 25% of adults globally and in Europe.[12] It is expected to become the leading indication for liver transplantation in the next decade.[13] NAFLD is referred to as the hepatic manifestation of the metabolic syndrome and recent consensus opinion has proposed a change in nomenclature to 'metabolic associated fatty liver disease, MAFLD'.[14] NAFLD is found in approximately 70% of patients with type 2 diabetes mellitus (T2DM)[15] and 70% of adults with obesity.[16,17] Around 1 in 11 adults worldwide are thought to have diabetes, of which 90% is type 2 and this figure has more than tripled over 20 years.[18] NAFLD is also an independent risk factor for diabetes.[19] In addition, current estimates suggest 65% of adults in England are overweight or obese, with rates having more than doubled since the 1990s.[20,21]

Two meta-analyses have conclusively demonstrated a higher incidence of CKD in individuals with NAFLD (HR 1.37 and HR 1.79).[22,23] Patients with more advanced fatty liver disease, i.e. NASH or fibrosis are at the greatest risk of developing CKD. This association is independent of potential confounders (age, gender, body mass index, diabetes status, lipids, hypertension and smoking).[22,23] CKD is an accelerator of the risk of CVD and an independent risk factor for cardiovascular events (CVEs);[24–26] indeed individuals with CKD are more likely to die from CVD than develop ESRD.[27] NAFLD is also an

independent risk factor for major CVEs,[28–32] although there remains uncertainty regarding its association with an increase in all-cause and cardiac-related mortality, [31,33–35] despite patients with NAFLD being more likely to die from CVD than liver disease.[36,37]

CKD and NAFLD frequently exist together, yet there is a sparsity of data to inform physicians and patients about clinical outcomes in this setting. Understanding if NAFLD plays a role in accelerating progression towards death and adverse clinical outcomes in patients with CKD would help improve risk stratification; permitting more aggressive lifestyle intervention, targeted pharmacological management of shared risk factors and enrolment in clinical trials in this potentially high risk group. We therefore asked what evidence is there for the influence of NAFLD on the risk of mortality, CVEs and progression of kidney disease in patients with established CKD?

Methods

The protocol for this systematic review was registered on PROSPERO a priori (CRD42020166508) (supplementary material 1).

Data sources, searches and study selection

We performed a computerized literature search using PubMed, EMBASE (using Ovid) and Web of Science using the following search terms: *"(chronic kidney disease or CKD or kidney disease or kidney failure or kidney injury or chronic renal disease or renal disease or renal failure or renal injury or renal insufficiency or impaired renal function or glomerular filtration rate or eGFR) and (fatty liver or non-alcoholic fatty liver disease or NAFLD or nonalcoholic steatohepatitis or NASH or liver fat or steatohepatitis or steatosis or hepatic fibrosis)"* (full details in supplementary material 2). We aimed to identify observational (prospective or retrospective) cohort studies that reported either the risk of mortality, CVEs or progression of kidney disease among adults (> 18 years old) with established CKD who have NAFLD compared with those without. We also performed manual searches of reference lists of relevant studies returned by the initial search. No restriction was placed on the earliest search date and searches were performed up to the current date (February 2020). Exclusion criteria included abstracts, case reports, reviews, editorials, practice guidelines, non-cohort design, non-human studies and unpublished studies.

Study participants included adults with established CKD with evidence of the presence or absence of NAFLD. Studies were excluded if they included individuals under 18 years, individuals undergoing renal replacement therapy (RRT) at the start of the study, kidney or liver transplant recipients and individuals with a known other cause of chronic liver disease. CKD was defined as an eGFR ≥ 60 ml/min/1.73m^2 with ACR > 3 mg/mmol (stage G1 and G2), or eGFR < 60 ml/min/1.73m^2 (stages G3a – G5) calculated using the CKD Epidemiology Collaboration (CKD-EPI) or Modified Diet in Renal Disease (MDRD) formula. NAFLD was defined using either biochemistry (elevations in serum aspartate transaminase, alanine transaminase or gamma glutamyl transferase), imaging (ultrasound, computer tomography, magnetic resonance imaging), liver biopsy or non-invasive scores (Fatty Liver Index, Steatotest, NAFLD Liver Fat Score).

Primary outcomes included differences in the risk of all-cause mortality, CVEs and progression of kidney disease in patients with CKD who had NAFLD compared to those without NAFLD. All-cause mortality was defined as any cause of death within the study follow up period. Within this we aimed to look at cardiovascular and non-cardiovascular related deaths. A CVE was defined as any one of the following: acute coronary syndrome, myocardial infarction, non-fatal cardiac arrest, coronary revascularization, new diagnosis of cardiac failure, hospitalisation with an exacerbation of cardiac failure, new diagnosis of peripheral vascular disease, or new diagnosis of cerebrovascular accident (all non-fatal). Progression of CKD was defined as either (1) mean or percentage annual rate of change in the eGFR, or mean or percentage change from baseline, (2) a decline in eGFR category accompanied by a ≥ 25% drop in eGFR from baseline (KDIGO definition), (3) the development of ESRD (eGFR of < 15 ml/min/1.73m^2, or the requirement of some form of RRT), or (4) doubling of creatinine.[3,38] Secondary outcomes included: (1) the risk of CVEs, progression of kidney disease and all-cause mortality in patients with CKD according to the severity of NAFLD, as determined by the presence of NASH or fibrosis (defined using histology, imaging or non-invasive serum biomarkers), and (2) the risk of CVEs, progression of kidney disease and all-cause mortality in patients with CKD according to baseline severity of CKD, as determined by CKD stage. Included and excluded studies were collected following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram (figure 1).

Data extraction and quality assessment

Two investigators (TH and RB) screened all titles and abstracts independently using the Covidence software as recommended by Cochrane. They obtained the full texts of potentially relevant papers to determine if they met the inclusion criteria. Discrepancies were resolved by returning to the original

article to reach a consensus. Data extraction was performed by TH and checked by RB. For all studies data was extracted data on (1) general information (title, authors, journal, country, publication year), (2) study design (population source, demographics, period of follow up, means of defining NAFLD and CKD, inclusion and exclusion criteria, study size, subgroup analysis (including severity of NAFLD and baseline CKD), adjustment for confounding factors) and (3) outcomes examined for NAFLD versus non-NAFLD patients (all-cause mortality, CVE, progression of kidney disease, and definition used, in addition to odds ratio, hazards ratio (HR), relative risk and 95% confidence intervals; or mean or percentage annual rate of change in the eGFR). Where there were multiple publications, we included the most up-to-date or comprehensive information.

The risk of bias was assessed independently by TH and RB. The results were then discussed to reach consensus. We used the Newcastle-Ottawa Score as recommended by Cochrane for the assessment of quality for non-randomised cohort studies.[39] This tool uses a star based system allocating a maximum of 9 points across three domains: (1) selection of study groups (max 4 points), (2) comparability of groups (max 2 points), (3) ascertainment of exposure and outcomes (max 3 points). Studies with an overall score of 9 are judged to be at a low risk of bias, those scoring 7-8 a moderate risk of bias and scores of 6 of less a high risk of bias. Where studies reported more than one primary outcome a separate bias assessment was performed for each.

Patient and public involvement

Patients or the public were not involved in the design, conduct, reporting or dissemination plans of our research.

Results

Details of the study selection process

The process for selecting the studies for inclusion in this systematic review is shown in figure 1. The searches returned 4,339 studies. Overall 1,735 duplicates were removed, leaving 2,604 citations for screening. TH and RB separately reviewed titles and abstracts and identified six potentially relevant studies. The most frequently encountered exclusion criteria were abstract only citations, laboratory-based or animal studies, review articles, studies of paediatric populations (eg polcystic kidney disease, Caroli's syndrome), studies which included transplant recipients, patients receiving RRT and

populations with non-NAFLD causes of liver disease, and publications for which the development of CKD was the outcome (eg those reporting the incidence of CKD in patients with NAFLD). After examination of the full texts (supplementary material 3), only three cohort studies remained and were included (figure 1).[40–42] As a result of the low number of studies identified, and the fact that primary outcomes reported differed between papers, we did not have sufficient data to perform a meta-analysis.

Characteristics of the included studies

Of the three studies, one recruited patients seen in a renal tertiary referral centre in Salford, UK (Chinnadurai et al, n=852, median follow up 5.4 years),[40] the second recruited individuals attending for comprehensive health screening at a preventive medical centre in South Korea (Jang et al, n=1,525, median follow up 6.5 years),[41] and the third presents results from a retrospective analysis of baseline cross-sectional data collected from the third National Health and Nutrition Examination Survey (NHANES) (United States, US) over time (Paik et al, n=1,413, median follow-up 19.2 years) (**Table 1**).[42]

Liver ultrasound was used to detect NAFLD in all three studies. Prevalence rates of NAFLD were highest in the Korean cohort (41%), compared to the UK (21%) and US (29%) populations, however the US group only included patients with moderate or severe steatosis. CKD was defined using the CKD-EPI equation in all papers; the Salford and US studies only included patients with CKD stage 3 and above (eGFR < 60 mL/min/1.73 m^2), whereas the Korean group also included patients with ≥ 2+ proteinuria, i.e. CKD stage 1 and above. As a result mean baseline eGFR levels were nearly double in the Korean cohort compared to the Salford study (59.1 vs 33.5 mL/min/1.73 m^2). In terms of demographics, the Salford group was slightly older, and the US group included a higher frequency of individuals with metabolic risk factors and was predominantly female in contrast to the other studies.

The influence of NAFLD on clinical outcomes in patients with CKD

(1) Mortality

Two publications analysed the impact of NAFLD on mortality within the CKD population. The Salford group concluded that CKD patients with NAFLD were not at higher risk of all-cause (NAFLD 27.3% vs no NAFLD 33.0%, p=0.14; unadjusted HR 0.79 [0.58-1.08]) or cardiovascular-related mortality (NAFLD 31.3% vs no NAFLD 40.5%, p=0.36), despite experiencing more non-fatal CVEs (**Table 2**). Significance

outcomes were unchanged in the propensity matched sample. The US based study reported an increase in overall mortality for CKD patients with NAFLD compared to those without (54.7% vs 46.5%, p<0.05). Statistical significance was lost however when adjusted for age and following multivariate analysis (p=ns when comparing adjusted HRs), and no significant impact was seen for NAFLD on cardiovascular-related mortality (16.0% NAFLD vs 16.2% no NAFLD). No significant association between advanced fibrosis and all-cause or cardiovascular-related mortality was seen for patients with NAFLD and CKD within the US cohort.

(2) Non-fatal cardiovascular events

The Salford group published the only study to analyse the incidence of non-fatal CVEs. A higher frequency of non-fatal CVEs was seen in patients with NAFLD vs those without NAFLD (25.1% vs 12.3%; p<0.001) over an average of 5 years (**Table 2**). Cox regression analysis revealed NAFLD to be strongly associated with the incidence of non-fatal CVEs in CKD patients (HR 2.07 [1.39-3.09], p<0.001). This remained the case following multivariate analysis for all confounders in the propensity-matched cohort (HR 2.00 [1.10-3.66], p=0.02). Significant differences were also reported between groups according to the type of CVE (cardiac events p=0.02, cerebrovascular events p=0.04, cardiac failure p=0.005), although individually significance values were lost following adjustment for confounders.

(3) Progression of CKD

The Salford and Korean groups analysed the impact of NAFLD on CKD progression. Both examined decline in eGFR; the Salford group presented this as rate of change of eGFR from baseline to the study end-point, whereas the Korean study examined the average percentage change in eGFR from baseline per year (**Table 2**). The Salford group reported a decline in the eGFR slope for patients with and without NAFLD (-2.54 vs -2.09 mL/min/1.73 m^2) over the course of the study, however no statistically significant differences were detected between groups (p=0.09). Conversely a greater rate of decline in the eGFR slope in patients with NAFLD vs those without, was seen in the Korean study (−0.79% vs 0.30% per year, p=0.002). This relationship remained significant after adjustment for all confounders (average difference in percentage decline of eGFR per year for NAFLD vs no NAFLD: -1.06%, p=0.002). The Salford group also reported no correlation between the presence of NAFLD and the development of ESRD (commencement of RRT or eGFR <10 mL/min/1.73 m^2). In terms of our secondary outcomes, the Korean group reported that patients with a NAFLD fibrosis score ≥ −1.455 and more advanced renal disease at baseline (eGFR < 45 ml/min/1.73 m^2) experienced the greatest average difference in

annual percent changes in eGFR compared to individuals without NAFLD, although the significance of a low baseline eGFR was lost following adjustment for all metabolic confounders (**Table 2**).

Discussion

Summary of findings

The key finding of this systematic review is the identification of a significant gap in the literature within this field. Only three studies examining the clinical impact or prognostic implications of NAFLD within the CKD population were identified preventing further meta-analysis and results were conflicting. Data from the US showed a significant association for NAFLD with all-cause (but not cardiovascular) mortality for individuals with CKD, although this relationship was lost following adjustment for age and metabolic risk factors.[42] No effect on all-cause or cardiovascular-related mortality was observed within the Salford CKD cohort despite the authors identifying NAFLD to be a strong independent risk factor for non-fatal CVEs and a high percentage of patients having significant co-morbidities.[40] Possible explanations include a significantly longer follow-up period for the US group. In addition the US study only included patients with moderate or severe steatosis, suggesting that perhaps the association between NAFLD and mortality is related to the degree of fat, and subsequent inflammation in the liver. The same group found no association between advanced fibrosis and mortality in this cohort however.[42]

Data was also conflicting for the progression of kidney disease. The Korean group reported a significantly greater adjusted rate of percentage decline in eGFR per year for patients with CKD and NAFLD, compared to individuals with CKD without NAFLD,[41] whereas the Salford study reported a non-significant trend in CKD progression for individuals with NAFLD versus those without, and no differences were seen for the incidence of ESRD.[40] The cause of these discrepancies is unclear, particularly given that participants in the Salford cohort had a lower baseline eGFR,[40] which was found to be associated with a greater rate of decline in renal function in the Korean study.[41] The incidence of ESRD was low in the Salford cohort, and the study may have been under-powered for this outcome. Of note the authors of the Salford study published a related paper examining the impact of NAFLD on mortality rates, incidence of non-fatal CVEs and progression of CKD in patients with diabetic kidney disease and reported similar findings.[43] This represented a subgroup of the main Salford cohort and therefore was excluded from this review.

Possible pathophysiological mechanisms linking NAFLD and clinical outcomes for CKD

Broadly the findings from this review mirror findings in the general population where NAFLD is an accepted risk factor for CVEs,[28–32] with debate over whether it is associated with all-cause and cardiovascular mortality. These are summarised in figure 2.[31,33–35] Several mechanisms may explain the influence of NAFLD on CKD incidence and progression, and the development of CVEs within this cohort beyond their shared cardiometabolic risk factors. NAFLD can exacerbate insulin resistance leading to the release of multiple pro-inflammatory, pro-oxidant and pro-fibrogenic mediators important in the pathogenesis of both CKD and CVD.[44,45] Insulin resistance can lead to activation of the renin-angiotensin system and atherogenic dyslipidaemia, key drivers of renal and vascular damage. Steatohepatitis can potentiate the production of inflammatory mediators including reactive oxygen species, cytokines and lipopolysaccharides, exacerbating insulin resistance, tissue inflammation and endothelial damage. None of the studies included in this review reported the prevalence rates of NASH in their cohorts, and this could be a significant factor accounting for the variation observed between study outcomes. Other emerging mechanistic links between NAFLD and CKD include impaired antioxidant defences, abnormal metabolism of lipoproteins, altered intestinal barrier integrity, dysbiosis of intestinal microbiota and dietary factors.[10]

Study strengths and limitations

This is the only systematic review to date to examine the influence of NAFLD on serious adverse clinical outcomes for patients with CKD. Our study benefits from a broad definition of NAFLD and CKD with a number of primary outcomes and no restriction on publication date, with the purpose of maximising the number of papers retrieved. All studies were judged to be of a low or moderate risk of bias (supplementary material 4) and recruited over 800 participants; they spanned three continents and were matched in terms of using ultrasound as their means of diagnosing NAFLD, which is recommended for first line screening.[46]

There are significant limitations associated with this review. Only three studies met our inclusion criteria, recruiting under 4000 individuals with CKD between them. We chose to limit the inclusion criteria to cohort studies and those which examined the influence of NAFLD within the CKD population (i.e excluding those looking at the influence of CKD in the NAFLD population), in order to design a review with the potential to provide clinically relevant answers that could influence practice and benefit patients. We aimed to address whether NAFLD should be considered a clinically relevant risk

factor for adverse outcomes within the CKD population. This would have implications for whether CKD patients who develop NAFLD should undergo more rigorous follow up and intervention and may have raised the question of whether the CKD population should undergo routine screening for NAFLD. We therefore wanted to be able to establish the causality of NAFLD within this population and to examine more than one clinical outcome. We accept however that given the small number of papers included a broader search criteria may have been more appropriate with the understanding that this would have provided more of a general view of the clinical consequences of having both CKD and NAFLD. During the systematic review process we identified only one cross-sectional study which would have otherwise met our inclusion criteria. This reported a negative correlation between the severity of hepatic steatosis, determined by controlled attenuation parameter, and eGFR in 62 patients with CKD stages 3 and 4 ($r=-0.413$; $p<0.01$).[47] A larger number of studies were excluded which examined the impact of having CKD for patients with NAFLD. Observational studies show consensus that CKD is associated with increased all-cause and cardiovascular-related mortality in patients with NAFLD, however there is disagreement regarding whether this effect is independent of metabolic confounders and mediators.[42,48,49] Individuals receiving RRT were also excluded given their unique pathophysiology; although evidence suggests that these patients are more likely to have CVD and experience non-fatal CVEs in the presence of NAFLD.[50–52]

In addition, significant variability was encountered in terms of method of recruitment for participants with CKD, definitions of CKD and NAFLD employed, outcomes assessed and method of adjustment for co-variates. The use of ultrasound for the detection of NAFLD introduced bias, as patients with CKD without an indication for a liver ultrasound scan were excluded. Patients with a pre-existing background of CVD were also included in both studies which examined the influence of NAFLD on mortality. None of the studies looked at the incidence of non-fatal and fatal CVEs in combination which is highly clinically relevant should represent an important end-point for future prospective studies.

Supporting literature and importance of research topic

Our findings highlight a potential interplay between NAFLD and CKD and clinical outcomes. This represents an extremely important topic for future research for a number of reasons. Firstly the incidence of both CKD and NAFLD is rising.[10–12] The prevalence risk of CKD among individuals with NAFLD is estimated to be two fold higher compared to individuals without NAFLD[22] and reported prevalence rates of NAFLD within CKD cohorts vary from 21%-86%.[40,41,47] The number of individuals in the US with both NAFLD and renal insufficiency was estimated to be 18.7 million persons in 2016

(prevalence rates 7.7% up from 5.7% in 1999).[48] CKD and NAFLD are profoundly linked to health inequalities globally. This is particularly apparent in advanced disease as a result of disparities in access to treatment, increased burden of lifestyle-related risk factors and the influence of socio-economic status and ethnicity on disease progression.[53–55] The development of end-stage disease also accounts for the overwhelming majority of healthcare costs for patients with kidney disease, with more than half of the CKD budget in England being spent on RRT, and the cost of excess strokes and myocardial infarctions in this population estimated to be £178 million.[56] Avoiding progression towards ESRD and cardiovascular complications associated with CKD via the recognition and management of NAFLD as a potential high risk co-morbidity could therefore be important to reduce these burdens.

Future research and implications for clinical practice

These findings emphasise a need for large prospective collaborative studies to better understand the clinical and prognostic implications for patients who have both CKD and NAFLD. Outcomes should include mortality, CVEs and CKD progression. Patients with NAFLD should also be assessed for NASH and advanced fibrosis. Large routinely collected datasets linked to clinical outcomes maybe less useful in this setting as NAFLD screening is likely to lack robust assessment of inflammation or markers of fibrosis (serum biomarkers, transient elastography and histology), instead being reliant on liver enzymes or simple ultrasound scan. It would also be beneficial to examine is there is an association with NAFLD and acute kidney injury outside the setting of cirrhosis. Other potential research opportunities include understanding the implications of having both CKD and NAFLD-related fibrosis or cirrhosis on drug metabolism. Furthermore shared pathophysiological pathways involving pro-inflammatory mediators, oxidative stress and the gut microbiome present promising therapeutic targets for both NAFLD, CKD and CVD within a co-morbid setting.[44,57]

Approximately 40,000–45,000 individuals with CKD die prematurely each year in England, primarily due to CVD.[58,59] There are currently no recommendations to screen for NAFLD in patients with CKD due to a lack of supportive evidence in terms of prevalence, outcomes and cost-effectiveness. However patients with CKD undergo annual health checks in primary care. Identification of the metabolic syndrome, T2DM and obesity should prompt ultrasound screening for NAFLD in accordance with current guidelines.[46,60] Awareness of these guidelines may be low within this setting currently. Liver enzymes are frequently normal in patients with NAFLD, especially those with CKD and should not be used to rule out liver disease.[40,41,47] Few specific treatments delay the clinical course of CKD, so the identification of NAFLD as a potential risk factor for future adverse events will hopefully provide a

further modifiable target for lifestyle (physical activity, Mediterranean diet) or pharmacological intervention (vitamin E, pioglitazone and newer agents).[46,60] Current UK guidelines suggest all patients with NAFLD should be assessed for advanced fibrosis using the Enhanced Liver Fibrosis score,[46] and this should also be the case for CKD patients where liver fibrosis has implications for CKD progression and mortality.[41,48] Patients with NAFLD will nearly certainly have an eGFR performed as part of their routine care, however it is vital that the clinical implications of an abnormal value are appreciated.[42,48,49] Encouragingly weight loss, currently the only proven effective intervention for patients with NAFLD,[61] can reduce the incidence of CKD in this cohort,[62] and improve renal function in individuals with biopsy-proven NASH.[63]

Summary

This systematic review has identified a significant gap in the literature regarding the clinical outcomes and prognostic implications of NAFLD within the CKD population. Studies are conflicting regarding an association between NAFLD and CKD progression and mortality in this cohort. While data suggests a positive correlation with non-fatal CVEs only one study has examined this outcome to date. The prevalence of NAFLD and CKD are rising and are frequently found together. It is therefore vital to understand if there is any synergism in terms of CVD risk, progression towards ESRD and death which would inform the need for aggressive intervention in this potentially high risk group.

Contributorship statement

TH, JP, PR, SF and OK were responsible for the study concept and design; TH and RB performed the searches and screened the papers; TH performed the data extraction which was checked by RB and drafted the manuscript; JP, PR, SF, OK and RB edited the revised manuscript.

Competing interests statement

None of authors have any competing interests

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Data sharing statement

Data was obtained from previously published cohort studies which are accessible to the public via the journals cited in this review.

