Decreased renal function is associated with incident dementia

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1. Title page

Title: Decreased renal function is associated with incident dementia: an IMRD-THIN retrospective cohort study in the UK

Short title: Decreased renal function and incident dementia

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2. Abstract

INTRODUCTION: Decreased renal function is a potential risk factor for dementia.

METHODS: This retrospective cohort study of 2.8 million adults aged ≥50 years used the IMRD-THIN database, representative of UK primary care, from 1/1/1995 to 24/2/2020. The associations between estimated glomerular filtration rate (eGFR) and urine albumin creatinine ratio (ACR) with incident all-cause dementia were analysed using Cox regression.

RESULTS: In the eGFR cohort (n=2,797,384), worsening renal dysfunction was associated with increased hazard of all-cause dementia, with greatest hazard at eGFR 15-30 ml/min/1.73min^2 (HR 1.26, 95% CI 1.19 – 1.33).

In the ACR cohort (n=641,912), the hazard of dementia increased from ACR 3-30mg/mmol (HR 1.13, 95% CI 1.10 – 1.15) to ACR>30mg/mmol (HR 1.25, 95% CI 1.18 – 1.33).

DISCUSSION: Worsening eGFR and albuminuria have graded associations with the risk of dementia, which may have significant implications for the care of patients with kidney disease.

142 words

3. Background

Dementia and chronic kidney disease (CKD) are chronic diseases that increase with age [1, 2]. With an aging population, the prevalence of both will be increasing in the next decade [2, 3]. Both diseases are important global health issues as they are leading causes of death, morbidity, and poor quality of life and present a substantial economic and social care burden [2-5].

There is currently no cure for dementia, but there are increasing efforts to address dementia risk factors[6]. About 40% of worldwide cases of dementia are attributable to 12 well-studied modifiable risk factors [6]. Recent evidence suggests that renal dysfunction is a potential risk factor [7].

There are two theories for this. First, the kidneys and brain share susceptibility to atherosclerotic disease and cardiovascular risk factors, and concomitant cerebrovascular disease is common in patients with CKD [7]. Second, retained uraemic toxins in CKD may cause direct neuronal injury [7].

However, the literature on renal dysfunction and albuminuria as risk factors for dementia remains limited and conflicting. Most studies used a combined outcome of cognitive impairment or dementia and have small sample sizes, particularly small numbers of patients with advanced CKD [8-16]. The evidence for albuminuria as a risk factor for dementia and vascular dementia is more consistent [9, 10, 15, 17]. A meta-analysis (n=27,805) found that participants with albuminuria had higher odds of cognitive impairment/dementia (OR 1.35, 95% CI 1.06-1.73) compared to no albuminuria [9].

In the UK, primary care records offer the opportunity for population-based observational studies as most people are registered with a general practitioner (GP) [18]. This study aims to

examine the association of decreased renal function and increased albuminuria with the risk of incident dementia in adults aged ≥50 years using the IQVIA Medical Research Data-The Health Improvement Network (IMRD-THIN) primary care database with a much larger sample size than that of previous literature [19].

4. Methods

4.1 Data source

Data for this study were extracted from IMRD that incorporates data from THIN using the DExtER tool [20]. Reference made to THIN is intended to be descriptive of the data asset licensed by IQVIA. THIN contains anonymised longitudinal patient records collected through routine primary care from 787 GP practices across the UK and covers approximately 6% of the UK population, GP practices sign up for inclusion to the database [19]. The database uses Read codes, a hierarchical clinical coding system used in UK primary care records [21]. This database includes patient demographics, diagnoses, investigations, prescriptions and mortality data [22]. It is representative of the UK population [22].

4.2 Study design

This was a population-based, open cohort, retrospective study from 1/1/1995 to 24/2/2020. The study is reported in accordance with the RECORD guidelines (Supplementary material 1) [23]. Two separate cohorts were selected based on the presence of estimated glomerular filtration rate (eGFR) and urine albumin creatinine ratio (ACR) measurements, respectively, after the study start date.

