Estimated Glomerular Filtration Rate is not Associated with Alzheimer's Disease in a Northern Ireland Cohort

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Renal function and Alzheimer's disease

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Abstract

Background: Alzheimer's disease (AD) prevalence is increasing globally and typically progresses for several years prior to clinical presentation of dementia. Renal dysfunction and vascular disease have been reported in association with dementia in several cross-sectional and longitudinal studies, and may contribute to AD risk. Experimental and observational studies suggest amyloid-β (Aβ) clearance may be impaired in chronic kidney disease (CKD) indicating a mechanism for increased AD risk. **Objective:** The objective of this study was to compare estimated glomerular filtration rate (eGFR) between individuals with AD and cognitively intact controls, controlling for potential confounding factors. **Methods:** A cross-sectional, case-control study was carried out in 317 cognitively normal participants and 253 cases with a clinical diagnosis of AD in a UK tertiary care dementia clinic. Associations were considered using logistic regression adjusting for confounding variables (age, *APOE e4* genotype, systolic blood pressure, education (left school at 14), and smoking status). **Results:** AD cases were older than cognitively intact controls, had lower MMSE scores, were more likely to have at least one *APOE e4* allele, had higher rates of smoking, were more likely to be taking aspirin and /or clopidogrel, and had lower blood pressure. We found no significant association between eGFR and AD both before and following adjustment for appropriate confounders. **Conclusion:** This study failed to find an association between eGFR and AD in a cross-sectional sample study of elderly white individuals. **Keywords:** Alzheimer disease, Chronic Renal Insufficiency, Dementia, glomerular filtration rate, kidney, Chronic Kidney Diseases.

Introduction

Alzheimer's disease (AD) is the most common dementia subtype accounting for nearly 80% of all cases with the number of those affected likely to rise considerably with increasing life expectancy [1]. There are currently more than 815,000 people with dementia in the UK (about 1.3% of the population) and 1 in 14 persons > 65 years have AD [2]. High prevalence rates have also been reported in the United States of America, with 1 in 9 individuals aged 65 years or more diagnosed with AD, increasing to 1 in 3 persons over the age of 85 years [3].

Chronic kidney disease (CKD) is characterised by a gradual loss of kidney function over months or years and identified by serial measurements of serum creatinine and estimated glomerular filtration rate (eGFR). An eGFR < 60 ml/min/1.73m^2 has been recognised as a potential risk factor for dementia [4–7]. The global prevalence of CKD is estimated at 11-13%, increasing with age to almost 28% in those 70 years or older [8]. Both the kidneys and brain are susceptible to vascular damage with similar haemodynamic and physiological characteristics and risk factors that include diabetes mellitus, hypertension and hyperlipidemia [9,10]. Renal dysfunction also accelerates vascular ageing and calcification, including the vasculature proximal to the brain, such as the circle of Willis [11], manifesting in structural alterations and increased risk of cerebrovascular disease [12].

In preclinical dementia, symptomless but pathogenic changes within the brain include abnormal protein deposition culminating in neuronal death. Amyloid-β (Aβ) is the hallmark constituent of AD plaques and renal clearance has been proposed as a mechanism that aids the removal of cerebral Aβ [13]. An imbalance between the processes of production and clearance leads to Aβ accumulation and AD development and has become a therapeutic target of disease-modifying agents [14]. CKD patients undergoing dialysis have been reported to have serum Aβ levels similar to cognitively intact controls, while those with CKD not receiving dialysis

had relatively higher serum Aβ levels that were negatively correlated with eGFR [15]. Systemic reduction in serum Aβ following haemodialysis has also been demonstrated [16] with associated improvement in cognitive function [17]. Furthermore, animal studies have shown renal clearance of peripheral Aβ has led to reduced cerebral levels in mice [18]. As such, the objective of this study was to compare renal function determined by eGFR, between individuals with AD and cognitively intact controls, controlling for potential confounding factors.

Materials and Methods

Study design and recruitment

A cross-sectional, case-control study design was used to compare prevalent AD cases to cognitively intact controls. All recruitment and testing was undertaken between August 2006 and 2008 by one investigator (MW) and has been described elsewhere [19]. An opportunistic recruitment strategy was used with probable AD cases identified in a non-systematic fashion as they appeared in a hospital memory clinic or from records of previous attendees diagnosed with probable AD by a senior clinician using the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS ADRDA) criteria. Other dementia types such as vascular or mixed dementia were not included. Participants with AD were not excluded on the basis of a history of cerebrovascular disease.