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Figure legends

Figure 1. A schematic showing the selection of relevant studies for inclusion in the systematic review

Figure 2. A summary of the evidence linking the clinical outcomes for chronic kidney disease and non-alcoholic fatty liver disease.

Acknowledgements

None

Table 1. Summary of study characteristics (n=3)

Study	Chinnadurai et al. *Nephrol Dial Transplant* (2019)[40]	Jang et al. *Scientific report* (2018)[41]	Paik et al. *Liver International* (2019)[42]
Country	United Kingdom	South Korea	United States
Median follow up	5.4 years	6.5 years	19.2 years
Years	Liver USS (01/01/2000 - 31/12/2014), end of analysis period 31/12/2015	January 2003 - December 2013	NHANES III 1988 – 1994 Linked mortality files up to 2011 or date of death
Population source	Salford Kidney Study	Individuals who had health screening at the Samsung Medical Centre, South Korea	Third National Health and Nutrition Examination Survey (NHANES) & linked mortality database
Study size	852 CKD patients	1,525 CKD patients	1,413 CKD patients (11,695 adults overall: (i) CKD+NAFLD+ 2.6%, (ii) CKD+NAFLD- 6.8%, (iii) CKD-NAFLD+ 16.1%, (iv) CKD-NAFLD- 74.6%)
Demographics	Mean age 66 years, males 60.7%, mean BMI 28, DM 34%, HTN 78%, hyperlipidaemia 49%, median eGFR 33.5 mL/min/1.73 m^2	Mean age 61 years, males 69.8%, mean BMI 25, DM 24%, HTN 60%, hyperlipidaemia 41%, median eGFR 59.1 mL/min/1.73 m^2	*CKD with NAFLD:* Mean age 54 years, males 45.6%, obesity 52.2%, DM 43.2%, HTN 77.4%, hyperlipidaemia 86.9% *CKD without NAFLD*: Mean age 53 years, males 36.1%, obesity 30.0%, DM 16.8%, HTN 66.4%, hyperlipidaemia 81.7%
NAFLD prevalence	21% (183/852)	41% (902/1,525)	29% (413/1,413)
NAFLD definition	Liver ultrasound scan	Liver ultrasound scan	Liver ultrasound (moderate / severe steatosis only)
CKD definition	eGFR <60 ml/min/1.73m^2	eGFR <60 ml/min/1.73m^2 or proteinuria ≥ 2+	eGFR <60 ml/min/1.73m^2 +/- albuminuria
Co-variate adjustments	Propensity matching (n=276) for: age, gender, BMI, SBP, DBP, baseline HTN, DM, hypercholesterolaemia, IHD, MI, CCF, CVA, PVD, malignancy, use of statin & renin–angiotensin blocking agents, eGFR	Stratified analyses according to pre-defined subgroups: age (<60 vs ≥ 60 yrs), gender, smoking (never/former vs current), alcohol (none vs moderate), BMI ≥ 25, HTN (SBP ≥ 140 mmHg / DBP ≥ 90 mmHg / use antihypertensives), DM (fasting glucose ≥ 126 mg/dl / HbA1c ≥ 6.5% / use antidiabetic drugs), hyperlipidaemia (HDL < 40 mg/dl men, < 50 mg/dl women / TG ≥ 150 mg/dl / use lipid-lowering drugs) & baseline eGFR (<45 vs ≥ 45 ml/min/1.73 m^2)	Age-adjustment based on the direct method to the Census 2000 population using the age groups 20-39, 40-59 & 60-74. Groups adjusted for the following in multivariable analysis: age category, gender, race, current smoker & the metabolic syndrome.

CKD: chronic kidney disease, NAFLD: non-alcoholic fatty liver disease, BMI: body mass index, DM: diabetes, HTN: hypertension, eGFR: estimated glomerular filtration rate, SBP: systolic blood pressure, DBP: diastolic blood pressure, IHD: ischaemic heart disease, MI: myocardial infarction, CCF: congestive cardiac failure, CVA: cerebrovascular accident, PVD: peripheral vascular disease, HDL: high density lipoprotein, TG: triglycerides, USS: Ultrasound scan

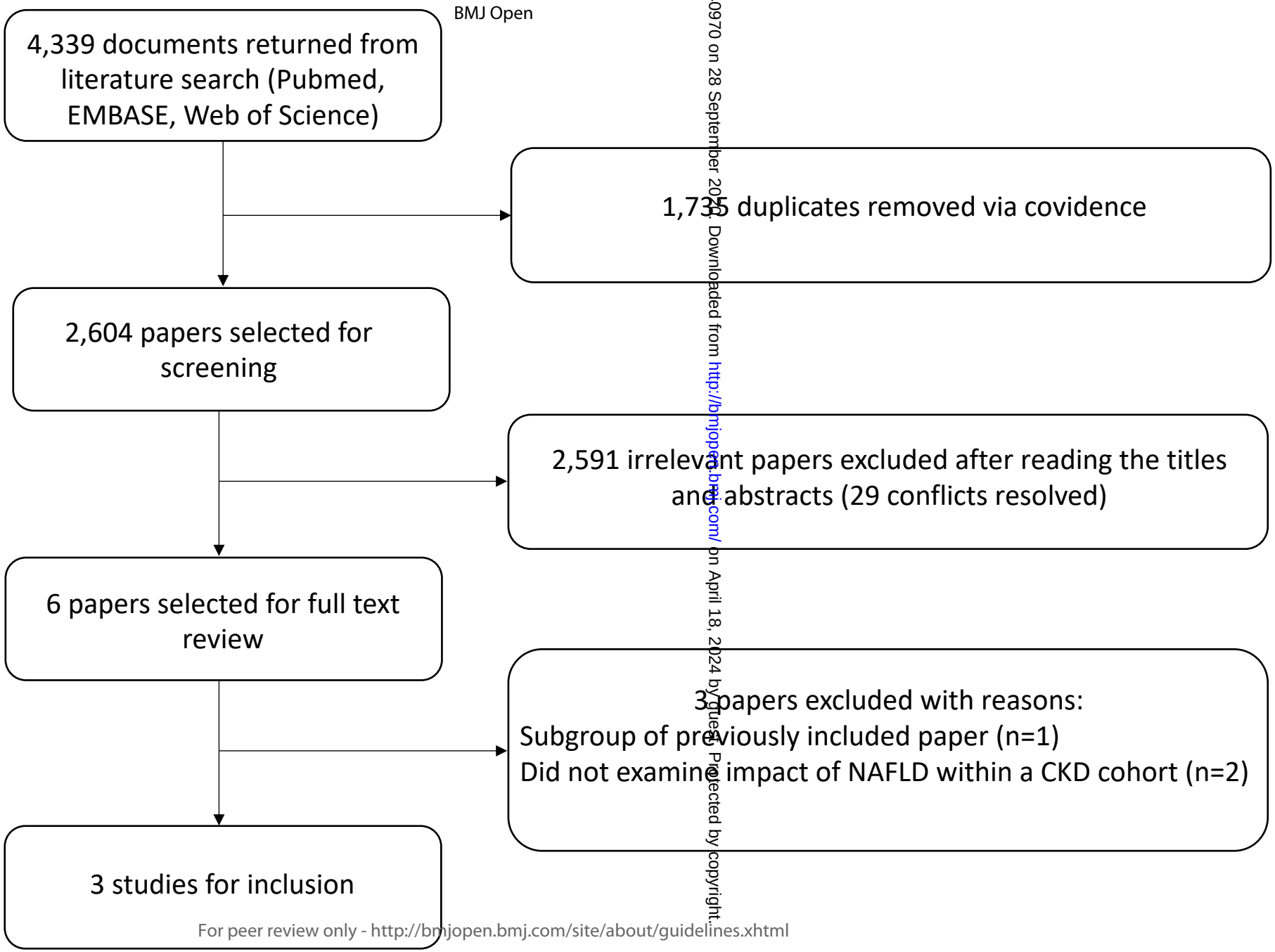
Table 2. Summary of study outcomes (n=3)

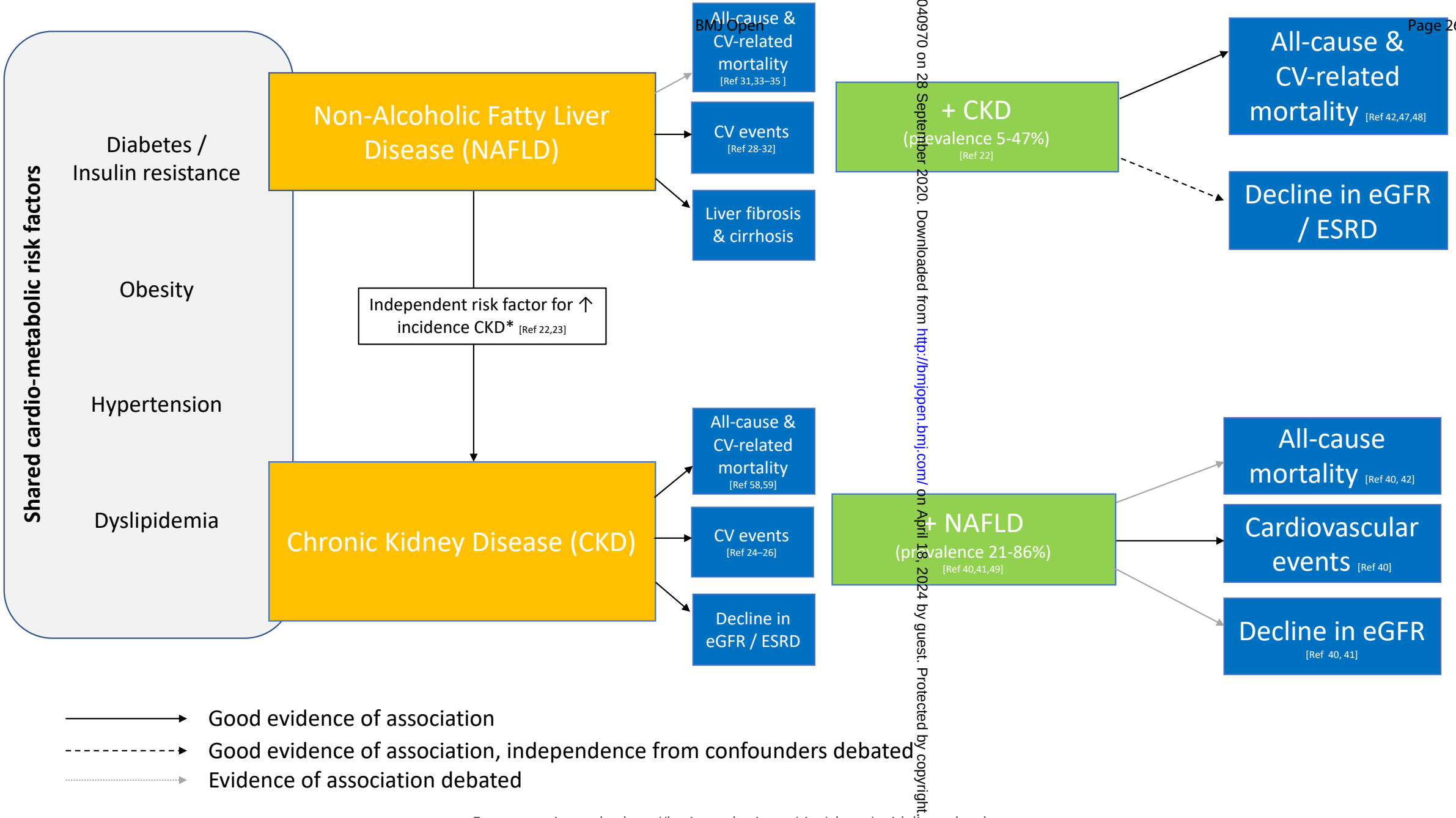
Study	Chinnadurai et al. *Nephrol Dial Transplant* (2019)[40]	Jang et al. *Scientific reports* (2018)[41]	Paik et al. *Liver International* (2019)[42]
Primary outcomes & definition	*(1) ESRD:* commencement of RRT or eGFR <10 mL/min/1.73 m^2 *(2) CKD progression*: rate of change of eGFR from baseline to study end-point (3) *NFCVE:* composite of ACS, non-fatal MIs, non-fatal cardiac arrest, coronary revascularization, new diagnosis CCF / admission with exacerbation of CCF, new diagnosis of PVD, CVAs (4) *All-cause mortality* *(5) Cardiovascular-related mortality:* Ia cause of death was due to cardiac event, CVA, CCF or PVD	(1) *CKD progression*: average annual percent change in eGFR from baseline	(1) *All-cause mortality* (2) *Cardiovascular-related mortality:* death due to heart diseases (ICD-10: I00-I09, I11, I13, I20-I51) & cerebrovascular diseases (ICD-10: I60-I69)
Secondary outcomes & definition	None	(1) *NAFLD severity according to NFS*: high-intermediate (NFS ≥ −1.455) & low probability (NFS < −1.455) of advanced fibrosis (2) *Severity of CKD at baseline*: eGFR ≥45 ml/min/1.73 m^2 vs <45 ml/min/1.73 m^2 (dividing stages 3a & 3b)	(1) *Presence of advanced liver fibrosis:* ≥ 1 of the following fibrosis markers – APRI > 1, FIB-4 score > 2.67 or NFS > 0.676
Cases	(1) *ESRD*: NAFLD n=26 (14.2%), no NAFLD n=134 (19.1%), p=0.07 (2) *CKD progression*: NAFLD -2.54 [-7.61 - 0.31] mL/min/1.73 m^2, no NAFLD -2.09 [-6.14 - 1.06] mL/min/1.73 m^2 (3) *NFCVE:* NAFLD n=46 (25.1%), no NAFLD n=82 (12.3%), p<0.001 (4) *All-cause mortality*: NAFLD n=50 (27.3%), no NAFLD n=221 (33.0%), p=0.14	(1) *Average annual percent change in eGFR from baseline:* NAFLD -0.79% [-1.31 - -0.27], no NAFLD 0.30% [-0.14 - 0.76] (2) *Average difference in % decline of eGFR per year NAFLD vs no NAFLD:* (i) Adjusted for age, sex, year of visit: -1.09% [-1.77 - -0.41] (ii) Adjusted for all confounders: -1.06% [-1.73 - -0.38]	(1) *All-cause mortality:* NAFLD 54.7% (SE 3.6), no NAFLD 46.5% (SE 2.4), p<0.05 (age adjusted: NAFLD 31.0% [25.0-37.0], no NAFLD 25.9% [22.0-29.7], p=ns) (2) *Cardiovascular-related mortality:* NAFLD 16.0% (SE 2.5), no NAFLD 16.2% (SE 1.7), p=ns (age adjusted: NAFLD 7.8% [3.7-11.9], no NAFLD 8.2% [5.6-10.9], p=ns)

	(5) *Cardiovascular-related mortality:* NAFLD n=10 (31.3%), no NAFLD n=67 (40.5%), p=0.36		
Risk of bias Newcastle Ottawa Score (NOS)	Mortality NOS = 8, non-fatal CVE NOS = 8, CKD progression NOS = 9	NOS = 9	NOS = 7
Primary outcome results	(1) *ESRD:* total sample HR 0.99 [0.65–1.52], p=0.90; matched HR 0.64 [0.35-1.16], p=0.145 (2) *CKD progression*: total sample p=0.09; matched p=0.58 (3) *NFCVE:* total sample HR 2.07 [1.39-3.09], p<0.001; matched HR 1.85 [1.04-3.30], p=0.04 (multivariate: total sample HR 2.03 [1.33-3.13], p<0.001; matched HR 2.00 [1.10-3.66], p=0.02) (4) *All-cause mortality*: total sample HR 0.79 [0.58-1.08], p=0.14; matched HR 0.88 [0.57–1.34], p=0.54 (5) *Cardiovascular-related mortality:* HR not published	*Average difference in % decline of eGFR per year NAFLD vs no NAFLD:* (i) Adjusted for age, sex, year of visit: p=0.002 (ii) Adjusted for all confounders: p=0.002	(1) *All-cause mortality:* CKD+NAFLD+ vs no CKD/NAFLD adjusted HR 2.34 [1.91-2.87], CKD+NAFLD- HR vs no CKD/NAFLD adjusted HR 2.08 [1.80-2.40], p=ns (2) *Cardiovascular-related mortality:* CKD+NAFLD+ vs no CKD/NAFLD adjusted HR 2.12 [1.44-3.13], CKD+NAFLD- HR vs no CKD/NAFLD adjusted HR 2.43 [1.8-3.28], p=ns
Secondary outcome results	None	(1) *Adjusted average difference in annual % change in eGFR:* low NFS vs no NAFLD 0.01% [−0.74 - 0.99]; high-intermediate NFS vs no NAFLD −2.12% [−2.93 - −1.31], p<0.0001 (2) *Adjusted average difference in annual % change in eGFR among patients with eGFR < 45 ml/min/1.73 m² at baseline for patients with NAFLD vs those without*: -5.61% [-11.43 – 0.59], p=0.075.	(1) *CKD + NAFLD + advanced fibrosis (n=60)* All-cause mortality: 73.1% [50.7-95.5], p=ns vs no advanced fibrosis; adjusted HR 3.49 [2.25-5.43], p=ns vs no advanced fibrosis Cardiovascular-related mortality: 14.6% [1.6-27.7], p=ns vs no advanced fibrosis; adjusted HR 2.83 [0.69-11.51], p=ns vs no advanced fibrosis (2) *CKD + NAFLD + no advanced fibrosis (n=97)* All-cause mortality: 52.1% [44.8-59.3]; adjusted HR 2.51 [1.98-3.18] Cardiovascular-related mortality: 16.5% [11.1-21.9]; adjusted HR 2.45 [1.61-3.73]

CKD: chronic kidney disease, ESRD: End-stage renal disease, RRT: renal replacement therapy, NFCVE: non-fatal cardiovascular event, ACS: acute coronary syndrome, MI: myocardial infarction, CCF: congestive cardiac failure, PVD: peripheral vascular disease, CVA: cerebrovascular accident, NAFLD: non-alcoholic fatty liver disease, HR: hazard ratio, NFS: NAFLD fibrosis score, APRI: AST to platelet ratio index, FIB-4, fibrosis-4, SE: standard error

95% confidence intervals are shown in square brackets.





* Predictors: hepatic fibrosis, age, male, obesity, hypertension, diabetes, dyslipidaemia, cardiovascular disease

Study Protocol

Background

Chronic kidney disease (CKD) is a long-standing condition resulting in impaired renal function associated with a reduced quality of life, increased risk of end-stage renal disease (ESRD), cardiovascular disease and premature death.(1) CKD is classified according to five stages largely based on estimated Glomerular Filtration Rate (eGFR), although persistent albuminuria also determines prognosis.(2) Moderate-severe CKD (stage 3-5) is defined as an eGFR of less than 60ml/min/1.73m^2 for more than 3 months. According to the Quality Outcomes Framework and Health Survey for England 2016 around 4-7% of UK adults have CKD stages 3-5.(3,4) The disease burden is particularly high in the elderly.(3) The global prevalence of CKD is higher at 11% for stages 3-5,(5) and it is estimated that the absolute global prevalence increased by 27% from 2007-2019.(6) CKD is forecasted to move from 16th (2016) to 5th (2040) in the rankings for years of life lost, predominantly as a result of aging, but also due to an increase in the prevalence of metabolic risk factors.(7) In addition to increasing age, hypertension, diabetes and obesity are major disease risk factors accounting for the majority of newly diagnosed cases of CKD in the developed world.(8,9) In terms of prognosis, it is estimated that 40,000–45,000 individuals with CKD die prematurely each year in England, with cardiovascular disease being the primary cause of morbidity and mortality.(10) The rate for individuals over 65 with CKD to progress to ESRD is reported to be 0.5 per 100 person-years and 6.8 per 100 person-years for all-cause mortality (3.0 for cardiovascular and 3.8 for non-cardiovascular mortality), i.e. patients with CKD are more likely to die from cardiovascular disease than develop ESRD.(11) CKD is both an accelerator of the risk of cardiovascular disease and an independent risk factor for cardiovascular events,(12–14) and is thought to account for 7000 extra strokes and 12,000 extra myocardial infarctions (MI) per year.(15)

Non-alcoholic fatty liver disease (NAFLD) refers to excessive fat accumulation in the liver affecting more than 5% of hepatocytes or liver volume. NAFLD is the most common cause of chronic liver disease worldwide, affecting approximately 25% of the adult population globally and in Europe.(16) It is expected to become the leading indication for liver transplantation in the next decade. It is estimated 90% of patients with type 2 diabetes mellitus (T2DM) have NAFLD, along with 70% of adults with obesity (17) and 90% of individuals who qualify for bariatric surgery.(18) While there is a lack of large prospective data in this field, paired liver biopsy studies from tertiary care suggest that around 23% of patients with simple steatosis are likely to develop non-alcoholic steatohepatitis (NASH) (hepatocytes injury (ballooning) and necro-inflammation) over a 3 year period, (19) and 44% over an average 8 year period.(20) Overall up to 30% of individuals with NAFLD are thought to have NASH,(21) and this is associated with a 25% risk of progression to cirrhosis over a 10 year period.(22) There is also evidence that NASH can lead to an elevated risk of hepatocellular carcinoma (HCC) even in the absence of cirrhosis.(23)

NAFLD and CKD share several cardiometabolic risk factors, many of which have now reached epidemic levels in the UK.(24) Current estimates suggest that 35.6% of adults in England are overweight and a further 28.7% are obese, with rates having more than doubled since 1991.(25,26) Around 1 in 11 adults worldwide (463 million) are thought to have diabetes, of which 90% is type 2.(27) This figure has more than tripled over the past 20 years, making diabetes one of the fastest growing health challenges of the 21st century.(27) Approximately 9% of men and 7% of women have diabetes in England,(28) however prevalence rates are as high as 25-30% in Pacific nations, followed by the Middle East and North Africa.(29) The International Diabetes Federation project the number of adults with diabetes worldwide will rise to 700 million by 2045, with the largest increases coming from regions experiencing economic transitions from low-income to middle-income levels.(27) While the prevalence of hypertension remains static it affects 30% of men and 26% of women.(28) Of huge concern is the fact that 22% and 34% of children starting primary school and secondary school

respectively are either overweight or obese.(30) While the incidence of T2DM for those under 17 years old in the UK remains low at 0.72 per 100,000 / year (2015/16), the number of cases diagnosed per year continues to rise,(31) and prevalence rates are significantly higher in the United States.(32)

It is well established that individuals with NAFLD are at increased risk of mortality from liver disease, cardiovascular disease and cancer (HCC and extra-hepatic) (33,34) however its association with kidney disease and its outcomes are less well understood. Two systematic reviews have now conclusively demonstrated a higher risk of incident CKD in individuals with NAFLD (hazard ratio (HR) 1.37 [95% CI 1.20-1.53] and 1.79 [95% CI 1.65-1.95].(35,36) Both reviews report that patients with more advanced fatty liver disease, i.e. NASH or hepatic fibrosis are at the greatest risk. Surprisingly this association has been consistently found to be independent of common risk factors and potential confounders, for example age, gender, body mass index, diabetes status, lipids, hypertension and smoking.(35,36) Of note NAFLD is also thought to be an independent risk factor for cardiovascular disease.(37) It has therefore been proposed that shared proinflammatory, prothrombotic and profibrotic molecular pathways may play a mediating role, in addition to the fact that NAFLD itself exacerbates insulin resistance, leading to atherogenic dyslipidaemia.(24) No causal link has been definitively demonstrated, however lifestyle modification has been shown not only to improve NAFLD histology but also kidney function in patients with biopsy proven NASH.(38). It is important to note that this association may manifest itself at an early stage, as children with NAFLD have been found to be at increased risk of developing renal dysfunction.(39) NAFLD is estimated to affect 3-10% of children worldwide.(40) It is possible that children and young adults with NAFLD may be at risk of an accelerated disease course in terms of cardiovascular complications, liver disease and kidney disease, especially given the increasing prevalence of shared cardiometabolic risk factors experienced by this age group.