4.3 Inclusion and exclusion criteria

Patients aged ≥50 years with a serum creatinine (for the eGFR cohort) or urine ACR (for the ACR cohort) recorded after the study start date were included. The minimal age of 50 years was chosen as the cut off as 96% of dementia diagnoses are in those aged ≥65 years [24]. In addition, kidney blood test results are likely to be recorded in this age group as they are eligible for the National Health Service Health Check, which includes tests for early detection of CKD [25]. To ensure exposure predates the outcome, patients with a recorded dementia diagnosis before the index date were excluded. Patients on dialysis were also excluded as their creatinine/eGFR are not interpretable.

4.4 Exposures

The exposure variables were the eGFR categories (G1-G5) and ACR categories (A1-A3) for the respective cohorts. This was defined by current international guidelines (Supplementary material 2) [26], taken as the first serum creatinine and the first urine ACR after the study start date, using the Additional Health Data (AHD) codes. eGFR was estimated from serum creatinine using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [26]. The reference groups were those with eGFR> 90 ml/min/1.73m^2 and with ACR <3mg/mmol.

4.5 Outcomes

Read codes were used to ascertain the outcome of incident diagnosis of all-cause dementia, Alzheimer's disease, and vascular dementia (Supplementary material 3). In the UK, the GP usually conducts the initial assessment for a person with suspected dementia and refers on to specialist dementia diagnostic services [27]. The diagnosis will then be recorded using Read

codes in the primary care health records. The validity of dementia diagnosis in routine health records in the UK were generally high and the diagnosis of dementia in THIN was found to be generalisable to the UK population [22, 28].

4.6 Covariates

Read codes for the following covariates were obtained at baseline: **confounders**: sociodemographic factors (age, gender, ethnicity and Townsend deprivation index) [29], cardiovascular risk factors (smoking, alcohol use, body mass index [BMI], hypertension, hyperlipidaemia and diabetes mellitus); **predictors of dementia**: hypothyroidism, hearing loss, depression, B12 deficiency and chronic obstructive pulmonary disease; and **mediators on the causal pathway**: cardiovascular disease (ischaemic heart disease, atrial fibrillation, heart failure, stroke and peripheral vascular disease) [9, 10, 17, 30-33].

5. Data analysis

STATA version 16 was used for the analysis.

For data quality assurance, the latest of the following was taken as the study entry date: study start date of 1/1/1995, one year after the GP practice began using the Vision electronic medical records, one year after the GP practice's accepted mortality recording date [34], and one year after the patient registered with the GP practice.

The index date was when eGFR or ACR data were first available after the study start date for the respective cohorts. Patients exited the study when they received a Read code of dementia, left the practice, died, reached the study end date of 24/2/2020 or when their practice stopped contributing to the database.

Descriptive analysis of baseline characteristics and incidence rates was conducted for the eGFR and ACR cohorts separately. Those with missing data were treated within a separate category for ethnicity, Townsend deprivation index, smoking status, alcohol intake status and BMI.

Cox proportional hazard models were used to estimate the hazard ratios for incident dementia. The proportional hazard assumption was assessed by eGFR and ACR category respectively using log-log plots. The confounders, predictors and mediators were adjusted for in stages using a hierarchical approach. Statistical tests were two-tailed, with an alpha level of 0.05.

For the final model, sensitivity analysis was performed by CKD Read codes, eGFR as a continuous variable for the eGFR cohort; and ACR as a continuous variable for the ACR cohort. Subgroup analysis was performed for Alzheimer's disease and vascular dementia.

6. Results

6.1 Estimated GFR cohort

6.1.1 Baseline characteristics

Supplementary material 4 outlines the patient selection. Overall, 2,797,384 patients were included in the analysis with a median follow up of 5.6 years (IQR 2.5-9.6). The median age was 62 years old (IQR 54-72), 46.8% were male; 53.4% did not have ethnicity recorded whilst 43.8% were White, followed by 1.4% South Asian and 0.8% Black. Townsend deprivation index was missing for 16.4%, 21.9% were in the least deprived quintile whilst 9.7% were in the most deprived quintile.

Only 5.8% of the cohort had ACR results available at baseline. 20.2% had an eGFR < 60 ml/min/1.73m^2 which, if present for three months or longer, would be consistent with CKD. This was six times higher than the 2.9% captured by CKD 3-5 Read codes. Amongst all eGFR categories, G2 (eGFR 60-89) had the largest proportion of patients (56.0%).

