



## Commentary

# Mapping the pathways underlying the associations of albuminuria with cognitive decline and dementia

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Among the growing older population, dementia, a debilitating condition marked by cognitive impairment, affects 50 million people globally, and effective treatments are lacking [1]. Increasing our understanding of the pathways between a risk factor and cognitive impairment may illuminate targets for prevention and treatment. A growing body of evidence from observational studies supports the association of albuminuria with dementia and cognitive impairment [2]. Albuminuria, measured by urine albumin-to-creatinine ratio, is a marker of vascular damage in the kidney [2]. In contrast, estimate glomerular filtration rate (eGFR), commonly calculated from serum creatinine, is an index of kidney function and has inconsistent associations with dementia and cognitive impairment [3]. Given that associations from observational studies cannot conclude causality due to potential unmeasured confounding factors, the causal mechanisms underlying the association of albuminuria with cognitive impairment need to be investigated by other types of studies. By applying Mendelian randomization analysis, Chen et al. reported a significant causal effect of albuminuria on lower cortical thickness, while the effect of eGFR on this outcome was not significant [4]. Cortical thickness decreases with age and may be affected by vascular factors [5]. Lower cortical thickness has been associated with cognitive impairment and might mediate the association between albuminuria and cognitive impairment [5]. The findings from Chen et al. in this issue of *EBioMedicine* may help to map the pathophysiological pathways from albuminuria to dementia.

Mendelian randomization analysis uses exposure-associated genetic variants as proxies of the exposure to draw causal inference between an exposure and an outcome. This is enabled by the random

segregation of alleles during meiosis mimicking the random assignment of treatment in clinical trials [6]. Chen et al. used summary statistics from large-scale genome-wide association studies (GWAS) of albuminuria and measures of brain structure quantified from magnetic resonance imaging (MRI). Their study found that a log unit higher in albuminuria would result in 0.07 mm lower in cortical thickness (95% confidence interval:  $-0.12$  to  $-0.02$ ). For a causal inference based on Mendelian randomization analysis to be valid, the genetic proxies of the exposure need to satisfy some assumptions [6]. One of the assumptions is that the genetic proxies of the exposure can only affect the outcome through the exposure, i.e. cannot have a pleiotropic effect on the outcome. Otherwise the effect of genetic proxies on the outcome can be attributable to other factors and cannot be interpreted as the causal effect of the exposure. Given that the biological functions of the genetic proxies of albuminuria are largely unknown, the absence of pleiotropy cannot be directly verified. Therefore, it is difficult to completely rule out pleiotropy based on the analysis in Chen et al. although the authors have used Mendelian randomization methods that are robust to pleiotropy based on statistics inference. With the limited available biological information on the genetic proxy of albuminuria, to further elucidate the mechanisms underlying albuminuria with cortical thickness and cognitive impairment, it may be useful to consider multiple hypotheses, including the potential presence of pleiotropy, such that some shared factors between the kidney and the brain drive the significant effect of albuminuria on cortical thickness.

Some have hypothesized shared factors of microvascular damage between the kidney and the brain might be the mechanism underlying the association between albuminuria and cognitive impairment [7]. Some potential shared factors could be diabetes and hypertension, risk factors of both chronic kidney disease (CKD) and dementia [1,8]. Protein overload in the kidney tubular compartment due to albuminuria could lead to more kidney damage, inflammation, and increased levels of circulating proinflammatory cytokines or chemokines [9]. Recently, basic science studies suggest systemic factors could affect or cross the blood-brain barrier and consequently affect the function of neuronal, glia, or mural cells leading to brain ageing and neurodegeneration [10]. Therefore, with a positive feedback loop among vascular damage, albuminuria, and inflammation, albuminuria might be a causal player even in the presence of pleiotropy.

Both albuminuria and eGFR are markers for the staging of CKD where higher albuminuria and lower eGFR indicate more severe CKD

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[8]. Individuals with low eGFR often have albuminuria [8]. Hence, one would expect that eGFR would have significant association with cognitive outcomes, paralleling those of albuminuria. However, the associations of eGFR with cognitive impairment have been inconsistent in observational studies [3]. In this study by Chen et al., albuminuria was significantly associated with lower cortical thickness but not eGFR. In early stages of CKD, kidney damage can be present without reduction in eGFR as a result of the compensatory effect of the remaining healthy nephrons [8]. The inconsistent association of eGFR with cognitive impairment might be partly due to the heterogeneity of the study population without reduction in eGFR in whom some might have kidney damage and albuminuria. To further investigate the relationship of albuminuria and eGFR with cognitive outcomes, observational studies could explore the association by CKD stages to assess the joint effect of albuminuria and eGFR. Mendelian randomization studies could consider multivariable methods to estimate the causal effects of albuminuria and eGFR in the presence of each other with brain structure and cognitive outcomes.

In summary, multifactorial pathways may link albuminuria, kidney function, cortical thickness, and cognitive impairment. The study by Chen et al. demonstrated that Mendelian randomization studies may help to illuminate these pathways. As more large-scale studies with data in genetic and brain features are available, there will be more opportunities for Mendelian randomization investigation to reveal potential causal mediators in the associations of albuminuria and kidney function with cognitive impairment and dementia.

#### Contributors

AT is the sole author.

#### Declaration of Competing Interest

Nothing to declare.

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