We are interested in whether the presence of NAFLD predisposes individuals with CKD to be at increased risk of cardiovascular events, progression of kidney disease and all-cause mortality (figure 1). A brief review of the literature has revealed two cohort studies from the same group which used data from the Salford Kidney Study database.(41,42) The first follows 1,148 patients with CKD who also had a liver ultrasound to look for hepatic steatosis, for a median of 5.4 years.(41) They concluded that NAFLD was a strong independent risk factor for cardiovascular events (HR 2.03) (even in advanced CKD associated with high levels of comorbidity), but was not associated with all-cause mortality (HR 0.79) or CKD progression (p=0.09 for the rate of decline of the eGFR slope). The second study was confined to diabetic patients with CKD (n=149) and demonstrated comparable findings.(42) A third study from South Korea reported a greater rate of decline in eGFR in patients with NAFLD vs those without (−0.79% [−1.31% - −0.27%] vs 0.30% [−0.14% - 0.76%], p=0.002) in a cohort of 1,525 individuals with CKD.(43) Differences persisted in a multivariable adjusted model demonstrating that NAFLD is independently associated with CKD progression. Similarly in the haemo- and peritoneal dialysis population, patients with NAFLD have been found to have significantly worse cardiovascular outcomes.(44–46) Within NAFLD cohorts, CKD is associated with increased overall mortality, however there is disagreement regarding whether this is independent or due to the greater prevalence of metabolic comorbidities.(47,48)

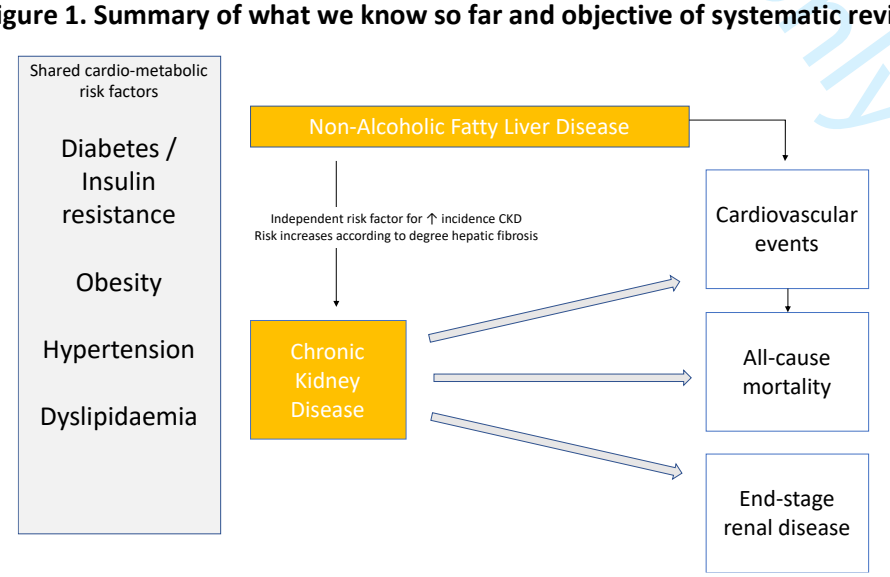
Importance of this review

Both CKD, NAFLD and their cardiometabolic risk factors (obesity and T2DM in particular) present huge challenges for both UK and global health providers.(16,49) In addition to the rising prevalence rates described above, both these conditions are profoundly linked to health inequalities. The incidence rates of CKD are estimated to be four times higher in low and middle income countries (LMIC), with Oceania, South East Asia, the Caribbean, Latin America, North Africa and the Middle East experiencing significant increases in disease burden.(6,50) Furthermore individuals of African descent experience

an accelerated course towards ESRD once they develop CKD.(51,52) With scarce resources for renal replacement therapy (RRT) in such countries, patients with ESRD are often faced with a death sentence. Similarly the burden of NAFLD is felt most heavily by low and middle income regions, including India (nearly 50%), South America and parts of the Middle East (approximately 30%).(53,54) Such inequalities nearly certainly result from a disparity in the prevalence of metabolic risk factors across economies. Nearly 80% of individuals with diabetes live in LMICs.(27) While obesity continues to predominantly affect higher income populations rates are levelling off, and instead are increasing in emerging economies.(55) Within England there is a large depravity gap in obesity prevalence for both adults and children which is increasing.(30) There is therefore a pressing need to address both the risk factor burden and predictors of clinical outcomes for both CKD in NAFLD, as LMIC and ethnic minorities are set to become disproportionately affected by these two conditions. Furthermore the financial costs associated with CKD are considerable. CKD was estimated to cost the English NHS £1.45 billion 2009-2010 (1.3% of all NHS spending).(15) More than half of this was spent on RRT serving 2% of the CKD population.(15) The cost of excess strokes and MIs was estimated to be up to £178 million.(15) Avoiding progression towards ESRD and the cardiovascular complications associated with CKD is therefore essential to reduce this huge cost burden.

CKD and NAFLD frequently exist together and independently contribute towards an increased risk of cardiovascular events and mortality. There is strong evidence that NAFLD is associated with an increased incidence of CKD, however research into the influence of NAFLD on the development of cardiovascular events, ESRD and premature death in the CKD population is at a much earlier stage. Understanding if there is a role for NAFLD in accelerating progression towards these adverse events could lead to improve health outcomes, reduced health inequalities and significant cost savings. This is a highly clinically relevant topic as individuals presenting to both primary and secondary care are increasingly likely to have both conditions. It is vital for their quality of care that clinicians are not only able to recognise the importance of looking for each of these diseases as a comorbidity, but also to identify patients who may be at the greatest risk for future cardiovascular events, rapid progression of kidney disease or early death. This would allow more aggressive lifestyle intervention, strict control of shared risk factors and enrolment in clinical trials. These findings are also likely to inform the need for improved cross-talk between diabetologists, cardiologists, hepatologists and renal physicians to help manage these patients optimally and lead to reductions in health care spending if end-stage events can be prevented. The findings of this review will be used to design an observational study which will further explore this question in an independent cohort.

Figure 1. Summary of what we know so far and objective of systematic review



HR: Hazard ratio, NAFLD: non-alcoholic fatty liver disease, CKD: Chronic kidney disease

Objective

To determine the influence of NAFLD on the risk of cardiovascular events, progression of kidney disease and all-cause mortality in patients with established CKD, and identify if this is independent of confounding factors

Methods

Types of studies

- Inclusion criteria: Observational (prospective or retrospective) cohort studies that report either the risk of cardiovascular events, progression of kidney disease or all-cause mortality among adults (> 18 year old) with established CKD who have NAFLD compared with those without NAFLD. Only studies that include meta-analysable outcomes will be included (mean difference, standardised difference, odds ratio (OR), HR or relative risk (RR)).
- Exclusion criteria: Abstracts, case reports, reviews, editorials, practice guidelines, non-cohort design, non-human studies, unpublished studies
- Search dates: No restriction on earliest publication date to present day
- Searches will be re-run just before the final analyses and any further studies identified, retrieved for inclusion
- We will register the protocol on PROSPERO a priori (https://www.crd.york.ac.uk/PROSPERO/)

Types of participants

- Inclusion criteria: Adults with established CKD with evidence of the presence or absence of NAFLD
- Exclusion criteria: Individuals under 18 years of age, individuals undergoing renal replacement therapy, eg haemodialysis, individuals who have had either a kidney or liver transplant, and individuals with a known other cause of chronic liver disease
- Definition of chronic kidney disease (CKD): eGFR ≥ 60 ml/min/1.73m^2 with albumin to creatinine ratio (ACR) > 3 mg/mmol (stage G1 and G2) or eGFR < 60 ml/min/1.73m^2 (stages G3a – G5) calculated using the CKD Epidemiology Collaboration (CKD-EPI) or Modified Diet in Renal Disease (MDRD) formula
- Definition of non-alcoholic fatty liver disease (NAFLD): biochemistry (elevations in serum AST, ALT, or GGT), imaging (ultrasound, computer tomography, magnetic resonance imaging), liver biopsy, non-invasive scores (Fatty Liver Index, Steatotest, NAFLD Liver Fat Score)

Primary outcome

- This review will aim to establish if there are any differences in the risk of cardiovascular events, progression of kidney disease and all-cause mortality in patients with CKD who have NAFLD compared to those without.
- Definition of cardiovascular events: Any one of the following - acute coronary syndrome, myocardial infarction, non-fatal cardiac arrest, coronary revascularization, new diagnosis of cardiac failure, hospitalisation with an exacerbation of cardiac failure, new diagnosis of peripheral vascular disease, new diagnosis of cerebrovascular accident (stroke / transient ischemic event) (all non-fatal).
- Definition of the progression of chronic kidney disease:
  1. Mean or percentage annual rate of change in the eGFR, or
  2. A decline in eGFR category accompanied by a ≥ 25% drop in eGFR from baseline, or
  3. The development of ESRD: eGFR of < 15 ml/min/1.73m^2, or the requirement of some form of renal replacement therapy, or

4. Doubling of creatinine

- Definition of all-cause mortality: Any cause of death within the study follow up period as determined by electronic patient records or the office of national statistics. Where possible we will break this down according to deaths due to a cardiovascular event, cancer or progression of kidney disease.

Secondary outcome

- The risk of cardiovascular events, progression of kidney disease and all-cause mortality in patients with CKD according to the severity of NAFLD, as determined by the presence of NASH or fibrosis.
- The risk of cardiovascular events, progression of kidney disease and all-cause mortality in patients with CKD according to the baseline severity of CKD, as determined by CKD stage.

Search methods for the identification of studies

- We will perform a computerized literature search in: PubMed, Embase (using Ovid) and Web of Science

Example of literature search strategy

"chronic kidney disease" [Title/Abstract] OR "CKD" [Title/Abstract] OR "kidney disease" [Title/Abstract] OR "kidney failure" [Title/Abstract] OR "kidney injury" [Title/Abstract] OR "chronic renal disease" [Title/Abstract] OR "renal disease" [Title/Abstract] OR "renal failure" [Title/Abstract] OR "renal injury" [Title/Abstract] OR "renal insufficiency" [Title/Abstract] OR "impaired renal function" [Title/Abstract] OR "glomerular filtration rate" [Title/Abstract] OR "eGFR" [Title/Abstract]
AND
"fatty liver" [Title/Abstract] OR "nonalcoholic fatty liver disease" [Title/Abstract] OR "NAFLD" [Title/Abstract] OR "nonalcoholic steatohepatitis" [Title/Abstract] OR "NASH" [Title/Abstract] OR "liver fat" [Title/Abstract] OR "steatohepatitis" [Title/Abstract] OR "steatosis" [Title/Abstract] OR "hepatic fibrosis" [Title/Abstract])

Study selection

- Relevant studies will be identified by systematically searching PubMed, Embase and Web of Science up to the present date using the free text terms described above
- Reference lists of relevant papers and previous review articles will be hand searched for other studies.
- Two investigators will examine all titles and abstracts, and obtain the full texts of potentially relevant papers. We will read the papers and determine if they met inclusion criteria.
- Discrepancies will be resolved by returning to the original article along with a third author in order to reach a consensus
- Inclusion criteria: Observational (prospective or retrospective) cohort studies that report either the risk of cardiovascular events, progression of kidney disease or all-cause mortality among adults (> 18 year old) with established CKD who have NAFLD compared with those without NAFLD. Only studies that include meta-analysable outcomes will be included (mean difference, standardised difference, OR, HR or RR).
- Exclusion criteria: Abstracts, case reports, reviews, editorials, practice guidelines, non-cohort design, non-human studies, unpublished studies

Data extraction

- Data will be extracted from each study independently by two authors and recorded on a standardised data extraction sheet
- We will use the Covidence software as recommended by Cochrane to upload search results, screen abstracts and full text, complete data collection, conduct risk of bias assessment, resolve disagreements and export data into Excel
- The following details will be extracted from all studies:
    - General information: title, authors, journal, funding, year of publication
    - Study design: population source and demographics, period of follow up and years, means of defining NAFLD, quality of study defined by the ACROBAT-NSRI tool, inclusion and exclusion criteria, study size, subgroups analysis (including severity of NAFLD and baseline CKD), confounding factors
    - Outcomes for NAFLD vs non-NAFLD patients: Outcome of interest (cardiovascular event / progression of kidney disease / all-cause mortality and definition used); OR, HR, RR and 95% confidence intervals; or mean/percentage annual rate of change in the eGFR
- In the event of missing data the researchers will attempt to contact the study investigators for unreported data or additional details. Contact information for study authors will be identified from PubMed or from the Internet and corresponding authors will be e-mailed or contacted by phone to ask if they are willing to share their study data. Up to 3 contact attempts will be made within a month. Manuscripts for which we are unable to obtain missing data will not be included in our analyses.
- Data will be reported according to the PRISMA guidelines

Assessment of bias (quality assessment)

- Two authors will independently be involved in the quality assessment
- Any discrepancies will be addressed by a revaluation of the original article by a third author
- We will use the Newcastle-Ottawa Score as recommended by Cochrane for the assessment of quality for non-randomised cohort studies.(56)
- This tool uses a star based system allocating a maximum of 9 points across three domains: (1) selection of study groups (max 4 points), (2) comparability of groups (max 2 points), (3) ascertainment of exposure and outcomes (max 3 points)
- Studies with an overall score of 9 are judged to be at a low risk of bias, those scoring 7-8 a moderate risk of bias and scores of 6 of less a high risk of bias.
- Where studies report more than one primary outcome a separate bias assessment will be performed for each.

Data synthesis

- Data will be synthesised if this review is able to identify 5 of more studies which meet the inclusion criteria described above, and that report the same outcome (either risk of a cardiovascular event, progression of kidney disease, or all-cause mortality)
- In the case of binary outcomes (risk of a cardiovascular event, ESRD, a decline in eGFR category accompanied by a ≥ 25% drop in eGFR from baseline, doubling of creatinine and all-cause mortality), adjusted and unadjusted HR/OR/RRs will be pooled with their 95% confidence intervals as a measure of effect size.
- In the case of continuous outcomes (mean/percentage annual rate of change in the eGFR) we will pool the adjusted and unadjusted mean or percentage differences

- Random-effects model: An overall estimate of effect size will be calculated using a random-effects model, as this takes into account any differences between studies even if there is no statistically significant heterogeneity.
- Statistical heterogeneity: The I^2 statistic will be used to investigate statistical heterogeneity. This estimates the percentage of variability in effect across studies resulting from heterogeneity rather than chance, to ensure that the effects found in the individual studies are similar enough that a combined estimate will be a meaningful. If heterogeneity between the effects found in single studies is too large ($I^2 > 0.5$) we will explore the source.
- Publication (small study bias): If the number of included studies is sufficient, publication bias will be examined using funnel plots and the Egger's regression test. We will use the trim and fill method to calculate adjusted estimates if publication bias is detected.
- Sensitivity analysis: For all outcomes we will use a meta-analysis influence test (involves repeating the meta-analysis after one study at a time is removed) to investigate any excessive influence of individual studies
- Meta-regression analysis: When 8 or more studies are available and report the same outcome, the effect of continuous variables (age, body mass index, waist circumference, insulin resistance estimated by homeostasis model assessment of insulin resistance index, and duration of follow-up) on the association between NAFLD and the reported outcome will be evaluated by meta-regression analysis

Analysis of subgroups or subsets

- If we are able to identify at least 5 cohort studies reporting the same outcome as described above, we will perform a sub-group analysis in order to address potential heterogeneity between studies
- Individuals may be stratified using any of the following criteria at the level of the study:
    - Quality of study as identified by the ACROBAT-NSRI tool
    - Follow-up duration
    - Age
    - Ethnicity
    - Means of defining NAFLD (biochemistry, imaging, liver biopsy, non-invasive scores)
    - Severity of NAFLD (NASH vs no NASH; fibrosis vs no fibrosis)
    - Severity of CKD according to disease stage at baseline
    - Patients with diabetes vs those without diabetes
    - Patients with cirrhosis vs those without cirrhosis
    - Patients with a history of excessive alcohol consumption vs those without
    - Whether the study has fully adjusted for covariates (age, gender, body mass index, hypertension, smoking, baseline eGFR, diabetes, dyslipidaemia, previous cardiovascular event)

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Supplementary material

Methods

Exact search criteria for online databases

1. PUBMED – 1,020 results

("chronic kidney disease" [Title/Abstract] OR "CKD" [Title/Abstract] OR "kidney disease" [Title/Abstract] OR "kidney failure" [Title/Abstract] OR "kidney injury" [Title/Abstract] OR "chronic renal disease" [Title/Abstract] OR "renal disease" [Title/Abstract] OR "renal failure" [Title/Abstract] OR "renal injury" [Title/Abstract] OR "renal insufficiency" [Title/Abstract] OR "impaired renal function" [Title/Abstract] OR "glomerular filtration rate" [Title/Abstract] OR "eGFR" [Title/Abstract]) AND ("fatty liver" [Title/Abstract] OR "nonalcoholic fatty liver disease" [Title/Abstract] OR "NAFLD" [Title/Abstract] OR "nonalcoholic steatohepatitis" [Title/Abstract] OR "NASH" [Title/Abstract] OR "liver fat" [Title/Abstract] OR "steatohepatitis" [Title/Abstract] OR "steatosis" [Title/Abstract] OR "hepatic fibrosis" [Title/Abstract])

2. EMBASE – 1,851 results

'Embase 1974 to 1/2/20' database used to achieve largest date range

((chronic kidney disease or CKD or kidney disease or kidney failure or kidney injury or chronic renal disease or renal disease or renal failure or renal injury or renal insufficiency or impaired renal function or glomerular filtration rate or eGFR) and (fatty liver or non-alcoholic fatty liver disease or NAFLD or nonalcoholic steatohepatitis or NASH or liver fat or steatohepatitis or steatosis or hepatic fibrosis)).ti,ab

3. Web of Science core collection - 1,476 results

'1970-2020' database used to achieve largest date range
Topic (TS): title, abstract, keywords

TS=(("chronic kidney disease" OR CKD OR "kidney disease" OR "kidney failure" OR "kidney injury" OR "chronic renal disease" OR "renal disease" OR "renal failure" OR "renal injury" OR "renal insufficiency" OR "impaired renal function" OR "glomerular filtration rate" OR eGFR) AND ("fatty liver" OR "nonalcoholic fatty liver disease" OR NAFLD OR "nonalcoholic steatohepatitis" OR NASH OR "liver fat" OR steatohepatitis OR steatosis OR "hepatic fibrosis"))

No further filters were used for any of the three databases.