6.1.2 Baseline characteristics: by eGFR categories

Table 1 presents the baseline characteristics by eGFR categories (G1-G5). Patients with an eGFR < 60 ml/min/1.73m^2 were older. There were more women with eGFR category G3-G4 (61.9-65.5%) but more men with eGFR category G1 (51.2%). The proportion of patients with cardiovascular disease increased with reducing eGFR.

6.1.3 Incident dementia

Four percent (n=102,277) of the eGFR cohort had incident all-cause dementia, giving a crude incidence rate of 5.8 per 1000 person-years. Incidence rates of dementia increased from eGFR categories G1-4. A similar pattern was observed in Alzheimer's disease and vascular dementia (Table 2).

6.1.4 Cox regression

When the covariates were adjusted for in steps from Model 1-4, the association were attenuated but a statistically significant association between eGFR and dementia remained (Supplementary material 5.1). Due to the large missing data in ACR, this variable was not adjusted for in the main model.

In the model adjusted for confounders (sociodemographics, cardiovascular risk factors) and predictors of dementia (Model 3, Table 3), there was a graded increasing hazard of all-cause dementia with worsening eGFR categories. The greatest association was observed in eGFR category G4 (HR 1.26 (955 CI 1.19 – 1.33)). eGFR category G5 was not significantly associated with incident dementia.

6.1.5 Subgroup and sensitivity analysis

In the subgroup analysis adjusted for confounders and dementia predictors, a similar pattern was observed in vascular dementia; the association of Alzheimer's dementia with decreased renal function was not observed in more severe grades of eGFR categories (Supplementary material 5.2). With every 5ml/min/1.73m^2 unit increase in eGFR (better renal function), the hazard of all-cause dementia decreased by 1% (95% CI 0.99-0.99). Patients with CKD Read codes had a 39% increased hazard of all-cause dementia compared to patients with no CKD Read codes (95% CI 1.36-1.43).

6.1.6 Interaction with age

As age was highly correlated with eGFR categories (Table 3), an interaction term was added as a post-hoc analysis. The eGFR-age interaction was statistically significant, indicating that there was a difference in the association of eGFR with dementia by age categories (Supplementary material 5.3). In the 10-yearly age-stratified Cox regression adjusted for sociodemographics, cardiovascular risk factors and dementia predictors, the graded association between worsening eGFR and all-cause dementia was attenuated in older age groups and not observed in those aged 80+ years: age 50-59 years, G4, HR 2.52 (95% CI 1.60-3.97) vs age 70-79 years, G4, HR 1.22 (95% CI 1.10-1.36), (Supplementary material 5.4).

6.2 ACR cohort

6.2.1 Baseline characteristics

The flowchart in Supplementary material 6 outlines the patient selection. Overall, 641,912 patients were included in the analysis with a median follow up of 4.3 years (IQR 2.0 – 7.0).

The ACR cohort (n=641,912) had a median age of 69 years old (IQR 61-78), 50.7% were male; 48.8% did not have ethnicity recorded whilst 47.4% were white, followed by 2.1% South Asian and 1.0% black. Townsend deprivation was missing for 15.5%, 19.7% were in the least deprived quintile whilst 11.3% were in the most deprived quintile.

6.2.2 Baseline characteristics: by ACR categories

Table 4 presents the baseline characteristics by ACR categories. The majority were in A1 (normal to mildly raised ACR, 69.1%). Only 4.1% were in A3 (severely raised ACR). Patients with A1 were younger. The distribution of other sociodemographic factors was similar across all ACR categories. A large proportion of patients in the ACR cohort had hypertension (63.4%), hyperlipidaemia (66.6%) and diabetes (49.0%). The proportion of patients with cardiovascular disease increased with worsening ACR.

6.2.3 Incident dementia

Four percent (n=28,884) of the ACR cohort had incident all-cause dementia, giving a crude incidence rate of 9.4 per 1000 person-years. Overall, the crude incidence rate of all-cause dementia increased from A1 (8.3 per 1000 person-years) to A3 (12.6 per 1000 person-years). Alzheimer's disease and vascular dementia followed a similar pattern (Table 2).

6.2.4 Cox regression

As covariates were added in steps from Model 1-5, the association was attenuated slightly (Supplementary material 7.1). In the model adjusted for confounders (sociodemographics and cardiovascular risk factors), predictors of dementia and eGFR categories, there was an increased hazard of all-cause dementia by 13% for A2 (95% CI 1.10 – 1.15) to 25% for A3 (95% CI 1.18 – 1.33, Model 5, Table 5).