A variety of recruitment strategies were employed in the enrolment of controls from several sources. Firstly, carers of patients attending any outpatient clinic in the study hospital were approached. Secondly, a university press release invited participation in the study. Thirdly, a series of talks given to AD patient-support groups in the region led to further volunteers coming

forward. All participants provided informed consent prior to their entry into the study. Exclusion criteria for controls included age under 65 years or a Mini-Mental State Examination (MMSE) score below 26 out of 30. Ethics and governance approval was obtained prior to commencement of the study, which adhered to the tenets of the Declaration of Helsinki.

Data collection

Upon enrolment, all study participants underwent an assessment that involved measuring blood pressure, drawing a blood sample and performing a MMSE. The final component of the assessment involved the completion of questionnaires via interviews with the subject, as well as their carer when appropriate.

Blood taken from participants using standard venepuncture was used to measure serum creatinine for eGFR using the CKD-EPI equation and for DNA extraction to determine *APOE e4* genotype using a 'Sequenom IPlex assay' as well as other blood measures. A family history of AD, medication use and all co-morbid health conditions were documented as present or absent as determined by self-report or consultation of medical notes. Smoking history was measured as a cumulative dose in pack-years.

Statistical Analysis

Summary statistics for continuous variables and relative frequencies by group were calculated. Independent t-tests (for continuous variables) or chi-square tests (for categorical variables) were used to compare participant characteristics between cases and controls. Pearson's correlation coefficients were performed to identify associations between cognitive indices with age and other continuous variables.

Logistic regression models with dementia status (AD or control) as the outcome and eGFR as a continuous explanatory variable, were used to calculate odds ratios (OR) for AD with 95%

confidence intervals (CI), per unit increase in eGFR. ORs were calculated before and after adjustment for confounders. In the adjusted analysis, variables were eligible for inclusion in the final regression model if a significant association was found ($p<0.05$) following univariate analysis or if there was sufficient prior plausibility for their association with AD. To determine the final model, a backward selection procedure was undertaken and only variables significantly associated with the dependent variable (AD) were retained. Following this procedure the final model used to calculate adjusted OR's contained age, number of *APOE e4* alleles, systolic blood pressure (SBP), smoking pack-years (calculated as the product of total years and average cigarettes per day) and educational attainment (recorded as leaving school before age fourteen or stayed in education beyond 14), and use of beta blockers. To examine the association between AD severity and eGFR, a sensitivity analysis was undertaken using multinomial logistic regression. AD severity was categorised by MMSE score: Severe: 0-9; Moderate: 10-20; Mild: 21-26; and pre-mild $\geq$ 27. Pre-mild AD was used as the reference category. The sensitivity analysis was adjusted for age, number of *APOE e4* alleles, SBP, smoking pack-years, educational attainment and use of beta blockers. All statistical analyses were performed using SPSS statistics version 23 (IBM Corp., Armonk, NY).

Results

Demographic and clinical characteristics of the study population (n=570) are presented in Table 1 for both cases (n=253) and controls (n=317). AD patients were more likely to be older than controls (80.2 vs. 76.5 years; $p<0.001$), with at least one *APOE e4* allele (69% vs. 25%; $p<0.001$). There was no significant difference in gender between cases and controls, with males constituting 36% of cases and 39% of controls. Cases with AD had a significantly lower MMSE score (18.0 vs. 28.8; $p<0.001$) and lower SBP (134 mmHg vs. 144 mmHg; $p<0.001$) compared