Title
Authors
Journal
Year publication
Country
Funding
Population source
Demographics
Period follow up
Years of study
Study size
Intervention'
NAFLD definition
CKD definition
Quality (Newcastle-Ottawa Score)
Inclusion criteria
Exclusion criteria
Study design
Subgroup analysis
Adjustments for confounding factors
Longitudinal f/u
Outcome examined & definition
Statistical analysis
NAFLD prevalence
Cases
Primary outcome results
Secondary outcome results
OUTCOME

Non-alcoholic fatty liver disease and clinical outcomes in chronic kidney disease	
Rajkumar Chinnadurai, James Ritchie, Darren Green and Philip A. Kalra	
Nephrol Dial Transplant	
2019	
UK	
?	
Salford Kidney Study (SKS) - extension of the Chronic Renal Insufficiency Standards Implementations Study (CRISIS)	
Mean age 66 years, males 60.7%, mean BMI 28, DM 34%, HTN 78%, hyperlipidaemia 49%, median eGFR 33.5 mL/min/1.73 m ^{2}	
Median 65 months	
Liver USS (01/01/2000 - 31/12/2014), end of analysis period 31/12/2015	
1148 CKD patients (205 NAFLD, 752 normal liver, 191 had other hepatic abnormalities on USS) 852 CKD patients (183 NAFLD, 669 normal liver) after excluding patients with incomplete follow-up data sets 276 CKD patients (138 NAFLD, 138 normal liver) with 1:1 propensity score matching	
NAFLD vs no NAFLD	
Liver USS (hyperechogenicity or echobright liver consistent with fatty infiltration)	
eGFR <60 mL/min/ 1.73 m^2 using CKD-EPI formula	
(1) Mortality NOS = 8, (2) non-fatal CVE NOS = 8, (3) CKD progression NOS = 9	
Patients ≥ 18 years old referred to Salford renal service (tertiary centre); eGFR <60 mL/min/ 1.73 m ^{2}, not needing immediate RRT	
Maintenance RRT at time of liver USS , drinking above 21 units men / 14 units women, history of chronic hepatitis B & C or other chronic liver diseases	
Retrospective observational longitudinal cohort study	
NFCVE outcomes subgroup analysis: cardiac event, cerebrovascular event, PVD CCF Deaths analysed according to: cardiac, non-cardiac No subgroup analysis according to severity of NAFLD / severity CKD at baseline	
Propensity matching for: age, gender, BMI, SBP, DBP, baseline hypertension, diabetes, hypercholesterolaemia, IHD, MI, CCF, CVA, PVD, malignancy, use of statin and renin–angiotensin blocking agents, eGFR (NB age difference, NAFLD 66 yrs, normal liver 68 yrs p=0.04)	
Annual review: comorbidities, hospital admissions, cardiovascular events, medications, blood results	
(1) ESRD: commencement of RRT or eGFR of <10 mL/min/1.73 m^2 (2) Rate of change of eGFR (eGFR slope) from baseline to study end-point (3) NFCVE: composite of ACS, non-fatal MIs, non-fatal cardiac arrest, coronary revascularizations, new diagnosis cardiac failure / admissions with exacerbations of cardiac failure, new diagnosis of PVD, CVAs (4) All-cause mortality	
Univariate & multivariate Cox proportional hazards models to determine HRs & 95% CI (outcomes 1,3,4) Linear regression slope generated using serial serum creatinine measurements (outcome 2)	
17.9% (205 / 1148)	
(1) ESRD: NAFLD 26 (14.2%), normal 134 (19.1%), p=0.07 (2) CKD progression (rate of decline of eGFR slope): NAFLD -2.54 [-7.61 - 0.31] mL/min/1.73 m^2, normal -2.09 [-6.14 - 1.06] mL/min/1.73 m^2 (3) NFCVE: NAFLD 46 (25.1%), normal 82 (12.3%), p<0.001 (4) All cause mortality: NAFLD 50 (27.3%), normal 22 (33.0%), p=0.14	
(1) ESRD: total sample HR 0.99 [0.65–1.52], p=0.90; matched HR 0.64 [0.35-1.16], p=0.145 (2) CKD progression (rate of decline of eGFR slope): total sample p<0.09; matched p=0.58 (3) NFCVE: total sample HR 2.07 [1.39-3.09], p<0.001; matched HR 1.85 [1.04-3.30], p<0.04 (multivariate: total sample HR 2.03 [1.33-3.13], p<0.001; matched HR 2.00 [1.10-3.66], p=0.02) (4) All-cause mortality: total sample HR 0.79 [0.58-1.08], p=0.14; matched HR 0.88 [0.57–1.34], p=0.54	
N/A	
INCLUDE	

Nonalcoholic fatty liver disease accelerates kidney function decline in patients with chronic kidney disease: a cohort study
Hye Ryoun Jang, Danbee Kang, Dong Hyun Sinn, Seonhye Gu, Soo Jin Cho, Jung Eun Lee, Wooseong Huh, Seung Woon Paik, Seungho Ryu, Yoosoo Chang, Tariq Shafi, Mariana Lazo, Eliseo Guallar, Juhee Cho, Geum-Youn Gwak
Scientific reports
2018
South Korea
?
Individuals who underwent a comprehensive health screening examination at the Samsung Medical Centre Health Promotion Centre, Seoul, South Korea
Mean age 60.8 years, males 70%, mean BMI 24.8, DM 24%, HTN 60%, hyperlipidaemia 41%, median eGFR 59.1 mL/min/1.73 m^2
Average 6.5 years
January 2003 through December 2013
1,525 CKD patients
NAFLD vs no NAFLD
USS based on standard criteria, including parenchymal brightness, liver-to-kidney contrast, deep beam attenuation and bright vessel walls
eGFR < 60 ml/min/1.73 m^2 using CKD-EPI formula, or proteinuria ≥2+ on urinalysis
NOS = 7
Patients ≥ 18 years old who underwent a comprehensive health screening examination at the Samsung Medical Centre Health Promotion Centre and were found to have CKD with at least 1 additional follow up serum creatinine
History of cancer, liver cirrhosis, positive hepatitis B surface antigen, or hepatitis C virus antibodies, alcohol intake ≥ 30 g/day in men or ≥20 g/day in women, previous kidney transplant or started dialysis within 1 year after baseline examination, missing information on alcohol intake, NFS, or less than 6 months follow up
Retrospective observational longitudinal cohort study
(1) Severity NAFLD assessed via NFS: −1.675 + 0.037 × age (years) + 0.094 × BMI + 1.13 × impaired fasting glucose/diabetes (yes = 1, no = 0) + 0.99 × AST/ALT ratio − 0.013 × platelet count (×10^9/l) − 0.66 × albumin (g/dl). Based on NFS, patients were classified as high-intermediate (NFS ≥ −1.455) and low probability (NFS < −1.455) of advanced fibrosis. (2) Severity of CKD at baseline: cut-off value eGFR ≥45 ml/min/1.73 m^2 vs. <45 ml/min/1.73 m^2 (dividing G3a and G3b)
Stratified analyses to evaluate if association of NAFLD with CKD progression differed in pre-specified subgroups: age (<60 vs. ≥ 60 years), sex, smoking (never or former vs. current), alcohol drinking (none vs. moderate), BMI ≥ 25 kg/m2, hypertension (SBP ≥ 140 mmHg, DBP ≥ 90 mmHg, or use of antihypertensives), diabetes (fasting serum glucose ≥ 126 mg/dl, HbA1c ≥ 6.5%, or use of antidiabetic medication), hyperlipidaemia (HDL < 40 mg/dl in men or < 50 mg/dl in women, TG ≥ 150 mg/dl, or use of lipid-lowering medication), or baseline eGFR (<45 vs. ≥ 45 ml/min/1.73 m^2).
At each visit demographic characteristics, smoking status, alcohol consumption, medical history and medication use were collected through standardized, self-administered questionnaires along with blood results
CKD progression: average annual percent change in eGFR from baseline eGFR
Compared serial changes in eGFR among CKD patients with or without NAFLD at baseline using linear mixed models for longitudinal data with random intercepts and random slopes. Used loge-transformed eGFR as outcome and estimated the average difference in annual % change in eGFR (with 95% CI).
40.9% (902/1525)
Average annual percent change in eGFR from baseline: NAFLD -0.79% [-1.31 - -0.27], no NAFLD 0.30% [-0.14 - 0.76]
Average difference in % decline of eGFR per year NAFLD vs no NAFLD: (i) Adjusted for age, sex, year of visit: -1.09% [-1.77 - -0.41] (ii) Adjusted for all confounders: -1.06% [-1.73 - -0.38]
Average difference in % decline of eGFR per year NAFLD vs no NAFLD: (i) Adjusted for age, sex, year of visit: p=0.002 (ii) Adjusted for all confounders: p=0.002
(1) Multivariable adjusted average difference in annual % changes in eGFR for low NFS (≤ 1.455) or intermediate to high NFS (≥ −1.455) & those without NAFLD: 0.01% [−0.74 - 0.99) & −2.12% (−2.93 - −1.31) respectively (2) Multivariable adjusted average difference in annual % changes in eGFR among patients with eGFR < 45 ml/min/1.73 m^2 at baseline -6.27% [-12.08 - - 0.08] (n=168) vs -0.76 [-1.32 - -0.19] (n=1357) for baseline eGFR ≥ 45
INCLUDE

Chronic kidney disease is independently associated with increased mortality in patients with nonalcoholic fatty liver disease.
James Paik, Pegah Golabi, Zahra Younoszai, Alita Mishra, Gregory Trimble, Zobair M. Younossi
Liver International
2019
USA
None
NHANES-III & linked mortality files
Mean age 43.3 years, males 48.4%, DM 6.5%, HTN 40.7% (total cohort)
Average 19.2 years
NHANES-III 1988 - 1994; linked mortality files up to 2011 or date of death
11,695 adult participants 'NAFLD- CKD-' 74.6%, 'NAFLD+ CKD-' 16.1%, 'NAFLD- CKD+' 6.8%, 'NAFLD+ CKD+' 2.5%
CKD vs no CKD in NAFLD cohort (main results reported in paper) NAFLD in CKD cohort (some data)
Liver USS (moderate/severe hepatic steatosis in absence of any other possible cause CLD)
eGFR < 60 ml/min/1.73 m2 using CKD-EPI formula +/- albuminuria
NOS = 9
Persons aged 20-74 at time of examination with complete data on ultrasound video images for hepatic steatosis assessment and serum creatinine measurements
Patients with other causes of chronic liver disease were excluded
Retrospective analysis of data collected from cross-sectional study
Presence of fat within hepatic parenchyma graded as normal, mild, moderate, or severe hepatic steatosis. NAFLD-associated advanced fibrosis was defined with ultrasound diagnosed NAFLD and at least one of the following fibrosis markers: APRI> 1, FIB-4 index >2.67, or NFS>0.676. Cardiovascular mortality was defined as death due to heart diseases (ICD-10: I00-I09, I11, I13, and I20-I51) and cerebrovascular diseases (ICD-10: I60-I69).
Age, gender, race, smoker, metabolic syndrome
Data linked with mortality files
(1) All-cause mortality (2) Cardiovascular-related mortality: death due to heart diseases (ICD-10: I00-I09, I11, I13, I20-I51) & cerebrovascular diseases (ICD-10: I60-I69)
Logistic regression & cox proportional hazards model
29% (410/1,413)
(1) All-cause mortality: NAFLD 54.7% (SE 3.6), no NAFLD 46.5% (SE 2.4), p<0.05 (age adjusted: NAFLD 31.0% [25.0-37.0], no NAFLD 25.9% [22.0-29.7], p=ns) (2) Cardiovascular-related mortality: NAFLD 16.0% (SE 2.5), no NAFLD 16.2% (SE 1.7), p=ns (age adjusted: NAFLD 7.8% [3.7-11.9], no NAFLD 8.2% [5.6-10.9], p=ns)
(1) All-cause mortality: adjusted HR NAFLD 2.34 [1.91-2.87], no NAFLD 2.08 [1.80-2.40], p=ns (2) Cardiovascular-related mortality: adjusted HR NAFLD 2.12 [1.44-3.13], no NAFLD 2.43 [1.8-3.2], p=ns
(1) CKD + NAFLD + advanced fibrosis (n=60) All-cause mortality: 73.1% [50.7-95.5], p=ns vs no advanced fibrosis; adjusted HR 3.49 [2.25-5.43], p=ns vs no advanced fibrosis Cardiovascular-related mortality: 14.6% [1.6-27.7], p=ns vs no advanced fibrosis; adjusted HR 2.83 [0.69-11.51], p=ns vs no advanced fibrosis (2) CKD + NAFLD + no advanced fibrosis (n=97) All-cause mortality: 52.1% [44.8-59.3]; adjusted HR 2.51 [1.98-3.18] Cardiovascular-related mortality: 16.5% [11.1-21.9]; adjusted HR 2.45 [1.61-3.73]
INCLUDE

Increased Risk for Cardiovascular Events in Patients with Diabetic Kidney Disease and Non-Alcoholic Fatty Liver Disease.
Rajkumar Chinnadurai, Constantina Chrysochou, Philip A. Kalra
Nephron
2018
UK
?
Salford Kidney Study (SKS) - extension of the Chronic Renal Insufficiency Standards Implementations Study (CRISIS)
Mean age 65 years, males 66%, mean BMI 30, DM 100%, HTN 87%, median eGFR 31.6 mL/min/1.73 m^2, hyperlipidaemia 79%
Median 69 months
Liver USS (01/01/2000 - 31/12/2014), end of analysis period 31/12/2015
192 patients with DKD (55 NAFLD, 113 normal liver, 24 had other hepatic abnormalities on USS) 149 patients with DKD (183 NAFLD, 669 normal liver) after excluding patients with incomplete follow-up data sets
NAFLD vs no NAFLD
Liver USS (hyperechogenicity or echobright liver consistent with fatty infiltration)
eGFR <60 mL/min/ 1.73 m^2 using CKD-EPI formula
Patients ≥ 18 years old referred to Salford renal service (tertiary centre); eGFR <60 mL/min/ 1.73 m^2, not needing immediate RRT
Maintenance RRT at time of liver USS , drinking above 21 units men / 14 units women, history of chronic hepatitis B & C or other chronic liver diseases
Retrospective observational longitudinal cohort study
NFCVE outcomes subgroup analysis: cardiac event, cerebrovascular event, PVD CCF Deaths analysed according to: cardiac, non-cardiac No subgroup analysis according to severity of NAFLD / severity CKD at baseline
Propensity matching for: age, gender, BMI, SBP, DBP, baseline hypertension, diabetes, hypercholesterolaemia, IHD, MI, CCF, CVA, PVD, malignancy, use of statin and renin–angiotensin blocking agents, eGFR (NB age difference, p=0.04)
Annual review: comorbidities, hospital admissions, cardiovascular events, medications, blood results
(1) ESRD: commencement of RRT or eGFR of <10 mL/min/1.73 m^2 (2) Rate of change of eGFR (eGFR slope) from baseline to study end-point (3) NFCVE: composite of ACS, non-fatal MIs, non-fatal cardiac arrest, coronary revascularizations, new diagnosis cardiac failure / admissions with exacerbations of cardiac failure, new diagnosis of PVD, CVAs (4) All-cause mortality
Univariate & multivariate Cox proportional hazards models to determine HRs & 95% CI (outcomes 1,3,4) Linear regression slope generated using serial serum creatinine measurements (outcome 2)
28.6% (55/192)
(1) ESRD: NAFLD 7 (14.6%), normal 17 (16.8%), p=0.73 (2) CKD progression (rate of decline of eGFR slope): NAFLD -3.97 [-7.2 - 0.12] mL/min/1.73 m^2, -2.95 [-9.07 - 0.407] normal mL/min/1.73 m^2 (3) NFCVE: NAFLD 20 (41.7%), normal 14 (13.9%), p<0.001 (4) All cause mortality: NAFLD 16 (33.3%), normal 36 (35.6%), p=0.78
(1) ESRD: not reported (2) CKD progression (rate of decline of eGFR slope): p=0.65 (3) NFCVE: HR 3.48 [1.59-7.6], p=0.002 (multivariate: HR 2.95 [1.31-6.60], p=0.01) (4) All-cause mortality: HR 0.72 [0.40-1.31], p=0.28
N/A
Sub group of previous paper by Chinnadurai

Nonalcoholic Fatty Liver Disease and Renal Function Impairment: A Cross-Sectional Population-Based Study on Its Relationship From 1999 to 2016
Michael H. Le, Yee Hui Yeo, Linda Henry, and Mindie H. Nguyen
Hepatology Communications
2019
USA
?
National Health and Nutrition Examination Survey (NHANES): cross-sectional survey conducted in US by the National Centre for Health Statistics of the Centres for Disease Control and Prevention (CDC)
Mean age 53 years, males 56%, mean BMI 34, DM 24%, HTN 52.3%, median eGFR 90.5 mL/min/1.73 m^2, dyslipidaemia 61%
1999 - 31 Dec 2015
14,255 adults (not all had renal insufficiency); 4680 NAFLD patients (population of interest for this study)
Renal insufficiency vs no renal insufficiency
U.S. Fatty Liver Index (USFLI) ≥30 to rule in fatty liver
eGFR determined CKD-EPI & ACR. Unable to determine if renal insufficiency was acute or chronic. Renal insufficiency divided into 4 stages: no RI, mild, moderate & severe
People aged 18 years and older, who participated in a medical examination at a mobile centre, and underwent fasting blood work during their examination.
Participants <18 years old, missing laboratory data needed to calculate the non-invasive indices (age, race/ethnicity, waist circumference, GGT, fasting insulin, fasting glucose, serum creatinine, urine creatinine, and urine albumin), those who had a diagnosis of viral hepatitis, and those with heavy alcohol use.
Cross-sectional study
Severity of liver fibrosis assessed using NAFLD Fibrosis Score (NFS). NFS >0.676 rule in stage 3-4 fibrosis, NFS <–1.455 rule out stage 3-4 fibrosis.
2 yearly cross-sectional interviews, examinations and laboratory data
(1) Trends in NAFLD +/- renal insufficiency prevalence over time in US (2) Predictors of RI in NAFLD patients (3) Health literacy levels for kidney & liver disease (4) Mortality (national death index): all-cause mortality, cause-specific mortality from diseases of heart and malignant neoplasms: compared NAFLD + renal insufficiency vs NAFLD without renal insufficiency (5) Risk factors predicting mortality in NAFLD cohort with & without renal insufficiency
Univariate & multivariate logistic regression; Kaplein Meier curves; cox regression
31.2% (not all patients had renal insufficiency)
(1) Prevalence 1999-2000: NAFLD without RI 23.5% [20.2-27.1], NAFLD-RI 5.7% [4.3-7.6]; prevalence 2015- 2016, NAFLD without RI 27.3% [23.7-31.1], NAFLD-RI 7.7% [6.2-9.5]. Trend analysis 1999-2016: prevalence of overall NAFLD, NAFLD without RI & NAFLD-RI all significantly increased over time (p=0.007, p=0.048, p=0.006 respectively). Among those with NAFLD, RI prevalence did not increase significantly 1999-2016 (p=0.221). No significant increases were observed in mild, moderate, or severe RI in those with NAFLD (p=0.448, p=0.222, p=0.478 respectively) (2) Significant independent predictors of RI in NAFLD: age > 65, HTN, DM, dyslipidaemia, CVD, high probability of fibrosis stage 3 and 4 (multivariate analysis) (3) Among those with NAFLD-RI, awareness of kidney disease was 8.56% [6.69-10.89], awareness of liver disease among all NAFLD was 4.49% [3.17-6.33] (4) 5 yr cumulative mortality incidence: NAFLD alone 4.5%; mild RI 14.2%, moderate 21.2%, and severe 36.0% RI (p<0.001). 15 yr cumulative mortality incidence: NAFLD alone 19.9%, mild RI 42.4%, moderate RI 80.6%, and severe RI 85.5% (p<0.001). 5 yr cumulative incidence CV-related mortality highest in NAFLD + severe RI at 10.5% (36.7% at 15 years). Independent risk factors for all-cause mortality in NAFLD: age, mild/mod/sever RI, high probability of fibrosis; former/current smoker; history of CVD. Independent risk factors for CV mortality in NAFLD: older age, moderate & severe RI, history of CVD.
Intervention is CKD in NAFLD cohort rather than NAFLD in CKD cohort.

Predicting timing of clinical outcomes in patients with chronic kidney disease and severely decreased glomerular filtration rate.

Grams ME1, Sang Y2, Ballew SH2, Carrero JJ3, Djurdjev O4, Heerspink HJL5, Ho K6, Ito S7, Marks A8, Naimark D9, Nash DM10, Navaneethan SD11, Sarnak M12, Stengel B13, Visseren FLJ14, Wang AY15, Köttgen A16, Levey AS12, Woodward M17, Eckardt KU18, Hemmelgarn B19, Coresh J20

Kidney Int.

2018

30 countries

Participants in International Chronic Kidney Disease Prognosis Consortium

Median eGFR 24 mL/min/1.73 m2

264,296 individuals

Age, sex, race, eGFR, ACR, SBP, smoking status, DM, history of CVD.

eGFR < 30 ml/min/1.73m2

Aim to develop 2 & 4 year models of the probability & timing of kidney failure requiring RRT, a non-fatal CVD event & death

Competing-risk regression, random-effect meta-analysis, and Markov processes with Monte Carlo simulations

NAFLD was not examined in this study

Newcastle-Ottawa Scale (NOS)	Questions	Chinnadurai R et al. Nep Mortality
1) Selection of study groups (max 4)	1) Representativeness of the exposed cohort a) truly representative of the average patient with CKD in the community * b) somewhat representative of the average patient with CKD in the community * c) selected group of users eg nurses, volunteers d) no description of the derivation of the cohort	* Only those who had an USS included
	2) Selection of the non exposed cohort a) drawn from the same community as the exposed cohort * b) drawn from a different source c) no description of the derivation of the non exposed cohort	*
	3) Ascertainment of exposure a) secure record (eg surgical records) * b) structured interview * c) written self report d) no description	*
	4) Demonstration that outcome of interest was not present at start of study a) yes * b) no	Some patients had disease, eg IHD at baseline
	TOTAL SCORE	3
2) Comparability of groups (max 2)	1) Comparability of cohorts on the basis of the design or analysis a) study controls for components of themetabolic syndrome * b) study controls for any additional factor (mortality: underlying CVD, baseline eGFR; CVE: underlying CVD; CKD progression: baseline eGFR)*	 * *
	TOTAL SCORE	2
3) Ascertainment of exposure and outcomes (max 3)	1) Assessment of outcome a) independent blind assessment* b) record linkage * c) self report d) no description	*
	2) Was follow-up long enough for outcomes to occur a) yes (select an adequate follow up period for outcome of interest) * b) no	*
	3) Adequacy of follow up of cohorts a) complete follow up - all subjects accounted for* b) subjects lost to follow up unlikely to introduce bias - small number lost (< 20%), or description provided of those lost* c) follow up rate < 80% and no description of those lost d) no statement	*
	TOTAL SCORE	3
	OVERALL SCORE	8

hrol Dial Transplant. 2019;34(3):449-457		Jang HR, et al. Sci Rep. 2018;8(1):4718.		Paik J et al. *Liver Int* . 2019;39(2):342-352.			
CVE	**CKD progression**	**Mortality**	**CVE**	**CKD progression**	**Mortality**	**CVE**	**CKD progression**
* Only those who had an USS included	* Only those who had an USS included			* Only those who had an USS included	* Only those who had an USS included & under 75s		
*	*			*	*		
*	*			*	*		
Some patients had disease, eg IHD at baseline	*			*	Some patients had disease, eg CVD at baseline		
3	4			4	3		
*	*			*	*		
*	*			*	No		
2	2			2	1		
*	*			*	*		
*	*			*	*		
*	*			* Included only participants with at least 1 f/u eGFR	* Participants with no death records were presumed alive through f/u		
3	3			3	3		
8	9			9	7		

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5-6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6-7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	N/A

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	N/A
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7-8, figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8 & table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	11 & table 2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	8-9 & table 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	N/A
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	11-12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	12-14
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	3

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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BMJ Open

Systematic review of the impact of non-alcoholic fatty liver disease on mortality and adverse clinical outcomes for individuals with chronic kidney disease

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Secondary Subject Heading:	Gastroenterology and hepatology, Cardiovascular medicine, Epidemiology, General practice / Family practice
Keywords:	Chronic renal failure < NEPHROLOGY, Hepatology < INTERNAL MEDICINE, Myocardial infarction < CARDIOLOGY, End stage renal failure < NEPHROLOGY

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Systematic review of the impact of non-alcoholic fatty liver disease on mortality and adverse clinical outcomes for individuals with chronic kidney disease

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Keywords

Chronic renal failure; Hepatology; Myocardial Infarction, End-stage renal failure

Abstract

Objectives: To investigate if non-alcoholic fatty liver disease (NAFLD) impacts mortality and adverse outcomes for individuals with chronic kidney disease (CKD).

Design*:* Systematic review

Data sources: PubMed, EMBASE and Web of Science were searched up to 1/2/2020 with no restriction on the earliest date.

Eligibility criteria for selecting studies: Observational cohort studies that reported either the risk of all-cause mortality, incidence of non-fatal cardiovascular events (CVE) or progression of kidney disease among adults with established CKD who have NAFLD compared to those without.

Data extraction and synthesis: Two reviewers extracted data and assessed bias independently.

Results: Of 2,604 records identified three studies were included (UK n=852, South Korea n=1,525, US n=1,413). All were judged to have a low or moderate risk of bias. Data were insufficient for meta-analysis. Two studies examined the influence of NAFLD on all-cause mortality. One reported a significant positive association for NAFLD with all-cause mortality for individuals with CKD ($p<0.05$) (cardiovascular-related mortality p=ns), which was lost following adjustment for metabolic risk factors; the second reported no effect in adjusted and unadjusted models. The latter was the only study to report outcomes for non-fatal CVEs and observed NAFLD to be an independent risk factor for this (propensity matched hazard ratio 2.00, p=0.02). Two studies examined CKD progression; in one adjusted rate of percentage decline in estimated glomerular filtration rate per year was increased in those with NAFLD (p=0.002), whereas the other found no significant difference.