6.2.5 Subgroup and sensitivity analysis

In the model adjusted for confounders, dementia predictors and eGFR categories, the hazard of Alzheimer's disease was higher in A2 than A1 (HR 1.06, 95% CI 1.02-1.11) but there was no significant difference for A3 (HR 1.07, 95% CI 0.96-1.19). However, there was a clear biological gradient for vascular dementia from A2 (HR 1.17, 95% CI 1.12-1.23) to A3 (HR 1.51, 95% CI 1.38-1.66). With every 5mg/mmol increase of ACR (worsening albuminuria), the hazard of all-cause dementia increased significantly by 0.5% (95% CI 1.004-1.007).

6.2.6 Interaction with age

Similar to the eGFR cohort, as age was highly correlated with ACR categories (Table 5), an interaction term was added as a post-hoc analysis. However, the ACR-age interaction was not statistically significant (Supplementary material 7.2). In the 10-yearly age-stratified Cox regression adjusted for sociodemographics, cardiovascular risk factors, dementia predictors, and eGFR categories, the graded association between worsening ACR and all-cause dementia was observed in all age categories. Although the point estimate was attenuated in the older age groups (age 50-59 years A2 HR1.19 [95% CI 1.00 – 1.42], A3 HR 1.38 [0.96 – 1.99] vs age 80+ years A2 HR 1.12 [1.08 – 1.16], A3 HR 1.26 [1.17 – 1.37], the confidence intervals overlapped between age groups (Supplementary material 7.3).

7. Discussion

7.1 Main findings

This cohort study examined the association of decreased renal function and increased albuminuria with the risk of incident dementia in adults aged ≥50 years using routine primary care health records in the UK. Lower eGFR and higher urine ACR were associated with a graded increased hazard of all-cause dementia. The association of all-cause dementia with ACR was independent of eGFR. These associations were more prominent in vascular dementia. The association of lower eGFR with risk of dementia was attenuated with advancing age suggesting a possibility that having decreased renal function at a younger age may have a greater impact on the hazard of dementia.

7.2 Comparison with existing literature

7.2.1 eGFR

The existing literature reported conflicting evidence on renal dysfunction as a risk factor for incident dementia. Non-significant results may have been driven by lack of power in some studies [9].

The interaction term demonstrated that having impaired eGFR at a younger age may have a greater impact on the risk of developing dementia. Cheng et al. also found that the age-specific CKD cohort to non-CKD cohort incidence rate ratio (IRR) for dementia decreased with age. The youngest age group had the highest IRR (20-39 years, IRR 16.0, 95% CI 2.00-128) [8]. One possible explanation is that having renal dysfunction at a younger age increases the length of exposure to renal dysfunction. Another possibility is that some decline in renal function in older age could be attributed to ageing, separate from kidney disease; hence, lower eGFRs in younger patients are more likely to reflect a disease process [35, 36].

298 eGFR category G5 was not significantly associated with all-cause dementia. This may be due
299 to the competing risk of death, i.e. those with severe renal dysfunction die before they go on
300 to develop dementia [37].

301

302 ### 7.2.2 ACR

303 Contrary to eGFR, the existing evidence for albuminuria as a risk factor for dementia and
304 vascular dementia is more consistent from two systematic reviews and two cohort studies [9,
305 10, 15, 17]. This study contributes to the current literature in support of the positive
306 association between increasing albuminuria and all-cause dementia, likely driven by vascular
307 dementia [9, 10, 15, 17]. Albuminuria is a marker of endothelial dysfunction and
308 atherosclerotic disease including stroke [38]. Takae et al's Japanese community cohort study
309 found that higher levels of ACR was associated with higher risk of vascular dementia,
310 especially those with a history of stroke [15]. In Georgakis et al's meta-analysis, although
311 albuminuria was also associated with Alzheimer's disease, the association was stronger in
312 vascular dementia [17]. Albuminuria may reflect the shared susceptibility of the kidney and
313 the brain to microvascular disease [17]. The endothelial dysfunction may also lead to
314 increased permeability of the blood-brain barrier and albuminuria has been found to be
315 associated with white matter hyperintensities [15, 17, 38].