to control subjects. Of the AD cases, 26 (10%) were categorised with severe AD (MMSE 0-9), 103 (41%) with moderate AD (MMSE 10-20), 81 (32%) with mild AD (MMSE 21-26), and 7 (3%) with pre-mild (MMSE ≥ 27). Markedly higher proportions of patients with AD had left school at or before 14 years of age (58% vs. 45%; p<0.01) compared to cognitively intact controls. Furthermore, on average patients with AD had accumulated twice as many smoking pack-years as participants in the control group (17.7 vs. 10.0 pack-years; p<0.01). No significant differences were detected between AD cases and controls for history of diabetes mellitus, cardiovascular disease, cerebrovascular disease, or hypercholesterolemia (Table1).A significantly greater proportion of AD patients were taking aspirin and/ or clopidogrel (48% vs. 39%; p=0.02) and non-thiazide diuretics (14% vs. 8%; p=0.03), than controls (Table 1). No difference in renal function was found between cases and controls (37.3 ml/min/1.73m^2 vs 37.4 ml/min/1.73m^2; p= 0.94). In a multivariate logistic regression (Table 2) there was no significant difference in eGFR between those with AD and cognitively intact controls following adjustment for *APOE* genotype, age, SBP, smoking status, educational status and beta blocker use (OR = 1.01; CI: 0.98-1.04; p = 0.50). In the sensitivity analysis of AD severity in cases only (categorised by MMSE score), no associations were reported between eGFR and AD severity categories following adjustment for *APOE* genotype, age, SBP, smoking status, educational status and beta blockers (data not shown).

Discussion

We found no significant association between eGFR and AD in this case-control study of 570 participants in an analysis adjusted for established AD risk factors. Additionally, we found no association between eGFR and disease severity as defined by MMSE score in AD cases only. Our findings support previous reports that showed no association between eGFR and cognitive

impairment [6,20–22], but contrast to those that did report a significant association [5,9,23–30]. In addition, other studies also reported significant associations between renal impairment characterised by the presence of microalbuminuria and cognitive impairment [10,20,21,31]. A recent meta-analysis of five population based prospective studies included 27,805 participants, demonstrated a non-significant increased risk of cognitive impairment or dementia in those with an eGFR < 60 ml/min/1.73m^2, with a significant association found only in those with albuminuria [7].

Unlike previous studies that examined cognitive impairment or dementia, we focused specifically on eGFR in AD. In an earlier study by this group with a smaller sample size and better renal function (eGFR > 60 ml/min/1.73m^2), an association between lower eGFR in 83 AD cases was identified compared to cognitively intact controls which remained significant following adjustment for known risk factors [4]. Other case-control studies of similar size have also reported lower eGFR in AD cases compared to controls [32,33] providing some support for the hypothesis that reduced renal function contributes to impaired Aβ clearance and increased cerebral deposition [13–18,34]. Our current findings support data from the Cardiovascular Health Cognition Study in 3,349 individuals, where an association with serum creatinine and vascular dementia was identified but not in those with AD [35]. Our findings were based on a largely clinically derived sample of older participants (mean age 78) with unexpectedly poor renal function compared to the same age group in other cohorts [36] for both cases and controls (eGFR = 37 ml/min/1.73m^2). Rates of hypertension and diabetes were not higher than expected in cases or controls. The low renal function observed in this study may result in part from the sampling method used. Any sampling bias favouring inclusion of participants with poor renal function would have increased the risk of type 2 error in this study. Recruitment of carers may have resulted in higher proportions of first-degree relatives and spousal recruitment. Spousal concordance of health risks and behaviours has been reported for

many diseases, including CKD and other conditions influenced by renal risk factors, such as cardiovascular disease, hypertension, metabolic syndrome, and elevated fasting glucose levels [37,38].

We used a serum creatinine based equation to estimate renal function and eGFR [39]. Other studies have shown that cystatin-C may be a more accurate indicator of GFR than serum creatinine in populations with more extensive co-morbidities [40]. Cystatin-C accumulates in the blood of those with CKD and may reduce AD risk by binding Aβ and inhibiting its deposition in the brain [41].

Major strengths of the present study were its reasonable sample size and extensive characterisation of the study population that enabled adjustment for major potential confounders. However, there are several potential limitations to our study. First, there may be residual confounding factors not measured in our sample that influence renal function but which have not been controlled for in our data. Second, any causal and temporal relationships between eGFR and AD cannot be determined due to the cross-sectional nature of our study, which prevents the inference of any causal or chronological relationship. Thirdly, the absence of direct measures of glomerular filtration rate limits the assumptions inferred from the eGFR formula which was based on a single laboratory measurement. Fourth, the potential for confounding bias may have been introduced through differences in the strategies for recruiting cases and controls. Fifth, the definition used for cognitively normal controls, MMSE $\geq$ 26, may have resulted in the inclusion of small number of individuals with prodromal AD. Finally, other methodological issues may further complicate the interpretation of our data. While the convenience sampling was instrumental in the recruitment of 570 participants in a timely manner, this approach may have inhibited subject demographics and limited the generalisability of conclusions. Future studies should aim to adopt a truly random approach to

recruitment, using population records for identifying controls and a comprehensive AD patient database to sample cases.