Conclusions: Few studies have examined the influence of NAFLD on prognosis and major adverse clinical outcomes within the CKD population. The studies identified were diverse in design and results were conflicting. This should be a focus for future research as both conditions continue to rise in prevalence and have end-stage events associated with significant health and economic costs.

PROSPERO registration number: CRD42020166508

Article Summary

Strengths and limitations of this study

- This is the only systematic review to date to examine the influence of non-alcoholic fatty liver disease on outcomes for patients with chronic kidney disease
- Only three cohort studies were eligible for inclusion
- A single study showed an association between NAFLD and cardiovascular events in patients with chronic kidney disease; results were conflicting for all-cause mortality and progression of renal disease
- In view of the small number of studies this is an important area for further research

Word count: 4,252

Number of figures: 2

Number of tables: 2

Introduction

Chronic kidney disease (CKD) is a long-standing condition incorporating impaired renal function and is often associated with a reduced quality of life, increased risk of end-stage renal disease (ESRD), cardiovascular disease (CVD) and premature death.[1,2] CKD is classified according to five stages based on estimated Glomerular Filtration Rate (eGFR), and in practice persistent albuminuria.[3] Around 4-7% of adults living in the United Kingdom (UK) have CKD stages 3-5 (eGFR < 60ml/min/1.73m^2),[4,5] with a higher global prevalence at 11%, although significant variation is recognised due to data availability, measurements used and reliance on coding.[6,7] Global prevalence is estimated to have increased by nearly 30% from 2007-2019[8] and CKD is forecast to move from 16th (2016) to 5th (2040) in the rankings for years of life lost.[9] The disease burden is particularly high in the elderly.[4] Increasing age, hypertension, diabetes and obesity account for the majority of newly diagnosed cases of CKD in the developed world.[10,11] CKD shares these risk factors, many of which are experiencing a significant rise in prevalence, with non-alcoholic fatty liver disease (NAFLD).[12]

NAFLD refers to excessive fat accumulation in the liver affecting more than 5% of hepatocyte and encompasses a spectrum of disease from simple steatosis to non-alcoholic steatohepatitis (NASH), fibrosis and cirrhosis. It is the most common cause of chronic liver disease worldwide, affecting approximately 25% of adults globally and in Europe.[12] It is expected to become the leading indication for liver transplantation in the next decade.[13] NAFLD is referred to as the hepatic manifestation of the metabolic syndrome and recent consensus opinion has proposed a change in nomenclature to 'metabolic associated fatty liver disease, MAFLD'.[14] NAFLD is found in approximately 70% of patients with type 2 diabetes mellitus (T2DM)[15] and 70% of adults with obesity.[16,17] Around 1 in 11 adults worldwide are thought to have diabetes, of which 90% is type 2 and this figure has more than tripled over 20 years.[18] NAFLD is also an independent risk factor for diabetes.[19] In addition, current estimates suggest 65% of adults in England are overweight or obese, with rates having more than doubled since the 1990s.[20,21]

Two meta-analyses have conclusively demonstrated a higher incidence of CKD in individuals with NAFLD (HR 1.37 and HR 1.79).[22,23] Patients with more advanced fatty liver disease, i.e. NASH or fibrosis are at the greatest risk of developing CKD. This association is independent of potential confounders (age, gender, body mass index, diabetes status, lipids, hypertension and smoking).[22,23] CKD is an accelerator of the risk of CVD and an independent risk factor for cardiovascular events (CVEs);[24–26] indeed individuals with CKD are more likely to die from CVD than develop ESRD.[27] NAFLD is also an

independent risk factor for major CVEs,[28–32] although there remains uncertainty regarding its association with an increase in all-cause and cardiac-related mortality, [31,33–35] despite patients with NAFLD being more likely to die from CVD than liver disease.[36,37]

CKD and NAFLD frequently exist together, yet there is a sparsity of data to inform physicians and patients about clinical outcomes in this setting. Understanding if NAFLD plays a role in accelerating progression towards death and adverse clinical outcomes in patients with CKD would help improve risk stratification; permitting more aggressive lifestyle intervention, targeted pharmacological management of shared risk factors and enrolment in clinical trials in this potentially high risk group. We therefore asked what evidence is there for the influence of NAFLD on the risk of mortality, CVEs and progression of kidney disease in patients with established CKD?

Methods

The protocol for this systematic review was registered on PROSPERO a priori (CRD42020166508) (supplementary material 1).

Data sources, searches and study selection

We performed a computerized literature search using PubMed, EMBASE (using Ovid) and Web of Science using the following search terms: *"(chronic kidney disease or CKD or kidney disease or kidney failure or kidney injury or chronic renal disease or renal disease or renal failure or renal injury or renal insufficiency or impaired renal function or glomerular filtration rate or eGFR) and (fatty liver or non-alcoholic fatty liver disease or NAFLD or nonalcoholic steatohepatitis or NASH or liver fat or steatohepatitis or steatosis or hepatic fibrosis)"* (full details in supplementary material 2). We aimed to identify observational (prospective or retrospective) cohort studies that reported either the risk of mortality, CVEs or progression of kidney disease among adults (> 18 years old) with established CKD who have NAFLD compared with those without. We also performed manual searches of reference lists of relevant studies returned by the initial search. No restriction was placed on the earliest search date and searches were performed up to the current date (February 2020). Exclusion criteria included abstracts, case reports, reviews, editorials, practice guidelines, non-cohort design, non-human studies and unpublished studies.

Study participants included adults with established CKD with evidence of the presence or absence of NAFLD. Studies were excluded if they included individuals under 18 years, individuals undergoing renal replacement therapy (RRT) at the start of the study, kidney or liver transplant recipients and individuals with a known other cause of chronic liver disease. CKD was defined as an eGFR ≥ 60 ml/min/1.73m^2 with ACR > 3 mg/mmol (stage G1 and G2), or eGFR < 60 ml/min/1.73m^2 (stages G3a – G5) calculated using the CKD Epidemiology Collaboration (CKD-EPI) or Modified Diet in Renal Disease (MDRD) formula. NAFLD was defined using either biochemistry (elevations in serum aspartate transaminase, alanine transaminase or gamma glutamyl transferase), imaging (ultrasound, computer tomography, magnetic resonance imaging), liver biopsy or non-invasive scores (Fatty Liver Index, Steatotest, NAFLD Liver Fat Score).

Primary outcomes included differences in the risk of all-cause mortality, CVEs and progression of kidney disease in patients with CKD who had NAFLD compared to those without NAFLD. All-cause mortality was defined as any cause of death within the study follow up period. Within this we aimed to look at cardiovascular and non-cardiovascular related deaths. A CVE was defined as any one of the following: acute coronary syndrome, myocardial infarction, non-fatal cardiac arrest, coronary revascularization, new diagnosis of cardiac failure, hospitalisation with an exacerbation of cardiac failure, new diagnosis of peripheral vascular disease, or new diagnosis of cerebrovascular accident (all non-fatal). Progression of CKD was defined as either (1) mean or percentage annual rate of change in the eGFR, or mean or percentage change from baseline, (2) a decline in eGFR category accompanied by a ≥ 25% drop in eGFR from baseline (KDIGO definition), (3) the development of ESRD (eGFR of < 15 ml/min/1.73m^2, or the requirement of some form of RRT), or (4) doubling of creatinine.[3,38] Secondary outcomes included: (1) the risk of CVEs, progression of kidney disease and all-cause mortality in patients with CKD according to the severity of NAFLD, as determined by the presence of NASH or fibrosis (defined using histology, imaging or non-invasive serum biomarkers), and (2) the risk of CVEs, progression of kidney disease and all-cause mortality in patients with CKD according to baseline severity of CKD, as determined by CKD stage. Included and excluded studies were collected following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram (figure 1).

Data extraction and quality assessment

Two investigators (TH and RB) screened all titles and abstracts independently using the Covidence software as recommended by Cochrane. They obtained the full texts of potentially relevant papers to determine if they met the inclusion criteria. Discrepancies were resolved by returning to the original

article to reach a consensus. Data extraction was performed by TH and checked by RB. For all studies data was extracted data on (1) general information (title, authors, journal, country, publication year), (2) study design (population source, demographics, period of follow up, means of defining NAFLD and CKD, inclusion and exclusion criteria, study size, subgroup analysis (including severity of NAFLD and baseline CKD), adjustment for confounding factors) and (3) outcomes examined for NAFLD versus non-NAFLD patients (all-cause mortality, CVE, progression of kidney disease, and definition used, in addition to odds ratio, hazards ratio (HR), relative risk and 95% confidence intervals; or mean or percentage annual rate of change in the eGFR). Where there were multiple publications, we included the most up-to-date or comprehensive information.

The risk of bias was assessed independently by TH and RB. The results were then discussed to reach consensus. We used the Newcastle-Ottawa Score as recommended by Cochrane for the assessment of quality for non-randomised cohort studies.[39] This tool uses a star based system allocating a maximum of 9 points across three domains: (1) selection of study groups (max 4 points), (2) comparability of groups (max 2 points), (3) ascertainment of exposure and outcomes (max 3 points). Studies with an overall score of 9 are judged to be at a low risk of bias, those scoring 7-8 a moderate risk of bias and scores of 6 of less a high risk of bias. Where studies reported more than one primary outcome a separate bias assessment was performed for each.

Patient and public involvement

Patients or the public were not involved in the design, conduct, reporting or dissemination plans of our research.

Results

Details of the study selection process

The process for selecting the studies for inclusion in this systematic review is shown in figure 1. The searches returned 4,339 studies. Overall 1,735 duplicates were removed, leaving 2,604 citations for screening. TH and RB separately reviewed titles and abstracts and identified six potentially relevant studies. The most frequently encountered exclusion criteria were abstract only citations, laboratory-based or animal studies, review articles, studies of paediatric populations (eg polycystic kidney disease, Caroli's syndrome), studies which included transplant recipients, patients receiving RRT and

populations with non-NAFLD causes of liver disease, and publications for which the development of CKD was the outcome (eg those reporting the incidence of CKD in patients with NAFLD). After examination of the full texts (supplementary material 3), only three cohort studies remained and were included (figure 1).[40–42] As a result of the low number of studies identified, and the fact that primary outcomes reported differed between papers, we did not have sufficient data to perform a meta-analysis.

Characteristics of the included studies

Of the three studies, one recruited patients seen in a renal tertiary referral centre in Salford, UK (Chinnadurai et al, n=852, median follow up 5.4 years),[40] the second recruited individuals attending for comprehensive health screening at a preventive medical centre in South Korea (Jang et al, n=1,525, median follow up 6.5 years),[41] and the third presents results from a retrospective analysis of baseline cross-sectional data collected from the third National Health and Nutrition Examination Survey (NHANES) (United States, US) over time (Paik et al, n=1,413, median follow-up 19.2 years) (**Table 1**).[42]

Liver ultrasound was used to detect NAFLD in all three studies. Prevalence rates of NAFLD were highest in the Korean cohort (41%), compared to the UK (21%) and US (29%) populations, however the US group only included patients with moderate or severe steatosis. CKD was defined using the CKD-EPI equation in all papers; the Salford and US studies only included patients with CKD stage 3 and above (eGFR < 60 mL/min/1.73 m^2), whereas the Korean group also included patients with ≥ 2+ proteinuria, i.e. CKD stage 1 and above. As a result mean baseline eGFR levels were nearly double in the Korean cohort compared to the Salford study (59.1 vs 33.5 mL/min/1.73 m^2). In terms of demographics, the Salford group was slightly older, and the US group included a higher frequency of individuals with metabolic risk factors and was predominantly female in contrast to the other studies.

The influence of NAFLD on clinical outcomes in patients with CKD

(1) Mortality

Two publications analysed the impact of NAFLD on mortality within the CKD population. The Salford group concluded that CKD patients with NAFLD were not at higher risk of all-cause (NAFLD 27.3% vs no NAFLD 33.0%, p=0.14; unadjusted HR 0.79 [0.58-1.08]) or cardiovascular-related mortality (NAFLD 31.3% vs no NAFLD 40.5%, p=0.36), despite experiencing more non-fatal CVEs (**Table 2**). Significance

outcomes were unchanged in the propensity matched sample. The US based study reported an increase in overall mortality for CKD patients with NAFLD compared to those without (54.7% vs 46.5%, p<0.05). Statistical significance was lost however when adjusted for age and following multivariate analysis (p=ns when comparing adjusted HRs), and no significant impact was seen for NAFLD on cardiovascular-related mortality (16.0% NAFLD vs 16.2% no NAFLD). No significant association between advanced fibrosis and all-cause or cardiovascular-related mortality was seen for patients with NAFLD and CKD within the US cohort.

(2) Non-fatal cardiovascular events

The Salford group published the only study to analyse the incidence of non-fatal CVEs. A higher frequency of non-fatal CVEs was seen in patients with NAFLD vs those without NAFLD (25.1% vs 12.3%; p<0.001) over an average of 5 years (**Table 2**). Cox regression analysis revealed NAFLD to be strongly associated with the incidence of non-fatal CVEs in CKD patients (HR 2.07 [1.39-3.09], p<0.001). This remained the case following multivariate analysis for all confounders in the propensity-matched cohort (HR 2.00 [1.10-3.66], p=0.02). Significant differences were also reported between groups according to the type of CVE (cardiac events p=0.02, cerebrovascular events p=0.04, cardiac failure p=0.005), although individually significance values were lost following adjustment for confounders.

(3) Progression of CKD

The Salford and Korean groups analysed the impact of NAFLD on CKD progression. Both examined decline in eGFR; the Salford group presented this as rate of change of eGFR from baseline to the study end-point, whereas the Korean study examined the average percentage change in eGFR from baseline per year (**Table 2**). The Salford group reported a decline in the eGFR slope for patients with and without NAFLD (-2.54 vs -2.09 mL/min/1.73 m^2) over the course of the study, however no statistically significant differences were detected between groups (p=0.09). Conversely a greater rate of decline in the eGFR slope in patients with NAFLD vs those without, was seen in the Korean study (−0.79% vs 0.30% per year, p=0.002). This relationship remained significant after adjustment for all confounders (average difference in percentage decline of eGFR per year for NAFLD vs no NAFLD: -1.06%, p=0.002). The Salford group also reported no correlation between the presence of NAFLD and the development of ESRD (commencement of RRT or eGFR <10 mL/min/1.73 m^2). In terms of our secondary outcomes, the Korean group reported that patients with a NAFLD fibrosis score ≥ −1.455 and more advanced renal disease at baseline (eGFR < 45 ml/min/1.73 m^2) experienced the greatest average difference in

annual percent changes in eGFR compared to individuals without NAFLD, although the significance of a low baseline eGFR was lost following adjustment for all metabolic confounders (**Table 2**).

Discussion

Summary of findings

The key finding of this systematic review is the identification of a significant gap in the literature within this field. Only three studies examining the clinical impact or prognostic implications of NAFLD within the CKD population were identified preventing further meta-analysis and results were conflicting. Data from the US showed a significant association for NAFLD with all-cause (but not cardiovascular) mortality for individuals with CKD, although this relationship was lost following adjustment for age and metabolic risk factors.[42] No effect on all-cause or cardiovascular-related mortality was observed within the Salford CKD cohort despite the authors identifying NAFLD to be a strong independent risk factor for non-fatal CVEs and a high percentage of patients having significant co-morbidities.[40] Possible explanations include a significantly longer follow-up period for the US group. In addition the US study only included patients with moderate or severe steatosis, suggesting that perhaps the association between NAFLD and mortality is related to the degree of fat, and subsequent inflammation in the liver. The same group found no association between advanced fibrosis and mortality in this cohort however.[42]

Data was also conflicting for the progression of kidney disease. The Korean group reported a significantly greater adjusted rate of percentage decline in eGFR per year for patients with CKD and NAFLD, compared to individuals with CKD without NAFLD,[41] whereas the Salford study reported a non-significant trend in CKD progression for individuals with NAFLD versus those without, and no differences were seen for the incidence of ESRD.[40] The cause of these discrepancies is unclear, particularly given that participants in the Salford cohort had a lower baseline eGFR,[40] which was found to be associated with a greater rate of decline in renal function in the Korean study.[41] The incidence of ESRD was low in the Salford cohort, and the study may have been under-powered for this outcome. Of note the authors of the Salford study published a related paper examining the impact of NAFLD on mortality rates, incidence of non-fatal CVEs and progression of CKD in patients with diabetic kidney disease and reported similar findings.[43] This represented a subgroup of the main Salford cohort and therefore was excluded from this review.

Possible pathophysiological mechanisms linking NAFLD and clinical outcomes for CKD

Broadly the findings from this review mirror findings in the general population where NAFLD is an accepted risk factor for CVEs,[28–32] with debate over whether it is associated with all-cause and cardiovascular mortality. These are summarised in figure 2.[31,33–35] Several mechanisms may explain the influence of NAFLD on CKD incidence and progression, and the development of CVEs within this cohort beyond their shared cardiometabolic risk factors. NAFLD can exacerbate insulin resistance leading to the release of multiple pro-inflammatory, pro-oxidant and pro-fibrogenic mediators important in the pathogenesis of both CKD and CVD.[44,45] Insulin resistance can lead to activation of the renin-angiotensin system and atherogenic dyslipidaemia, key drivers of renal and vascular damage. Steatohepatitis can potentiate the production of inflammatory mediators including reactive oxygen species, cytokines and lipopolysaccharides, exacerbating insulin resistance, tissue inflammation and endothelial damage. None of the studies included in this review reported the prevalence rates of NASH in their cohorts, and this could be a significant factor accounting for the variation observed between study outcomes. Other emerging mechanistic links between NAFLD and CKD include impaired antioxidant defences, abnormal metabolism of lipoproteins, altered intestinal barrier integrity, dysbiosis of intestinal microbiota and dietary factors.[10]

Study strengths and limitations

This is the only systematic review to date to examine the influence of NAFLD on serious adverse clinical outcomes for patients with CKD. Our study benefits from a broad definition of NAFLD and CKD with a number of primary outcomes and no restriction on publication date, with the purpose of maximising the number of papers retrieved. All studies were judged to be of a low or moderate risk of bias (supplementary material 4) and recruited over 800 participants; they spanned three continents and were matched in terms of using ultrasound as their means of diagnosing NAFLD, which is recommended for first line screening.[46]

There are limitations associated with this review. Only three studies met our inclusion criteria, recruiting under 4000 individuals with CKD between them. We chose to limit the inclusion criteria to cohort studies as a temporal element is imperative to establish potential causality and to answer the prognostic question raised. This is essential in order to draw conclusions that may have had the potential to influence practice and benefit patients, had a larger number of papers been identified. Understanding whether NAFLD should be considered a clinically relevant risk factor for adverse

outcomes within the CKD population would have implications for whether CKD patients who develop NAFLD should undergo more rigorous follow up and intervention, and may have raised the question of whether the CKD population should undergo routine screening for NAFLD. Of note during the systematic review process we identified only one cross-sectional study which would have otherwise met our inclusion criteria. This reported a negative correlation between the severity of hepatic steatosis, determined by controlled attenuation parameter, and eGFR in 62 patients with CKD stages 3 and 4 ($r=-0.413$; $p<0.01$).[47] Studies which examined the impact of having CKD for patients with NAFLD were also not included within this review, as while this represents a group with the same dual morbidity, it raises a separate prognostic question with different implications for clinical practice. Observational studies show consensus that CKD is associated with increased all-cause and cardiovascular-related mortality in patients with NAFLD, however there is disagreement regarding whether this effect is independent of metabolic confounders and mediators.[42,48,49] Individuals receiving RRT were also excluded given their unique pathophysiology; although evidence suggests that these patients are more likely to have CVD and experience non-fatal CVEs in the presence of NAFLD.[50–52]

In addition, significant variability was encountered in terms of method of recruitment for participants with CKD, definitions of CKD and NAFLD employed, outcomes assessed and method of adjustment for co-variates. The use of ultrasound for the detection of NAFLD introduced bias, as patients with CKD without an indication for a liver ultrasound scan were excluded. Patients with a pre-existing background of CVD were also included in both studies which examined the influence of NAFLD on mortality. None of the studies looked at the incidence of non-fatal and fatal CVEs in combination which is highly clinically relevant should represent an important end-point for future prospective studies.

Supporting literature and importance of research topic

Our findings highlight a potential interplay between NAFLD and CKD and clinical outcomes. This represents an extremely important topic for future research for a number of reasons. Firstly the incidence of both CKD and NAFLD is rising.[10–12] The prevalence risk of CKD among individuals with NAFLD is estimated to be two fold higher compared to individuals without NAFLD[22] and reported prevalence rates of NAFLD within CKD cohorts vary from 21%-86%.[40,41,47] The number of individuals in the US with both NAFLD and renal insufficiency was estimated to be 18.7 million persons in 2016 (prevalence rates 7.7% up from 5.7% in 1999).[48] CKD and NAFLD are profoundly linked to health inequalities globally. This is particularly apparent in advanced disease as a result of disparities in access

to treatment, increased burden of lifestyle-related risk factors and the influence of socio-economic status and ethnicity on disease progression.[53–55] The development of end-stage disease also accounts for the overwhelming majority of healthcare costs for patients with kidney disease, with more than half of the CKD budget in England being spent on RRT, and the cost of excess strokes and myocardial infarctions in this population estimated to be £178 million.[56] Avoiding progression towards ESRD and cardiovascular complications associated with CKD via the recognition and management of NAFLD as a potential high risk co-morbidity could therefore be important to reduce these burdens.