316 ## 7.3 Strengths

317 Compared to existing literature, this is the largest study to date of the associations between
318 eGFR and albuminuria and dementia, with 2.8 million patients. Unlike most literature that
319 dichotomised the exposure into eGFR<60, the large sample size allowed the exposure to be
320 categorised into the standard eGFR and ACR categories and confirmed the presence of
321 graded associations and thus increases our confidence of a causal relationship.

7.4 Limitations

eGFR and ACR have been chosen instead of CKD Read codes as a national CKD audit found that 30% of patients with biochemical CKD 3-5 (defined by two eGFR readings <60 ml/min/1.73m^2 at least 90 days apart) did not have a primary care Read code of CKD [39].

Single eGFR and ACR measurements were used to ascertain the exposure status in this study. Significant intra-patient variability in these measurements is recognised and in clinical practice, when these renal function tests are abnormal, the test would usually be repeated, and some may reflect an acute kidney injury and resolve spontaneously [40]. Thus, the use of a single measurement may have reduced the magnitude of our observed association. However, the use of single baseline measures is the methodology employed in the vast majority of CKD prognosis and risk prediction studies [41].

As only a limited number of patients in the eGFR cohort had data for ACR, ACR could not be adjusted for as a covariate. For the ACR cohort, many patients in the study database had no ACR within the study period and were excluded. ACR is likely tested more frequently in people with underlying cardiovascular disease or risk factors that require routine ACR monitoring, potentially resulting in a selection bias. This is reflected by the high proportion of patients with hypertension, hyperlipidaemia, and diabetes in the ACR cohort. The true association for ACR and dementia is, therefore, likely to be greater. This may also be a possible reason why the age interaction observed in the eGFR cohort was not observed in the ACR cohort.

Although the dementia diagnosis rate in the UK is one of the highest in the world, there is still 34% of cases that are not diagnosed, with under-diagnosis more likely in early stage dementia [42]. The diagnosis rate would also have changed over the years with incentive schemes to drive diagnosis rate and increased public awareness with public health campaigns

[43]. Although previous literature showed good validity of dementia diagnosis in primary care records [28], documentation of the subtypes of dementia may be less consistent. Therefore, the accuracy of outcome ascertainment in this retrospective study will not be as good as prospective cohort studies that do regular cognitive assessment for all participants.

Significant missing ethnicity data is also recognised, and although there is an adjustment in the CKD-EPI eGFR equation for patients with black ethnicity, inaccurate estimation is likely to affect a small proportion of the study population as black ethnicity only comprised 3% of the population in England and Wales [44].

Education level, an important confounder, is not routinely captured in primary care records and not adjusted for in this study [45]. This may have led to over-estimation of the observed association.

7.5 Implications and recommendation for future research

This study has identified decreased eGFR and increased albuminuria as risk factors for incident all-cause dementia. ACR in particular is a risk factor for vascular dementia. The results are generalisable to older adults in the UK primary care settings, who typically have their renal function and urine protein tested routinely, especially if they have known cardiovascular or renal risk factors.

These results may have important implications for the management of people with CKD, especially given its increasing prevalence. First, health professionals should be aware of the higher risk of dementia associated with a reduced eGFR or increased urine ACR, and future research should evaluate the value of dementia screening in patients with CKD. Second, our results, along with results from the 3City studies, which showed an eGFR decline of >4 per year increases the risk of dementia five times [11], should prompt further research to

establish whether slowing disease progression and vascular risk factor modification reduces the risk of dementia in patients with CKD.

8. Conclusion

This large retrospective cohort study of adults aged ≥50 years in a UK primary care population showed that reduced kidney function is associated with an increased hazard of all-cause dementia, Alzheimer's disease and vascular dementia. Albuminuria was also an independent risk factor for dementia, likely driven by its association with vascular dementia. These findings highlight the need for further research into whether good CKD care reduces dementia risk and whether active surveillance for signs of early dementia is indicated in patients with CKD.

Ethical approval

The UK National Health Service South-East Multi-centre Research Ethics Committee approved THIN data collection in 2003. Under the terms of approval, an independent Scientific Review Committee (SRC) administered by IQVIA reviews and approves protocols for the use of the database. The SRC approved the use of the THIN database for this study (SRC Reference Number: 20SRC013 Date: 18th February 2020).

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