This study provides cross-sectional evidence in a large sample that eGFR is not associated with AD in an elderly white population with poor renal function.

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Conflict of Interest/Disclosure Statement

The authors have no conflict of interest to report. The authors have no financial disclosures.

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Table 1: Summary statistics of subject characteristics.

Characteristic	All (n=570)	Controls (n=317)	Cases (n=253)	P-value
Mean age, yrs (SD)	78.1 (7.4)	76.5 (6.7)	80.2 (7.7)	<0.001
Male, n (%)	216 (38)	125 (39)	91 (36)	0.40
Mean MMSE (SD)	24.4 (6.8)	28.8 (1.2)	18.0 (6.5)	<0.001
Presence of *APOE e4* allele, n (%)	240 (45)	71 (25)	169 (69)	<0.001
Mean systolic blood pressure, mmHg (SD)	139 (18)	144 (18)	134 (18)	<0.001
Mean eGFR CKD-EPI, ml/min/1.73m^2 (SD)	37.4 (8.9)	37.3 (8.4)	37.4 (9.4)	0.94
Education –left school at 14, n (%)	274 (48)	138 (45)	136 (58)	<0.01
Never smoked, n (%)	321 (59)	191 (62)	130 (54)	0.10
Diabetes mellitus, n (%)	59 (10)	37 (12)	22 (9)	0.28
Hypertension, n (%)	221 (39)	131 (43)	90 (38)	0.25
Cardiovascular disease, n (%)	129 (23)	76 (25)	53 (22)	0.47
Cerebrovascular disease, n (%)	70 (12)	38 (12)	32 (13)	0.74
Hypercholesterolaemia, n (%)	216 (38)	124 (41)	92 (39)	0.68
Aspirin and /or clopidogrel, n (%)*	229 (40)	116 (39)	113 (48)	0.03
Antacids, n (%)*	144 (27)	71 (24)	73 (31)	0.06
Thiazide, n (%)*	100 (19)	54 (19)	46 (20)	0.70
Non-thiazide diuretics, n (%)*	57 (11)	24 (8)	33 (14)	0.03

NSAIDs, n (%)*	33 (6)	22 (7)	11 (5)	0.20
Thyroxine, n (%)*	59 (11)	30 (10)	29 (12)	0.39
CCBs, n (%)*	62 (12)	28 (10)	34 (15)	0.08
Beta blockers, n (%)*	118 (23)	75 (26)	43 (19)	0.05

Abbreviations: SD, standard deviation; MMSE, Mini-Mental State Examination; eGFR CKD-EPI, Estimated glomerular filtration rate calculated using the CKD-EPI equation; NSAIDs, non-steroidal anti-inflammatory drugs; CCBs, calcium channel blockers.

*Medications recorded with a frequency >5%.

Table 2: Estimated glomerular filtration rate association in subjects with Alzheimer's disease and controls

Variable	Odds ratio (95% CI)	p-value
APOE e4 alleles	5.85 (3.82 – 8.95)	<0.001
Age (years)	1.08 (1.04 - 1.12)	<0.001
Systolic blood pressure	0.97 (0.96 - 0.99)	<0.001
Smoking (packyears)	1.01 (1.00 - 1.02)	0.02
Education > 14 years	1.67 (1.05 - 2.67)	0.03
Beta blockers	2.07 (1.16 – 3.68	0.01
eGFR (CKD-EPI)	1.01 (0.98 - 1.04)	0.50

Abbreviations: SD, standard deviation; OR, odds ratio; CI, confidence intervals; eGFR (CKD-EPI), Estimated glomerular filtration rate calculated using the CKD-EPI equation.

*Multiple logistic regression analysis adjusted for age (years), number of *APOE e4* alleles, smoking (pack years), systolic blood pressure (mmHg), education (leaving school at or before 14), beta blockers.