Future research and implications for clinical practice

These findings emphasise a need for large prospective collaborative studies to better understand the clinical and prognostic implications for patients who have both CKD and NAFLD. Outcomes should include mortality, CVEs and CKD progression. Patients with NAFLD should also be assessed for NASH and advanced fibrosis. Large routinely collected datasets linked to clinical outcomes maybe less useful in this setting as NAFLD screening is likely to lack robust assessment of inflammation or markers of fibrosis (serum biomarkers, transient elastography and histology), instead being reliant on liver enzymes or simple ultrasound scan. It would also be beneficial to examine is there is an association with NAFLD and acute kidney injury outside the setting of cirrhosis. Other potential research opportunities include understanding the implications of having both CKD and NAFLD-related fibrosis or cirrhosis on drug metabolism. Furthermore shared pathophysiological pathways involving pro-inflammatory mediators, oxidative stress and the gut microbiome present promising therapeutic targets for both NAFLD, CKD and CVD within a co-morbid setting.[44,57]

Approximately 40,000–45,000 individuals with CKD die prematurely each year in England, primarily due to CVD.[58,59] There are currently no recommendations to screen for NAFLD in patients with CKD due to a lack of supportive evidence in terms of prevalence, outcomes and cost-effectiveness. However patients with CKD undergo annual health checks in primary care. Identification of the metabolic syndrome, T2DM and obesity should prompt ultrasound screening for NAFLD in accordance with current guidelines.[46,60] Awareness of these guidelines may be low within this setting currently. Liver enzymes are frequently normal in patients with NAFLD, especially those with CKD and should not be used to rule out liver disease.[40,41,47] Few specific treatments delay the clinical course of CKD, so the identification of NAFLD as a potential risk factor for future adverse events will hopefully provide a further modifiable target for lifestyle (physical activity, Mediterranean diet) or pharmacological intervention (vitamin E, pioglitazone and newer agents).[46,60] Current UK guidelines suggest all patients

with NAFLD should be assessed for advanced fibrosis using the Enhanced Liver Fibrosis score,[46] and this should also be the case for CKD patients where liver fibrosis has implications for CKD progression and mortality.[41,48] Patients with NAFLD will nearly certainly have an eGFR performed as part of their routine care, however it is vital that the clinical implications of an abnormal value are appreciated.[42,48,49] Encouragingly weight loss, currently the only proven effective intervention for patients with NAFLD,[61] can reduce the incidence of CKD in this cohort,[62] and improve renal function in individuals with biopsy-proven NASH.[63]

Summary

This systematic review has identified a significant gap in the literature regarding the clinical outcomes and prognostic implications of NAFLD within the CKD population. Studies are conflicting regarding an association between NAFLD and CKD progression and mortality in this cohort. While data suggests a positive correlation with non-fatal CVEs only one study has examined this outcome to date. The prevalence of NAFLD and CKD are rising and are frequently found together. It is therefore vital to understand if there is any synergism in terms of CVD risk, progression towards ESRD and death which would inform the need for aggressive intervention in this potentially high risk group.

Contributorship statement

TH, JP, PR, SF and OK were responsible for the study concept and design; TH and RB performed the searches and screened the papers; TH performed the data extraction which was checked by RB and drafted the manuscript; JP, PR, SF, OK and RB edited the revised manuscript.

Competing interests statement

None of authors have any competing interests

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Data sharing statement

Data was obtained from previously published cohort studies which are accessible to the public via the journals cited in this review.

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Figure legends

Figure 1. A schematic showing the selection of relevant studies for inclusion in the systematic review

Figure 2. A summary of the evidence linking the clinical outcomes for chronic kidney disease and non-alcoholic fatty liver disease.

Acknowledgements

None

Table 1. Summary of study characteristics (n=3)

Study	Chinnadurai et al. *Nephrol Dial Transplant* (2019)[40]	Jang et al. *Scientific report* (2018)[41]	Paik et al. *Liver International* (2019)[42]
Country	United Kingdom	South Korea	United States
Median follow up	5.4 years	6.5 years	19.2 years
Years	Liver USS (01/01/2000 - 31/12/2014), end of analysis period 31/12/2015	January 2003 - December 2013	NHANES III 1988 – 1994 Linked mortality files up to 2011 or date of death
Population source	Salford Kidney Study	Individuals who had health screening at the Samsung Medical Centre, South Korea	Third National Health and Nutrition Examination Survey (NHANES) & linked mortality database
Study size	852 CKD patients	1,525 CKD patients	1,413 CKD patients (11,695 adults overall: (i) CKD+NAFLD+ 2.6%, (ii) CKD+NAFLD- 6.8%, (iii) CKD-NAFLD+ 16.1%, (iv) CKD-NAFLD- 74.6%)
Demographics	Mean age 66 years, males 60.7%, mean BMI 28, DM 34%, HTN 78%, hyperlipidaemia 49%, median eGFR 33.5 mL/min/1.73 m^2	Mean age 61 years, males 69.8%, mean BMI 25, DM 24%, HTN 60%, hyperlipidaemia 41%, median eGFR 59.1 mL/min/1.73 m^2	*CKD with NAFLD:* Mean age 54 years, males 45.6%, obesity 52.2%, DM 43.2%, HTN 77.4%, hyperlipidaemia 86.9% *CKD without NAFLD*: Mean age 53 years, males 36.1%, obesity 30.0%, DM 16.8%, HTN 66.4%, hyperlipidaemia 81.7%
NAFLD prevalence	21% (183/852)	41% (902/1,525)	29% (413/1,413)
NAFLD definition	Liver ultrasound scan	Liver ultrasound scan	Liver ultrasound (moderate / severe steatosis only)
CKD definition	eGFR <60 ml/min/1.73m^2	eGFR <60 ml/min/1.73m^2 or proteinuria ≥ 2+	eGFR <60 ml/min/1.73m^2 +/- albuminuria
Co-variate adjustments	Propensity matching (n=276) for: age, gender, BMI, SBP, DBP, baseline HTN, DM, hypercholesterolaemia, IHD, MI, CCF, CVA, PVD, malignancy, use of statin & renin–angiotensin blocking agents, eGFR	Stratified analyses according to pre-defined subgroups: age (<60 vs ≥ 60 yrs), gender, smoking (never/former vs current), alcohol (none vs moderate), BMI ≥ 25, HTN (SBP ≥ 140 mmHg / DBP ≥ 90 mmHg / use antihypertensives), DM (fasting glucose ≥ 126 mg/dl / HbA1c ≥ 6.5% / use antidiabetic drugs), hyperlipidaemia (HDL < 40 mg/dl men, < 50 mg/dl women / TG ≥ 150 mg/dl / use lipid-lowering drugs) & baseline eGFR (<45 vs ≥ 45 ml/min/1.73 m^2)	Age-adjustment based on the direct method to the Census 2000 population using the age groups 20-39, 40-59 & 60-74. Groups adjusted for the following in multivariable analysis: age category, gender, race, current smoker & the metabolic syndrome.

CKD: chronic kidney disease, NAFLD: non-alcoholic fatty liver disease, BMI: body mass index, DM: diabetes, HTN: hypertension, eGFR: estimated glomerular filtration rate, SBP: systolic blood pressure, DBP: diastolic blood pressure, IHD: ischaemic heart disease, MI: myocardial infarction, CCF: congestive cardiac failure, CVA: cerebrovascular accident, PVD: peripheral vascular disease, HDL: high density lipoprotein, TG: triglycerides, USS: Ultrasound scan

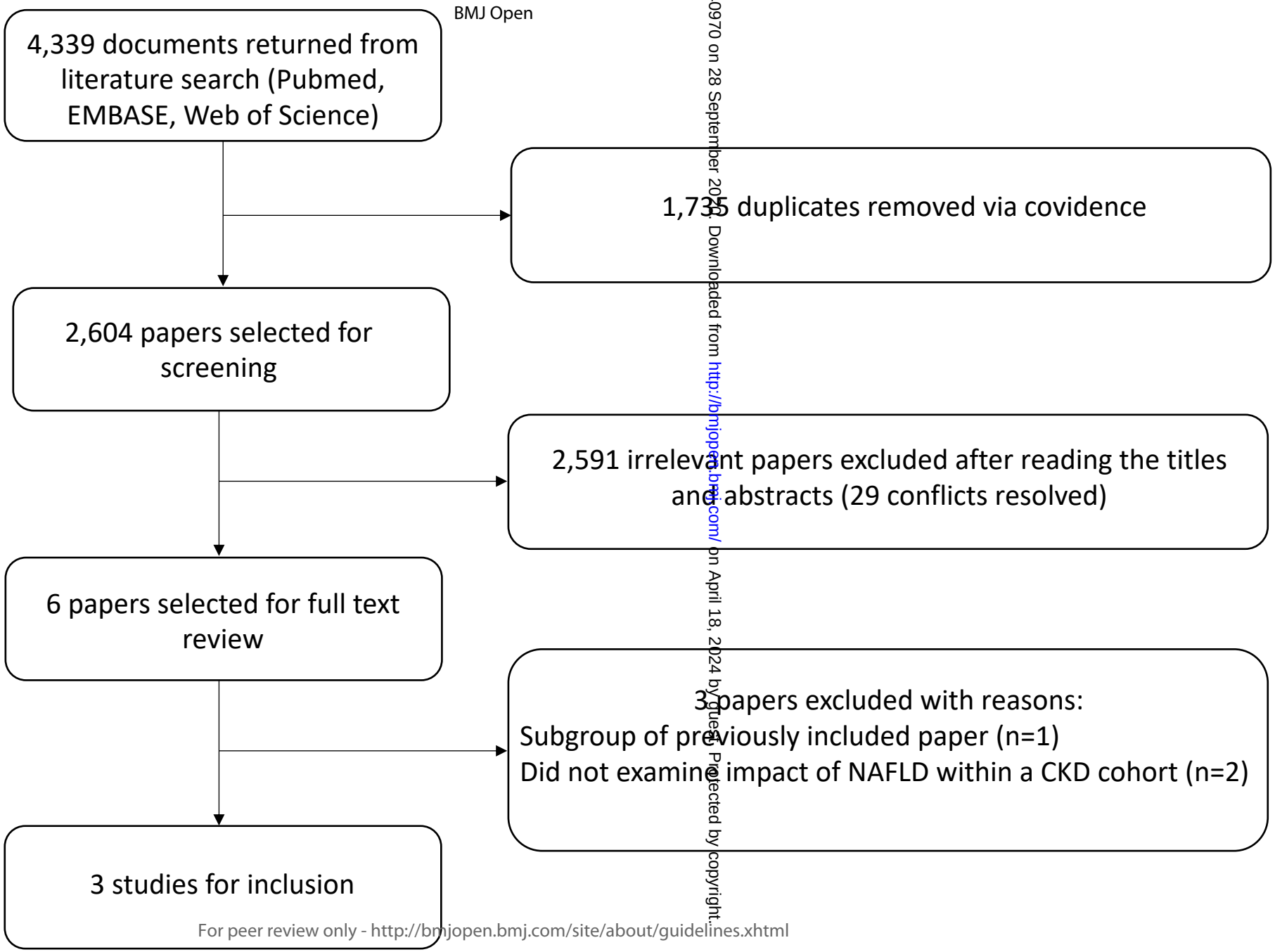
Table 2. Summary of study outcomes (n=3)

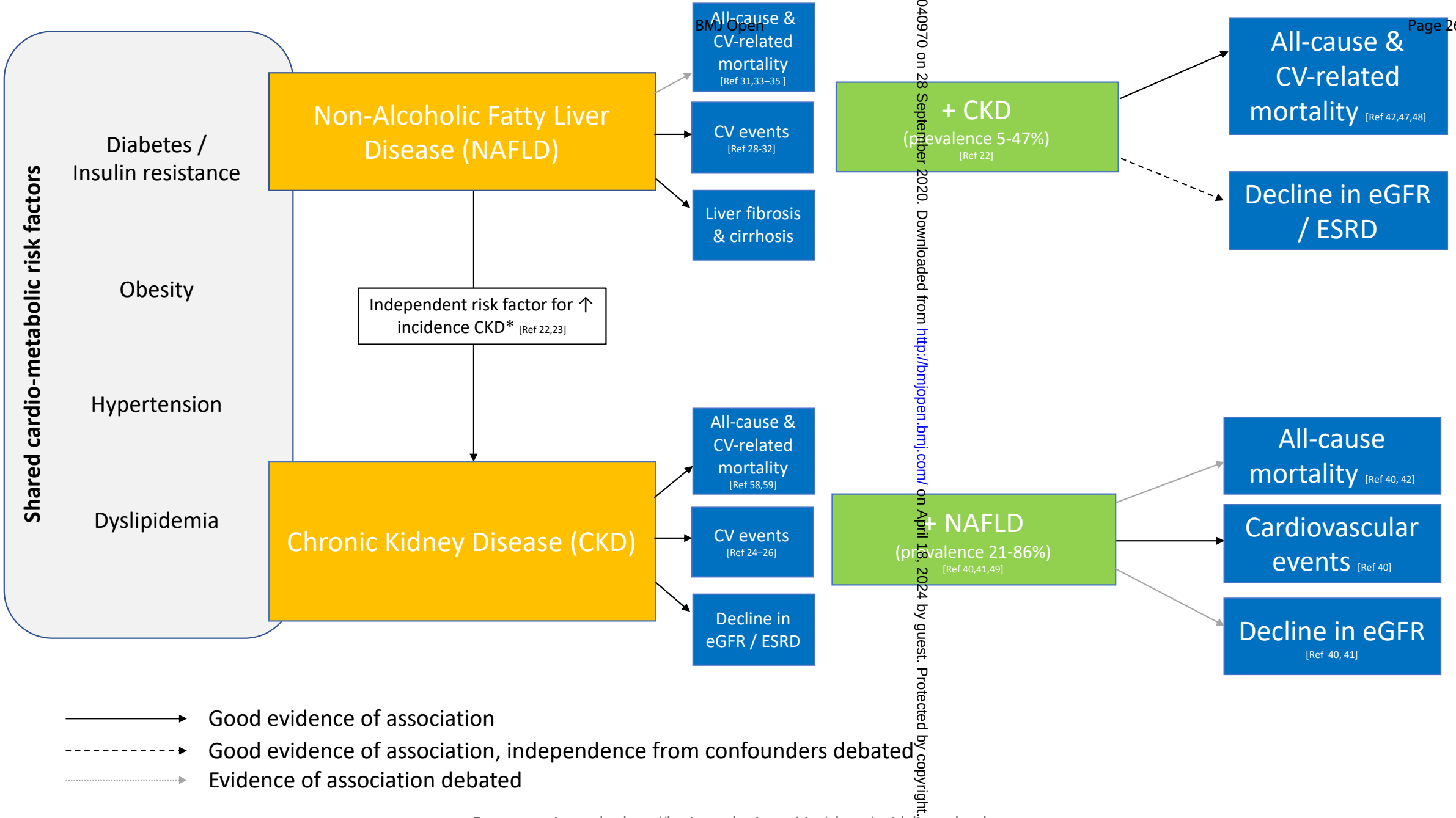
Study	Chinnadurai et al. *Nephrol Dial Transplant* (2019)[40]	Jang et al. *Scientific reports* (2018)[41]	Paik et al. *Liver International* (2019)[42]
Primary outcomes & definition	*(1) ESRD:* commencement of RRT or eGFR <10 mL/min/1.73 m^2 *(2) CKD progression*: rate of change of eGFR from baseline to study end-point (3) *NFCVE:* composite of ACS, non-fatal MIs, non-fatal cardiac arrest, coronary revascularization, new diagnosis CCF / admission with exacerbation of CCF, new diagnosis of PVD, CVAs (4) *All-cause mortality* *(5) Cardiovascular-related mortality:* Ia cause of death was due to cardiac event, CVA, CCF or PVD	(1) *CKD progression*: average annual percent change in eGFR from baseline	(1) *All-cause mortality* (2) *Cardiovascular-related mortality:* death due to heart diseases (ICD-10: I00-I09, I11, I13, I20-I51) & cerebrovascular diseases (ICD-10: I60-I69)
Secondary outcomes & definition	None	(1) *NAFLD severity according to NFS*: high-intermediate (NFS ≥ −1.455) & low probability (NFS < −1.455) of advanced fibrosis (2) *Severity of CKD at baseline*: eGFR ≥45 ml/min/1.73 m^2 vs <45 ml/min/1.73 m^2 (dividing stages 3a & 3b)	(1) *Presence of advanced liver fibrosis:* ≥ 1 of the following fibrosis markers – APRI > 1, FIB-4 score > 2.67 or NFS > 0.676
Cases	(1) *ESRD*: NAFLD n=26 (14.2%), no NAFLD n=134 (19.1%), p=0.07 (2) *CKD progression*: NAFLD -2.54 [-7.61 - 0.31] mL/min/1.73 m^2, no NAFLD -2.09 [-6.14 - 1.06] mL/min/1.73 m^2 (3) *NFCVE:* NAFLD n=46 (25.1%), no NAFLD n=82 (12.3%), p<0.001 (4) *All-cause mortality*: NAFLD n=50 (27.3%), no NAFLD n=221 (33.0%), p=0.14	(1) *Average annual percent change in eGFR from baseline:* NAFLD -0.79% [-1.31 - -0.27], no NAFLD 0.30% [-0.14 - 0.76] (2) *Average difference in % decline of eGFR per year NAFLD vs no NAFLD:* (i) Adjusted for age, sex, year of visit: -1.09% [-1.77 - -0.41] (ii) Adjusted for all confounders: -1.06% [-1.73 - -0.38]	(1) *All-cause mortality:* NAFLD 54.7% (SE 3.6), no NAFLD 46.5% (SE 2.4), p<0.05 (age adjusted: NAFLD 31.0% [25.0-37.0], no NAFLD 25.9% [22.0-29.7], p=ns) (2) *Cardiovascular-related mortality:* NAFLD 16.0% (SE 2.5), no NAFLD 16.2% (SE 1.7), p=ns (age adjusted: NAFLD 7.8% [3.7-11.9], no NAFLD 8.2% [5.6-10.9], p=ns)

	(5) *Cardiovascular-related mortality:* NAFLD n=10 (31.3%), no NAFLD n=67 (40.5%), p=0.36		
Risk of bias Newcastle Ottawa Score (NOS)	Mortality NOS = 8, non-fatal CVE NOS = 8, CKD progression NOS = 9	NOS = 9	NOS = 7
Primary outcome results	(1) *ESRD:* total sample HR 0.99 [0.65–1.52], p=0.90; matched HR 0.64 [0.35-1.16], p=0.145 (2) *CKD progression*: total sample p=0.09; matched p=0.58 (3) *NFCVE:* total sample HR 2.07 [1.39-3.09], p<0.001; matched HR 1.85 [1.04-3.30], p=0.04 (multivariate: total sample HR 2.03 [1.33-3.13], p<0.001; matched HR 2.00 [1.10-3.66], p=0.02) (4) *All-cause mortality*: total sample HR 0.79 [0.58-1.08], p=0.14; matched HR 0.88 [0.57–1.34], p=0.54 (5) *Cardiovascular-related mortality:* HR not published	*Average difference in % decline of eGFR per year NAFLD vs no NAFLD:* (i) Adjusted for age, sex, year of visit: p=0.002 (ii) Adjusted for all confounders: p=0.002	(1) *All-cause mortality:* CKD+NAFLD+ vs no CKD/NAFLD adjusted HR 2.34 [1.91-2.87], CKD+NAFLD- HR vs no CKD/NAFLD adjusted HR 2.08 [1.80-2.40], p=ns (2) *Cardiovascular-related mortality:* CKD+NAFLD+ vs no CKD/NAFLD adjusted HR 2.12 [1.44-3.13], CKD+NAFLD- HR vs no CKD/NAFLD adjusted HR 2.43 [1.8-3.28], p=ns
Secondary outcome results	None	(1) *Adjusted average difference in annual % change in eGFR:* low NFS vs no NAFLD 0.01% [−0.74 - 0.99]; high-intermediate NFS vs no NAFLD −2.12% [−2.93 - −1.31], p<0.0001 (2) *Adjusted average difference in annual % change in eGFR among patients with eGFR < 45 ml/min/1.73 m² at baseline for patients with NAFLD vs those without*: -5.61% [-11.43 – 0.59], p=0.075.	(1) *CKD + NAFLD + advanced fibrosis (n=60)* All-cause mortality: 73.1% [50.7-95.5], p=ns vs no advanced fibrosis; adjusted HR 3.49 [2.25-5.43], p=ns vs no advanced fibrosis Cardiovascular-related mortality: 14.6% [1.6-27.7], p=ns vs no advanced fibrosis; adjusted HR 2.83 [0.69-11.51], p=ns vs no advanced fibrosis (2) *CKD + NAFLD + no advanced fibrosis (n=97)* All-cause mortality: 52.1% [44.8-59.3]; adjusted HR 2.51 [1.98-3.18] Cardiovascular-related mortality: 16.5% [11.1-21.9]; adjusted HR 2.45 [1.61-3.73]

CKD: chronic kidney disease, ESRD: End-stage renal disease, RRT: renal replacement therapy, NFCVE: non-fatal cardiovascular event, ACS: acute coronary syndrome, MI: myocardial infarction, CCF: congestive cardiac failure, PVD: peripheral vascular disease, CVA: cerebrovascular accident, NAFLD: non-alcoholic fatty liver disease, HR: hazard ratio, NFS: NAFLD fibrosis score, APRI: AST to platelet ratio index, FIB-4, fibrosis-4, SE: standard error

95% confidence intervals are shown in square brackets.





* Predictors: hepatic fibrosis, age, male, obesity, hypertension, diabetes, dyslipidaemia, cardiovascular disease

Study Protocol

Background

Chronic kidney disease (CKD) is a long-standing condition resulting in impaired renal function associated with a reduced quality of life, increased risk of end-stage renal disease (ESRD), cardiovascular disease and premature death.(1) CKD is classified according to five stages largely based on estimated Glomerular Filtration Rate (eGFR), although persistent albuminuria also determines prognosis.(2) Moderate-severe CKD (stage 3-5) is defined as an eGFR of less than 60ml/min/1.73m^2 for more than 3 months. According to the Quality Outcomes Framework and Health Survey for England 2016 around 4-7% of UK adults have CKD stages 3-5.(3,4) The disease burden is particularly high in the elderly.(3) The global prevalence of CKD is higher at 11% for stages 3-5,(5) and it is estimated that the absolute global prevalence increased by 27% from 2007-2019.(6) CKD is forecasted to move from 16th (2016) to 5th (2040) in the rankings for years of life lost, predominantly as a result of aging, but also due to an increase in the prevalence of metabolic risk factors.(7) In addition to increasing age, hypertension, diabetes and obesity are major disease risk factors accounting for the majority of newly diagnosed cases of CKD in the developed world.(8,9) In terms of prognosis, it is estimated that 40,000–45,000 individuals with CKD die prematurely each year in England, with cardiovascular disease being the primary cause of morbidity and mortality.(10) The rate for individuals over 65 with CKD to progress to ESRD is reported to be 0.5 per 100 person-years and 6.8 per 100 person-years for all-cause mortality (3.0 for cardiovascular and 3.8 for non-cardiovascular mortality), i.e. patients with CKD are more likely to die from cardiovascular disease than develop ESRD.(11) CKD is both an accelerator of the risk of cardiovascular disease and an independent risk factor for cardiovascular events,(12–14) and is thought to account for 7000 extra strokes and 12,000 extra myocardial infarctions (MI) per year.(15)

Non-alcoholic fatty liver disease (NAFLD) refers to excessive fat accumulation in the liver affecting more than 5% of hepatocytes or liver volume. NAFLD is the most common cause of chronic liver disease worldwide, affecting approximately 25% of the adult population globally and in Europe.(16) It is expected to become the leading indication for liver transplantation in the next decade. It is estimated 90% of patients with type 2 diabetes mellitus (T2DM) have NAFLD, along with 70% of adults with obesity (17) and 90% of individuals who qualify for bariatric surgery.(18) While there is a lack of large prospective data in this field, paired liver biopsy studies from tertiary care suggest that around 23% of patients with simple steatosis are likely to develop non-alcoholic steatohepatitis (NASH) (hepatocytes injury (ballooning) and necro-inflammation) over a 3 year period, (19) and 44% over an average 8 year period.(20) Overall up to 30% of individuals with NAFLD are thought to have NASH,(21) and this is associated with a 25% risk of progression to cirrhosis over a 10 year period.(22) There is also evidence that NASH can lead to an elevated risk of hepatocellular carcinoma (HCC) even in the absence of cirrhosis.(23)

NAFLD and CKD share several cardiometabolic risk factors, many of which have now reached epidemic levels in the UK.(24) Current estimates suggest that 35.6% of adults in England are overweight and a further 28.7% are obese, with rates having more than doubled since 1991.(25,26) Around 1 in 11 adults worldwide (463 million) are thought to have diabetes, of which 90% is type 2.(27) This figure has more than tripled over the past 20 years, making diabetes one of the fastest growing health challenges of the 21st century.(27) Approximately 9% of men and 7% of women have diabetes in England,(28) however prevalence rates are as high as 25-30% in Pacific nations, followed by the Middle East and North Africa.(29) The International Diabetes Federation project the number of adults with diabetes worldwide will rise to 700 million by 2045, with the largest increases coming from regions experiencing economic transitions from low-income to middle-income levels.(27) While the prevalence of hypertension remains static it affects 30% of men and 26% of women.(28) Of huge concern is the fact that 22% and 34% of children starting primary school and secondary school

respectively are either overweight or obese.(30) While the incidence of T2DM for those under 17 years old in the UK remains low at 0.72 per 100,000 / year (2015/16), the number of cases diagnosed per year continues to rise,(31) and prevalence rates are significantly higher in the United States.(32)

It is well established that individuals with NAFLD are at increased risk of mortality from liver disease, cardiovascular disease and cancer (HCC and extra-hepatic) (33,34) however its association with kidney disease and its outcomes are less well understood. Two systematic reviews have now conclusively demonstrated a higher risk of incident CKD in individuals with NAFLD (hazard ratio (HR) 1.37 [95% CI 1.20-1.53] and 1.79 [95% CI 1.65-1.95].(35,36) Both reviews report that patients with more advanced fatty liver disease, i.e. NASH or hepatic fibrosis are at the greatest risk. Surprisingly this association has been consistently found to be independent of common risk factors and potential confounders, for example age, gender, body mass index, diabetes status, lipids, hypertension and smoking.(35,36) Of note NAFLD is also thought to be an independent risk factor for cardiovascular disease.(37) It has therefore been proposed that shared proinflammatory, prothrombotic and profibrotic molecular pathways may play a mediating role, in addition to the fact that NAFLD itself exacerbates insulin resistance, leading to atherogenic dyslipidaemia.(24) No causal link has been definitively demonstrated, however lifestyle modification has been shown not only to improve NAFLD histology but also kidney function in patients with biopsy proven NASH.(38). It is important to note that this association may manifest itself at an early stage, as children with NAFLD have been found to be at increased risk of developing renal dysfunction.(39) NAFLD is estimated to affect 3-10% of children worldwide.(40) It is possible that children and young adults with NAFLD may be at risk of an accelerated disease course in terms of cardiovascular complications, liver disease and kidney disease, especially given the increasing prevalence of shared cardiometabolic risk factors experienced by this age group.

We are interested in whether the presence of NAFLD predisposes individuals with CKD to be at increased risk of cardiovascular events, progression of kidney disease and all-cause mortality (figure 1). A brief review of the literature has revealed two cohort studies from the same group which used data from the Salford Kidney Study database.(41,42) The first follows 1,148 patients with CKD who also had a liver ultrasound to look for hepatic steatosis, for a median of 5.4 years.(41) They concluded that NAFLD was a strong independent risk factor for cardiovascular events (HR 2.03) (even in advanced CKD associated with high levels of comorbidity), but was not associated with all-cause mortality (HR 0.79) or CKD progression (p=0.09 for the rate of decline of the eGFR slope). The second study was confined to diabetic patients with CKD (n=149) and demonstrated comparable findings.(42) A third study from South Korea reported a greater rate of decline in eGFR in patients with NAFLD vs those without (−0.79% [−1.31% - −0.27%] vs 0.30% [−0.14% - 0.76%], p=0.002) in a cohort of 1,525 individuals with CKD.(43) Differences persisted in a multivariable adjusted model demonstrating that NAFLD is independently associated with CKD progression. Similarly in the haemo- and peritoneal dialysis population, patients with NAFLD have been found to have significantly worse cardiovascular outcomes.(44–46) Within NAFLD cohorts, CKD is associated with increased overall mortality, however there is disagreement regarding whether this is independent or due to the greater prevalence of metabolic comorbidities.(47,48)

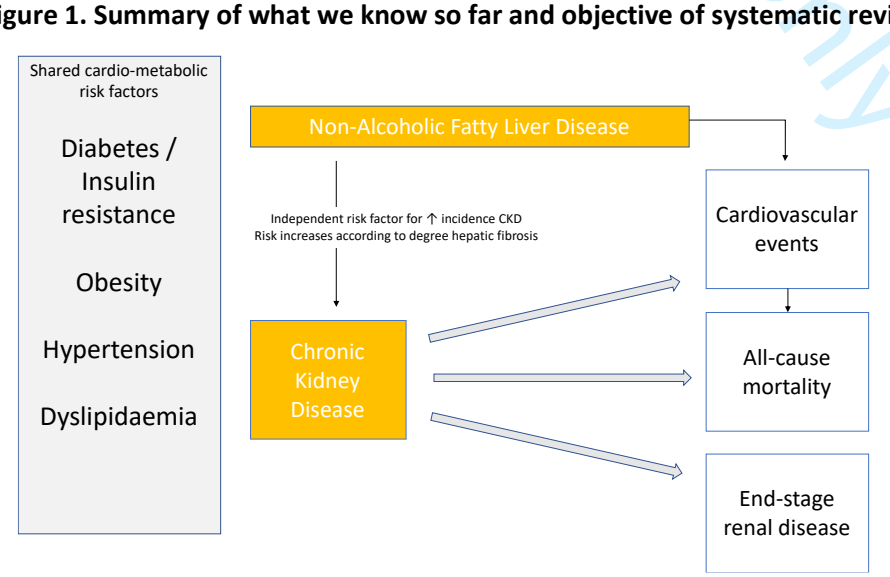
Importance of this review

Both CKD, NAFLD and their cardiometabolic risk factors (obesity and T2DM in particular) present huge challenges for both UK and global health providers.(16,49) In addition to the rising prevalence rates described above, both these conditions are profoundly linked to health inequalities. The incidence rates of CKD are estimated to be four times higher in low and middle income countries (LMIC), with Oceania, South East Asia, the Caribbean, Latin America, North Africa and the Middle East experiencing significant increases in disease burden.(6,50) Furthermore individuals of African descent experience

an accelerated course towards ESRD once they develop CKD.(51,52) With scarce resources for renal replacement therapy (RRT) in such countries, patients with ESRD are often faced with a death sentence. Similarly the burden of NAFLD is felt most heavily by low and middle income regions, including India (nearly 50%), South America and parts of the Middle East (approximately 30%).(53,54) Such inequalities nearly certainly result from a disparity in the prevalence of metabolic risk factors across economies. Nearly 80% of individuals with diabetes live in LMICs.(27) While obesity continues to predominantly affect higher income populations rates are levelling off, and instead are increasing in emerging economies.(55) Within England there is a large depravity gap in obesity prevalence for both adults and children which is increasing.(30) There is therefore a pressing need to address both the risk factor burden and predictors of clinical outcomes for both CKD in NAFLD, as LMIC and ethnic minorities are set to become disproportionately affected by these two conditions. Furthermore the financial costs associated with CKD are considerable. CKD was estimated to cost the English NHS £1.45 billion 2009-2010 (1.3% of all NHS spending).(15) More than half of this was spent on RRT serving 2% of the CKD population.(15) The cost of excess strokes and MIs was estimated to be up to £178 million.(15) Avoiding progression towards ESRD and the cardiovascular complications associated with CKD is therefore essential to reduce this huge cost burden.

CKD and NAFLD frequently exist together and independently contribute towards an increased risk of cardiovascular events and mortality. There is strong evidence that NAFLD is associated with an increased incidence of CKD, however research into the influence of NAFLD on the development of cardiovascular events, ESRD and premature death in the CKD population is at a much earlier stage. Understanding if there is a role for NAFLD in accelerating progression towards these adverse events could lead to improve health outcomes, reduced health inequalities and significant cost savings. This is a highly clinically relevant topic as individuals presenting to both primary and secondary care are increasingly likely to have both conditions. It is vital for their quality of care that clinicians are not only able to recognise the importance of looking for each of these diseases as a comorbidity, but also to identify patients who may be at the greatest risk for future cardiovascular events, rapid progression of kidney disease or early death. This would allow more aggressive lifestyle intervention, strict control of shared risk factors and enrolment in clinical trials. These findings are also likely to inform the need for improved cross-talk between diabetologists, cardiologists, hepatologists and renal physicians to help manage these patients optimally and lead to reductions in health care spending if end-stage events can be prevented. The findings of this review will be used to design an observational study which will further explore this question in an independent cohort.

Figure 1. Summary of what we know so far and objective of systematic review



HR: Hazard ratio, NAFLD: non-alcoholic fatty liver disease, CKD: Chronic kidney disease

Objective

To determine the influence of NAFLD on the risk of cardiovascular events, progression of kidney disease and all-cause mortality in patients with established CKD, and identify if this is independent of confounding factors

Methods

Types of studies

- Inclusion criteria: Observational (prospective or retrospective) cohort studies that report either the risk of cardiovascular events, progression of kidney disease or all-cause mortality among adults (> 18 year old) with established CKD who have NAFLD compared with those without NAFLD. Only studies that include meta-analysable outcomes will be included (mean difference, standardised difference, odds ratio (OR), HR or relative risk (RR)).
- Exclusion criteria: Abstracts, case reports, reviews, editorials, practice guidelines, non-cohort design, non-human studies, unpublished studies
- Search dates: No restriction on earliest publication date to present day
- Searches will be re-run just before the final analyses and any further studies identified, retrieved for inclusion
- We will register the protocol on PROSPERO a priori (https://www.crd.york.ac.uk/PROSPERO/)

Types of participants

- Inclusion criteria: Adults with established CKD with evidence of the presence or absence of NAFLD
- Exclusion criteria: Individuals under 18 years of age, individuals undergoing renal replacement therapy, eg haemodialysis, individuals who have had either a kidney or liver transplant, and individuals with a known other cause of chronic liver disease
- Definition of chronic kidney disease (CKD): eGFR ≥ 60 ml/min/1.73m^2 with albumin to creatinine ratio (ACR) > 3 mg/mmol (stage G1 and G2) or eGFR < 60 ml/min/1.73m^2 (stages G3a – G5) calculated using the CKD Epidemiology Collaboration (CKD-EPI) or Modified Diet in Renal Disease (MDRD) formula
- Definition of non-alcoholic fatty liver disease (NAFLD): biochemistry (elevations in serum AST, ALT, or GGT), imaging (ultrasound, computer tomography, magnetic resonance imaging), liver biopsy, non-invasive scores (Fatty Liver Index, Steatotest, NAFLD Liver Fat Score)

Primary outcome

- This review will aim to establish if there are any differences in the risk of cardiovascular events, progression of kidney disease and all-cause mortality in patients with CKD who have NAFLD compared to those without.
- Definition of cardiovascular events: Any one of the following - acute coronary syndrome, myocardial infarction, non-fatal cardiac arrest, coronary revascularization, new diagnosis of cardiac failure, hospitalisation with an exacerbation of cardiac failure, new diagnosis of peripheral vascular disease, new diagnosis of cerebrovascular accident (stroke / transient ischemic event) (all non-fatal).
- Definition of the progression of chronic kidney disease:
  1. Mean or percentage annual rate of change in the eGFR, or
  2. A decline in eGFR category accompanied by a ≥ 25% drop in eGFR from baseline, or
  3. The development of ESRD: eGFR of < 15 ml/min/1.73m^2, or the requirement of some form of renal replacement therapy, or

4. Doubling of creatinine

- Definition of all-cause mortality: Any cause of death within the study follow up period as determined by electronic patient records or the office of national statistics. Where possible we will break this down according to deaths due to a cardiovascular event, cancer or progression of kidney disease.

Secondary outcome

- The risk of cardiovascular events, progression of kidney disease and all-cause mortality in patients with CKD according to the severity of NAFLD, as determined by the presence of NASH or fibrosis.
- The risk of cardiovascular events, progression of kidney disease and all-cause mortality in patients with CKD according to the baseline severity of CKD, as determined by CKD stage.

Search methods for the identification of studies

- We will perform a computerized literature search in: PubMed, Embase (using Ovid) and Web of Science

Example of literature search strategy

"chronic kidney disease" [Title/Abstract] OR "CKD" [Title/Abstract] OR "kidney disease" [Title/Abstract] OR "kidney failure" [Title/Abstract] OR "kidney injury" [Title/Abstract] OR "chronic renal disease" [Title/Abstract] OR "renal disease" [Title/Abstract] OR "renal failure" [Title/Abstract] OR "renal injury" [Title/Abstract] OR "renal insufficiency" [Title/Abstract] OR "impaired renal function" [Title/Abstract] OR "glomerular filtration rate" [Title/Abstract] OR "eGFR" [Title/Abstract]
AND
"fatty liver" [Title/Abstract] OR "nonalcoholic fatty liver disease" [Title/Abstract] OR "NAFLD" [Title/Abstract] OR "nonalcoholic steatohepatitis" [Title/Abstract] OR "NASH" [Title/Abstract] OR "liver fat" [Title/Abstract] OR "steatohepatitis" [Title/Abstract] OR "steatosis" [Title/Abstract] OR "hepatic fibrosis" [Title/Abstract])

Study selection

- Relevant studies will be identified by systematically searching PubMed, Embase and Web of Science up to the present date using the free text terms described above
- Reference lists of relevant papers and previous review articles will be hand searched for other studies.
- Two investigators will examine all titles and abstracts, and obtain the full texts of potentially relevant papers. We will read the papers and determine if they met inclusion criteria.
- Discrepancies will be resolved by returning to the original article along with a third author in order to reach a consensus
- Inclusion criteria: Observational (prospective or retrospective) cohort studies that report either the risk of cardiovascular events, progression of kidney disease or all-cause mortality among adults (> 18 year old) with established CKD who have NAFLD compared with those without NAFLD. Only studies that include meta-analysable outcomes will be included (mean difference, standardised difference, OR, HR or RR).
- Exclusion criteria: Abstracts, case reports, reviews, editorials, practice guidelines, non-cohort design, non-human studies, unpublished studies

Data extraction

- Data will be extracted from each study independently by two authors and recorded on a standardised data extraction sheet
- We will use the Covidence software as recommended by Cochrane to upload search results, screen abstracts and full text, complete data collection, conduct risk of bias assessment, resolve disagreements and export data into Excel
- The following details will be extracted from all studies:
    - General information: title, authors, journal, funding, year of publication
    - Study design: population source and demographics, period of follow up and years, means of defining NAFLD, quality of study defined by the ACROBAT-NSRI tool, inclusion and exclusion criteria, study size, subgroups analysis (including severity of NAFLD and baseline CKD), confounding factors
    - Outcomes for NAFLD vs non-NAFLD patients: Outcome of interest (cardiovascular event / progression of kidney disease / all-cause mortality and definition used); OR, HR, RR and 95% confidence intervals; or mean/percentage annual rate of change in the eGFR
- In the event of missing data the researchers will attempt to contact the study investigators for unreported data or additional details. Contact information for study authors will be identified from PubMed or from the Internet and corresponding authors will be e-mailed or contacted by phone to ask if they are willing to share their study data. Up to 3 contact attempts will be made within a month. Manuscripts for which we are unable to obtain missing data will not be included in our analyses.
- Data will be reported according to the PRISMA guidelines

Assessment of bias (quality assessment)

- Two authors will independently be involved in the quality assessment
- Any discrepancies will be addressed by a revaluation of the original article by a third author
- We will use the Newcastle-Ottawa Score as recommended by Cochrane for the assessment of quality for non-randomised cohort studies.(56)
- This tool uses a star based system allocating a maximum of 9 points across three domains: (1) selection of study groups (max 4 points), (2) comparability of groups (max 2 points), (3) ascertainment of exposure and outcomes (max 3 points)
- Studies with an overall score of 9 are judged to be at a low risk of bias, those scoring 7-8 a moderate risk of bias and scores of 6 of less a high risk of bias.
- Where studies report more than one primary outcome a separate bias assessment will be performed for each.

Data synthesis

- Data will be synthesised if this review is able to identify 5 of more studies which meet the inclusion criteria described above, and that report the same outcome (either risk of a cardiovascular event, progression of kidney disease, or all-cause mortality)
- In the case of binary outcomes (risk of a cardiovascular event, ESRD, a decline in eGFR category accompanied by a ≥ 25% drop in eGFR from baseline, doubling of creatinine and all-cause mortality), adjusted and unadjusted HR/OR/RRs will be pooled with their 95% confidence intervals as a measure of effect size.
- In the case of continuous outcomes (mean/percentage annual rate of change in the eGFR) we will pool the adjusted and unadjusted mean or percentage differences

- Random-effects model: An overall estimate of effect size will be calculated using a random-effects model, as this takes into account any differences between studies even if there is no statistically significant heterogeneity.
- Statistical heterogeneity: The I^2 statistic will be used to investigate statistical heterogeneity. This estimates the percentage of variability in effect across studies resulting from heterogeneity rather than chance, to ensure that the effects found in the individual studies are similar enough that a combined estimate will be a meaningful. If heterogeneity between the effects found in single studies is too large ($I^2 > 0.5$) we will explore the source.
- Publication (small study bias): If the number of included studies is sufficient, publication bias will be examined using funnel plots and the Egger's regression test. We will use the trim and fill method to calculate adjusted estimates if publication bias is detected.
- Sensitivity analysis: For all outcomes we will use a meta-analysis influence test (involves repeating the meta-analysis after one study at a time is removed) to investigate any excessive influence of individual studies
- Meta-regression analysis: When 8 or more studies are available and report the same outcome, the effect of continuous variables (age, body mass index, waist circumference, insulin resistance estimated by homeostasis model assessment of insulin resistance index, and duration of follow-up) on the association between NAFLD and the reported outcome will be evaluated by meta-regression analysis

Analysis of subgroups or subsets

- If we are able to identify at least 5 cohort studies reporting the same outcome as described above, we will perform a sub-group analysis in order to address potential heterogeneity between studies
- Individuals may be stratified using any of the following criteria at the level of the study:
    - Quality of study as identified by the ACROBAT-NSRI tool
    - Follow-up duration
    - Age
    - Ethnicity
    - Means of defining NAFLD (biochemistry, imaging, liver biopsy, non-invasive scores)
    - Severity of NAFLD (NASH vs no NASH; fibrosis vs no fibrosis)
    - Severity of CKD according to disease stage at baseline
    - Patients with diabetes vs those without diabetes
    - Patients with cirrhosis vs those without cirrhosis
    - Patients with a history of excessive alcohol consumption vs those without
    - Whether the study has fully adjusted for covariates (age, gender, body mass index, hypertension, smoking, baseline eGFR, diabetes, dyslipidaemia, previous cardiovascular event)

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Supplementary material

Methods

Exact search criteria for online databases

1. PUBMED – 1,020 results

("chronic kidney disease" [Title/Abstract] OR "CKD" [Title/Abstract] OR "kidney disease" [Title/Abstract] OR "kidney failure" [Title/Abstract] OR "kidney injury" [Title/Abstract] OR "chronic renal disease" [Title/Abstract] OR "renal disease" [Title/Abstract] OR "renal failure" [Title/Abstract] OR "renal injury" [Title/Abstract] OR "renal insufficiency" [Title/Abstract] OR "impaired renal function" [Title/Abstract] OR "glomerular filtration rate" [Title/Abstract] OR "eGFR" [Title/Abstract]) AND ("fatty liver" [Title/Abstract] OR "nonalcoholic fatty liver disease" [Title/Abstract] OR "NAFLD" [Title/Abstract] OR "nonalcoholic steatohepatitis" [Title/Abstract] OR "NASH" [Title/Abstract] OR "liver fat" [Title/Abstract] OR "steatohepatitis" [Title/Abstract] OR "steatosis" [Title/Abstract] OR "hepatic fibrosis" [Title/Abstract])

2. EMBASE – 1,851 results

'Embase 1974 to 1/2/20' database used to achieve largest date range

((chronic kidney disease or CKD or kidney disease or kidney failure or kidney injury or chronic renal disease or renal disease or renal failure or renal injury or renal insufficiency or impaired renal function or glomerular filtration rate or eGFR) and (fatty liver or non-alcoholic fatty liver disease or NAFLD or nonalcoholic steatohepatitis or NASH or liver fat or steatohepatitis or steatosis or hepatic fibrosis)).ti,ab

3. Web of Science core collection - 1,476 results

'1970-2020' database used to achieve largest date range
Topic (TS): title, abstract, keywords

TS=(("chronic kidney disease" OR CKD OR "kidney disease" OR "kidney failure" OR "kidney injury" OR "chronic renal disease" OR "renal disease" OR "renal failure" OR "renal injury" OR "renal insufficiency" OR "impaired renal function" OR "glomerular filtration rate" OR eGFR) AND ("fatty liver" OR "nonalcoholic fatty liver disease" OR NAFLD OR "nonalcoholic steatohepatitis" OR NASH OR "liver fat" OR steatohepatitis OR steatosis OR "hepatic fibrosis"))

No further filters were used for any of the three databases.

Title
Authors
Journal
Year publication
Country
Funding
Population source
Demographics
Period follow up
Years of study
Study size
Intervention'
NAFLD definition
CKD definition
Quality (Newcastle-Ottawa Score)
Inclusion criteria
Exclusion criteria
Study design
Subgroup analysis
Adjustments for confounding factors
Longitudinal f/u
Outcome examined & definition
Statistical analysis
NAFLD prevalence
Cases
Primary outcome results
Secondary outcome results
OUTCOME

Non-alcoholic fatty liver disease and clinical outcomes in chronic kidney disease	
Rajkumar Chinnadurai, James Ritchie, Darren Green and Philip A. Kalra	
Nephrol Dial Transplant	
2019	
UK	
?	
Salford Kidney Study (SKS) - extension of the Chronic Renal Insufficiency Standards Implementations Study (CRISIS)	
Mean age 66 years, males 60.7%, mean BMI 28, DM 34%, HTN 78%, hyperlipidaemia 49%, median eGFR 33.5 mL/min/1.73 m ^{2}	
Median 65 months	
Liver USS (01/01/2000 - 31/12/2014), end of analysis period 31/12/2015	
1148 CKD patients (205 NAFLD, 752 normal liver, 191 had other hepatic abnormalities on USS) 852 CKD patients (183 NAFLD, 669 normal liver) after excluding patients with incomplete follow-up data sets 276 CKD patients (138 NAFLD, 138 normal liver) with 1:1 propensity score matching	
NAFLD vs no NAFLD	
Liver USS (hyperechogenicity or echobright liver consistent with fatty infiltration)	
eGFR <60 mL/min/ 1.73 m^2 using CKD-EPI formula	
(1) Mortality NOS = 8, (2) non-fatal CVE NOS = 8, (3) CKD progression NOS = 9	
Patients ≥ 18 years old referred to Salford renal service (tertiary centre); eGFR <60 mL/min/ 1.73 m ^{2}, not needing immediate RRT	
Maintenance RRT at time of liver USS , drinking above 21 units men / 14 units women, history of chronic hepatitis B & C or other chronic liver diseases	
Retrospective observational longitudinal cohort study	
NFCVE outcomes subgroup analysis: cardiac event, cerebrovascular event, PVD CCF Deaths analysed according to: cardiac, non-cardiac No subgroup analysis according to severity of NAFLD / severity CKD at baseline	
Propensity matching for: age, gender, BMI, SBP, DBP, baseline hypertension, diabetes, hypercholesterolaemia, IHD, MI, CCF, CVA, PVD, malignancy, use of statin and renin–angiotensin blocking agents, eGFR (NB age difference, NAFLD 66 yrs, normal liver 68 yrs p=0.04)	
Annual review: comorbidities, hospital admissions, cardiovascular events, medications, blood results	
(1) ESRD: commencement of RRT or eGFR of <10 mL/min/1.73 m^2 (2) Rate of change of eGFR (eGFR slope) from baseline to study end-point (3) NFCVE: composite of ACS, non-fatal MIs, non-fatal cardiac arrest, coronary revascularizations, new diagnosis cardiac failure / admissions with exacerbations of cardiac failure, new diagnosis of PVD, CVAs (4) All-cause mortality	
Univariate & multivariate Cox proportional hazards models to determine HRs & 95% CI (outcomes 1,3,4) Linear regression slope generated using serial serum creatinine measurements (outcome 2)	
17.9% (205 / 1148)	
(1) ESRD: NAFLD 26 (14.2%), normal 134 (19.1%), p=0.07 (2) CKD progression (rate of decline of eGFR slope): NAFLD -2.54 [-7.61 - 0.31] mL/min/1.73 m^2, normal -2.09 [-6.14 - 1.06] mL/min/1.73 m^2 (3) NFCVE: NAFLD 46 (25.1%), normal 82 (12.3%), p<0.001 (4) All cause mortality: NAFLD 50 (27.3%), normal 22 (33.0%), p=0.14	
(1) ESRD: total sample HR 0.99 [0.65–1.52], p=0.90; matched HR 0.64 [0.35-1.16], p=0.145 (2) CKD progression (rate of decline of eGFR slope): total sample p<0.09; matched p=0.58 (3) NFCVE: total sample HR 2.07 [1.39-3.09], p<0.001; matched HR 1.85 [1.04-3.30], p<0.04 (multivariate: total sample HR 2.03 [1.33-3.13], p<0.001; matched HR 2.00 [1.10-3.66], p=0.02) (4) All-cause mortality: total sample HR 0.79 [0.58-1.08], p=0.14; matched HR 0.88 [0.57–1.34], p=0.54	
N/A	
INCLUDE	

Nonalcoholic fatty liver disease accelerates kidney function decline in patients with chronic kidney disease: a cohort study
Hye Ryoun Jang, Danbee Kang, Dong Hyun Sinn, Seonhye Gu, Soo Jin Cho, Jung Eun Lee, Wooseong Huh, Seung Woon Paik, Seungho Ryu, Yoosoo Chang, Tariq Shafi, Mariana Lazo, Eliseo Guallar, Juhee Cho, Geum-Youn Gwak
Scientific reports
2018
South Korea
?
Individuals who underwent a comprehensive health screening examination at the Samsung Medical Centre Health Promotion Centre, Seoul, South Korea
Mean age 60.8 years, males 70%, mean BMI 24.8, DM 24%, HTN 60%, hyperlipidaemia 41%, median eGFR 59.1 mL/min/1.73 m^2
Average 6.5 years
January 2003 through December 2013
1,525 CKD patients
NAFLD vs no NAFLD
USS based on standard criteria, including parenchymal brightness, liver-to-kidney contrast, deep beam attenuation and bright vessel walls
eGFR < 60 ml/min/1.73 m^2 using CKD-EPI formula, or proteinuria ≥2+ on urinalysis
NOS = 7
Patients ≥ 18 years old who underwent a comprehensive health screening examination at the Samsung Medical Centre Health Promotion Centre and were found to have CKD with at least 1 additional follow up serum creatinine
History of cancer, liver cirrhosis, positive hepatitis B surface antigen, or hepatitis C virus antibodies, alcohol intake ≥ 30 g/day in men or ≥20 g/day in women, previous kidney transplant or started dialysis within 1 year after baseline examination, missing information on alcohol intake, NFS, or less than 6 months follow up
Retrospective observational longitudinal cohort study
(1) Severity NAFLD assessed via NFS: −1.675 + 0.037 × age (years) + 0.094 × BMI + 1.13 × impaired fasting glucose/diabetes (yes = 1, no = 0) + 0.99 × AST/ALT ratio − 0.013 × platelet count (×10^9/l) − 0.66 × albumin (g/dl). Based on NFS, patients were classified as high-intermediate (NFS ≥ −1.455) and low probability (NFS < −1.455) of advanced fibrosis. (2) Severity of CKD at baseline: cut-off value eGFR ≥45 ml/min/1.73 m^2 vs. <45 ml/min/1.73 m^2 (dividing G3a and G3b)
Stratified analyses to evaluate if association of NAFLD with CKD progression differed in pre-specified subgroups: age (<60 vs. ≥ 60 years), sex, smoking (never or former vs. current), alcohol drinking (none vs. moderate), BMI ≥ 25 kg/m2, hypertension (SBP ≥ 140 mmHg, DBP ≥ 90 mmHg, or use of antihypertensives), diabetes (fasting serum glucose ≥ 126 mg/dl, HbA1c ≥ 6.5%, or use of antidiabetic medication), hyperlipidaemia (HDL < 40 mg/dl in men or < 50 mg/dl in women, TG ≥ 150 mg/dl, or use of lipid-lowering medication), or baseline eGFR (<45 vs. ≥ 45 ml/min/1.73 m^2).
At each visit demographic characteristics, smoking status, alcohol consumption, medical history and medication use were collected through standardized, self-administered questionnaires along with blood results
CKD progression: average annual percent change in eGFR from baseline eGFR
Compared serial changes in eGFR among CKD patients with or without NAFLD at baseline using linear mixed models for longitudinal data with random intercepts and random slopes. Used loge-transformed eGFR as outcome and estimated the average difference in annual % change in eGFR (with 95% CI).
40.9% (902/1525)
Average annual percent change in eGFR from baseline: NAFLD -0.79% [-1.31 - -0.27], no NAFLD 0.30% [-0.14 - 0.76]
Average difference in % decline of eGFR per year NAFLD vs no NAFLD: (i) Adjusted for age, sex, year of visit: -1.09% [-1.77 - -0.41] (ii) Adjusted for all confounders: -1.06% [-1.73 - -0.38]
Average difference in % decline of eGFR per year NAFLD vs no NAFLD: (i) Adjusted for age, sex, year of visit: p=0.002 (ii) Adjusted for all confounders: p=0.002
(1) Multivariable adjusted average difference in annual % changes in eGFR for low NFS (≤ 1.455) or intermediate to high NFS (≥ −1.455) & those without NAFLD: 0.01% [−0.74 - 0.99) & −2.12% (−2.93 - −1.31) respectively (2) Multivariable adjusted average difference in annual % changes in eGFR among patients with eGFR < 45 ml/min/1.73 m^2 at baseline -6.27% [-12.08 - - 0.08] (n=168) vs -0.76 [-1.32 - -0.19] (n=1357) for baseline eGFR ≥ 45
INCLUDE

Chronic kidney disease is independently associated with increased mortality in patients with nonalcoholic fatty liver disease.
James Paik, Pegah Golabi, Zahra Younoszai, Alita Mishra, Gregory Trimble, Zobair M. Younossi
Liver International
2019
USA
None
NHANES-III & linked mortality files
Mean age 43.3 years, males 48.4%, DM 6.5%, HTN 40.7% (total cohort)
Average 19.2 years
NHANES-III 1988 - 1994; linked mortality files up to 2011 or date of death
11,695 adult participants 'NAFLD- CKD-' 74.6%, 'NAFLD+ CKD-' 16.1%, 'NAFLD- CKD+' 6.8%, 'NAFLD+ CKD+' 2.5%
CKD vs no CKD in NAFLD cohort (main results reported in paper) NAFLD in CKD cohort (some data)
Liver USS (moderate/severe hepatic steatosis in absence of any other possible cause CLD)
eGFR < 60 ml/min/1.73 m2 using CKD-EPI formula +/- albuminuria
NOS = 9
Persons aged 20-74 at time of examination with complete data on ultrasound video images for hepatic steatosis assessment and serum creatinine measurements
Patients with other causes of chronic liver disease were excluded
Retrospective analysis of data collected from cross-sectional study
Presence of fat within hepatic parenchyma graded as normal, mild, moderate, or severe hepatic steatosis. NAFLD-associated advanced fibrosis was defined with ultrasound diagnosed NAFLD and at least one of the following fibrosis markers: APRI> 1, FIB-4 index >2.67, or NFS>0.676. Cardiovascular mortality was defined as death due to heart diseases (ICD-10: I00-I09, I11, I13, and I20-I51) and cerebrovascular diseases (ICD-10: I60-I69).
Age, gender, race, smoker, metabolic syndrome
Data linked with mortality files
(1) All-cause mortality (2) Cardiovascular-related mortality: death due to heart diseases (ICD-10: I00-I09, I11, I13, I20-I51) & cerebrovascular diseases (ICD-10: I60-I69)
Logistic regression & cox proportional hazards model
29% (410/1,413)
(1) All-cause mortality: NAFLD 54.7% (SE 3.6), no NAFLD 46.5% (SE 2.4), p<0.05 (age adjusted: NAFLD 31.0% [25.0-37.0], no NAFLD 25.9% [22.0-29.7], p=ns) (2) Cardiovascular-related mortality: NAFLD 16.0% (SE 2.5), no NAFLD 16.2% (SE 1.7), p=ns (age adjusted: NAFLD 7.8% [3.7-11.9], no NAFLD 8.2% [5.6-10.9], p=ns)
(1) All-cause mortality: adjusted HR NAFLD 2.34 [1.91-2.87], no NAFLD 2.08 [1.80-2.40], p=ns (2) Cardiovascular-related mortality: adjusted HR NAFLD 2.12 [1.44-3.13], no NAFLD 2.43 [1.8-3.2], p=ns
(1) CKD + NAFLD + advanced fibrosis (n=60) All-cause mortality: 73.1% [50.7-95.5], p=ns vs no advanced fibrosis; adjusted HR 3.49 [2.25-5.43], p=ns vs no advanced fibrosis Cardiovascular-related mortality: 14.6% [1.6-27.7], p=ns vs no advanced fibrosis; adjusted HR 2.83 [0.69-11.51], p=ns vs no advanced fibrosis (2) CKD + NAFLD + no advanced fibrosis (n=97) All-cause mortality: 52.1% [44.8-59.3]; adjusted HR 2.51 [1.98-3.18] Cardiovascular-related mortality: 16.5% [11.1-21.9]; adjusted HR 2.45 [1.61-3.73]
INCLUDE

Increased Risk for Cardiovascular Events in Patients with Diabetic Kidney Disease and Non-Alcoholic Fatty Liver Disease.
Rajkumar Chinnadurai, Constantina Chrysochou, Philip A. Kalra
Nephron
2018
UK
?
Salford Kidney Study (SKS) - extension of the Chronic Renal Insufficiency Standards Implementations Study (CRISIS)
Mean age 65 years, males 66%, mean BMI 30, DM 100%, HTN 87%, median eGFR 31.6 mL/min/1.73 m^2, hyperlipidaemia 79%
Median 69 months
Liver USS (01/01/2000 - 31/12/2014), end of analysis period 31/12/2015
192 patients with DKD (55 NAFLD, 113 normal liver, 24 had other hepatic abnormalities on USS) 149 patients with DKD (183 NAFLD, 669 normal liver) after excluding patients with incomplete follow-up data sets
NAFLD vs no NAFLD
Liver USS (hyperechogenicity or echobright liver consistent with fatty infiltration)
eGFR <60 mL/min/ 1.73 m^2 using CKD-EPI formula
Patients ≥ 18 years old referred to Salford renal service (tertiary centre); eGFR <60 mL/min/ 1.73 m^2, not needing immediate RRT
Maintenance RRT at time of liver USS , drinking above 21 units men / 14 units women, history of chronic hepatitis B & C or other chronic liver diseases
Retrospective observational longitudinal cohort study
NFCVE outcomes subgroup analysis: cardiac event, cerebrovascular event, PVD CCF Deaths analysed according to: cardiac, non-cardiac No subgroup analysis according to severity of NAFLD / severity CKD at baseline
Propensity matching for: age, gender, BMI, SBP, DBP, baseline hypertension, diabetes, hypercholesterolaemia, IHD, MI, CCF, CVA, PVD, malignancy, use of statin and renin–angiotensin blocking agents, eGFR (NB age difference, p=0.04)
Annual review: comorbidities, hospital admissions, cardiovascular events, medications, blood results
(1) ESRD: commencement of RRT or eGFR of <10 mL/min/1.73 m^2 (2) Rate of change of eGFR (eGFR slope) from baseline to study end-point (3) NFCVE: composite of ACS, non-fatal MIs, non-fatal cardiac arrest, coronary revascularizations, new diagnosis cardiac failure / admissions with exacerbations of cardiac failure, new diagnosis of PVD, CVAs (4) All-cause mortality
Univariate & multivariate Cox proportional hazards models to determine HRs & 95% CI (outcomes 1,3,4) Linear regression slope generated using serial serum creatinine measurements (outcome 2)
28.6% (55/192)
(1) ESRD: NAFLD 7 (14.6%), normal 17 (16.8%), p=0.73 (2) CKD progression (rate of decline of eGFR slope): NAFLD -3.97 [-7.2 - 0.12] mL/min/1.73 m^2, -2.95 [-9.07 - 0.407] normal mL/min/1.73 m^2 (3) NFCVE: NAFLD 20 (41.7%), normal 14 (13.9%), p<0.001 (4) All cause mortality: NAFLD 16 (33.3%), normal 36 (35.6%), p=0.78
(1) ESRD: not reported (2) CKD progression (rate of decline of eGFR slope): p=0.65 (3) NFCVE: HR 3.48 [1.59-7.6], p=0.002 (multivariate: HR 2.95 [1.31-6.60], p=0.01) (4) All-cause mortality: HR 0.72 [0.40-1.31], p=0.28
N/A
Sub group of previous paper by Chinnadurai

Nonalcoholic Fatty Liver Disease and Renal Function Impairment: A Cross-Sectional Population-Based Study on Its Relationship From 1999 to 2016
Michael H. Le, Yee Hui Yeo, Linda Henry, and Mindie H. Nguyen
Hepatology Communications
2019
USA
?
National Health and Nutrition Examination Survey (NHANES): cross-sectional survey conducted in US by the National Centre for Health Statistics of the Centres for Disease Control and Prevention (CDC)
Mean age 53 years, males 56%, mean BMI 34, DM 24%, HTN 52.3%, median eGFR 90.5 mL/min/1.73 m^2, dyslipidaemia 61%
1999 - 31 Dec 2015
14,255 adults (not all had renal insufficiency); 4680 NAFLD patients (population of interest for this study)
Renal insufficiency vs no renal insufficiency
U.S. Fatty Liver Index (USFLI) ≥30 to rule in fatty liver
eGFR determined CKD-EPI & ACR. Unable to determine if renal insufficiency was acute or chronic. Renal insufficiency divided into 4 stages: no RI, mild, moderate & severe
People aged 18 years and older, who participated in a medical examination at a mobile centre, and underwent fasting blood work during their examination.
Participants <18 years old, missing laboratory data needed to calculate the non-invasive indices (age, race/ethnicity, waist circumference, GGT, fasting insulin, fasting glucose, serum creatinine, urine creatinine, and urine albumin), those who had a diagnosis of viral hepatitis, and those with heavy alcohol use.
Cross-sectional study
Severity of liver fibrosis assessed using NAFLD Fibrosis Score (NFS). NFS >0.676 rule in stage 3-4 fibrosis, NFS <–1.455 rule out stage 3-4 fibrosis.
2 yearly cross-sectional interviews, examinations and laboratory data
(1) Trends in NAFLD +/- renal insufficiency prevalence over time in US (2) Predictors of RI in NAFLD patients (3) Health literacy levels for kidney & liver disease (4) Mortality (national death index): all-cause mortality, cause-specific mortality from diseases of heart and malignant neoplasms: compared NAFLD + renal insufficiency vs NAFLD without renal insufficiency (5) Risk factors predicting mortality in NAFLD cohort with & without renal insufficiency
Univariate & multivariate logistic regression; Kaplein Meier curves; cox regression
31.2% (not all patients had renal insufficiency)
(1) Prevalence 1999-2000: NAFLD without RI 23.5% [20.2-27.1], NAFLD-RI 5.7% [4.3-7.6]; prevalence 2015- 2016, NAFLD without RI 27.3% [23.7-31.1], NAFLD-RI 7.7% [6.2-9.5]. Trend analysis 1999-2016: prevalence of overall NAFLD, NAFLD without RI & NAFLD-RI all significantly increased over time (p=0.007, p=0.048, p=0.006 respectively). Among those with NAFLD, RI prevalence did not increase significantly 1999-2016 (p=0.221). No significant increases were observed in mild, moderate, or severe RI in those with NAFLD (p=0.448, p=0.222, p=0.478 respectively) (2) Significant independent predictors of RI in NAFLD: age > 65, HTN, DM, dyslipidaemia, CVD, high probability of fibrosis stage 3 and 4 (multivariate analysis) (3) Among those with NAFLD-RI, awareness of kidney disease was 8.56% [6.69-10.89], awareness of liver disease among all NAFLD was 4.49% [3.17-6.33] (4) 5 yr cumulative mortality incidence: NAFLD alone 4.5%; mild RI 14.2%, moderate 21.2%, and severe 36.0% RI (p<0.001). 15 yr cumulative mortality incidence: NAFLD alone 19.9%, mild RI 42.4%, moderate RI 80.6%, and severe RI 85.5% (p<0.001). 5 yr cumulative incidence CV-related mortality highest in NAFLD + severe RI at 10.5% (36.7% at 15 years). Independent risk factors for all-cause mortality in NAFLD: age, mild/mod/sever RI, high probability of fibrosis; former/current smoker; history of CVD. Independent risk factors for CV mortality in NAFLD: older age, moderate & severe RI, history of CVD.
Intervention is CKD in NAFLD cohort rather than NAFLD in CKD cohort.

Predicting timing of clinical outcomes in patients with chronic kidney disease and severely decreased glomerular filtration rate.
Grams ME1, Sang Y2, Ballew SH2, Carrero JJ3, Djurdjev O4, Heerspink HJL5, Ho K6, Ito S7, Marks A8, Naimark D9, Nash DM10, Navaneethan SD11, Sarnak M12, Stengel B13, Visseren FLJ14, Wang AY15, Köttgen A16, Levey AS12, Woodward M17, Eckardt KU18, Hemmelgarn B19, Coresh J20
Kidney Int.
2018
30 countries
Participants in International Chronic Kidney Disease Prognosis Consortium
Median eGFR 24 mL/min/1.73 m2
264,296 individuals
Age, sex, race, eGFR, ACR, SBP, smoking status, DM, history of CVD.
eGFR < 30 ml/min/1.73m2
Aim to develop 2 & 4 year models of the probability & timing of kidney failure requiring RRT, a non-fatal CVD event & death
Competing-risk regression, random-effect meta-analysis, and Markov processes with Monte Carlo simulations
NAFLD was not examined in this study

Newcastle-Ottawa Scale (NOS)	Questions	Chinnadurai R et al. Nep Mortality
1) Selection of study groups (max 4)	1) Representativeness of the exposed cohort a) truly representative of the average patient with CKD in the community * b) somewhat representative of the average patient with CKD in the community * c) selected group of users eg nurses, volunteers d) no description of the derivation of the cohort	* Only those who had an USS included
	2) Selection of the non exposed cohort a) drawn from the same community as the exposed cohort * b) drawn from a different source c) no description of the derivation of the non exposed cohort	*
	3) Ascertainment of exposure a) secure record (eg surgical records) * b) structured interview * c) written self report d) no description	*
	4) Demonstration that outcome of interest was not present at start of study a) yes * b) no	Some patients had disease, eg IHD at baseline
	TOTAL SCORE	3
2) Comparability of groups (max 2)	1) Comparability of cohorts on the basis of the design or analysis a) study controls for components of themetabolic syndrome * b) study controls for any additional factor (mortality: underlying CVD, baseline eGFR; CVE: underlying CVD; CKD progression: baseline eGFR)*	 * *
	TOTAL SCORE	2
3) Ascertainment of exposure and outcomes (max 3)	1) Assessment of outcome a) independent blind assessment* b) record linkage * c) self report d) no description	*
	2) Was follow-up long enough for outcomes to occur a) yes (select an adequate follow up period for outcome of interest) * b) no	*
	3) Adequacy of follow up of cohorts a) complete follow up - all subjects accounted for* b) subjects lost to follow up unlikely to introduce bias - small number lost (< 20%), or description provided of those lost* c) follow up rate < 80% and no description of those lost d) no statement	*
	TOTAL SCORE	3
	OVERALL SCORE	8

hrol Dial Transplant. 2019;34(3):449-457		Jang HR, et al. Sci Rep. 2018;8(1):4718.		Paik J et al. *Liver Int* . 2019;39(2):342-352.			
CVE	**CKD progression**	**Mortality**	**CVE**	**CKD progression**	**Mortality**	**CVE**	**CKD progression**
* Only those who had an USS included	* Only those who had an USS included			* Only those who had an USS included	* Only those who had an USS included & under 75s		
*	*			*	*		
*	*			*	*		
Some patients had disease, eg IHD at baseline	*			*	Some patients had disease, eg CVD at baseline		
3	4			4	3		
*	*			*	*		
*	*			*	No		
2	2			2	1		
*	*			*	*		
*	*			*	*		
*	*			* Included only participants with at least 1 f/u eGFR	* Participants with no death records were presumed alive through f/u		
3	3			3	3		
8	9			9	7		

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5-6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6-7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	N/A

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	N/A
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7-8, figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8 & table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	11 & table 2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	8-9 & table 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	N/A
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	11-12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	12-14
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	3

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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